P-001

Acute Lymphoblastic Leukaemia

THE CHARACTERISTIC OF IG/TCR GENE ARRANGEMENTS PATTERNS AND ITS APPLICATION IN MRD DETECTION IN CHINESE CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

According to analyze the characteristics of *Ig/TCR* gene rearrangements patterns and the correlation with the clinical and biological features in childhood ALL, we established up the quantitative detection system targeted by *Ig/TCR* gene rearrangement.

Methods

Using the standardization *Ig/TCR* amplification system proposed by Europe Biomed-2 collaboration group, the clonal gene rearrangement of *IgH*?*IgK*(including *Kde*)?*IgL*?*TRD*?*TRB*?*TRG* were screened in 259 children with ALL (including 233 B cell precursor ALL and 26 T cell ALL), then sequenced and analyzed for the junction domain for the preparation of RQ-PCR.

Resultsf clonal *Ig/TCR* gene rearrangements in childhood B-ALL and T-ALL was 98.3% and 92.3% respectively. In B-ALL, the positive rate of clonal rearrangement: *IgH* (85.8%)> *IgK* (51.1%)> *TRD* (49.4%)> *TRG* (46.7%)> *TRB* (33.9%)> *IGL* (6%); In T-ALL: the *TRB* (76.9%)> *TRG* (73.1%)> *TRD* (38.5%)> *IgH* (11.5%). The incidence of *TRG* rearrangement in the *TEL-AML1*$^+$ and *BCR-ABL*$^+$ B-ALL was significantly higher than that in the *E2A-PBX1*$^+$ and *MLL*$^+$ rearrangement B-ALL (80.9%, 57.1% and 16.7%, 0 respectively, p <0.001). In childhood B-ALL, *TRG* rearrangement pattern was associated with age, initial WBC count (p =0.031;p <0.001). *IgH* rearrangement occurred mostly in patients who had good prednisone (p = 0.051). We established a RQ-PCR quantitative detection system in 91.9% children with ALL.

Conclusions

The incidence of clonal *Ig/TCR* gene rearrangements was high in childhood ALL, and there was diversity in the junction. The rearrangement pattern was different significantly in childhood ALL with different fusion genes, and it was associated with age and initial WBC count. This RQ-PCR by *Ig/TCR* as target displayed wide coverage of molecular markers and higher sensitivity and specificity of quantitative approach, which was applied in MRD detection in childhood ALL.

P-002

Acute Lymphoblastic Leukaemia

LOSS OF TUMOR SUPPRESSOR BTG1 PROMOTES CELL SURVIVAL BY CONTROLLING ATF4 FUNCTION

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Objectives

The B cell Translocation Gene 1 (BTG1) locus is affected by genomic deletions in 9% of pediatric acute lymphoblastic leukemia patients. However, it remains unclear how loss of BTG1 promotes clonal outgrowth.

Methods

We detected an up to 15-fold increases of BTG1 expression when cells are exposed to various challenge conditions. To test for a functional role for BTG1 in the cellular response to stress, we challenged BTG1 knockout cells with nutrient deprivation and found that BTG1 knockout cells show a 20-30% improved survival rate as compared to wildtype cells.

Results

As Activating Transcription Factor 4 (ATF4) is a master regulator of cellular stress signaling, we hypothesized that the improved survival after BTG1 loss is regulated via ATF4. Indeed, ATF4 target genes are differentially regulated in BTG1 knockout cells. In addition, we showed that BTG1 complexes with ATF4 in immunoprecipitation experiments.

BTG1 functions as a transcriptional co-regulator that acts by recruiting Protein Arginine Methyl Transferase 1 (PRMT1) to transcription factor complexes. Methylation assays showed that ATF4 is a direct target for PRMT1 mediated methylation. Furthermore, we found that the PRMT1 interacting domain in BTG1 is essential for BTG1 mediated modulation of ATF4 function. In search for additional evidence for the functional interaction between BTG1 and ATF4 we performed global expression analysis on cells expressing B-cell marker B220. This revealed a significant deregulation of ATF4 target genes in BTG1 knockout cells when compared to wildtype cells.

Conclusions

Together, our data indicate that BTG1 suppresses activation of ATF4 in response to cellular stress. Loss of BTG1 function, as it occurs during leukemia development, enhances ATF4 activity, thereby promoting cell survival under cellular stress conditions such as nutrient deprivation or ER stress. Leukemic cells carrying BTG1 deletions may thus benefit from this increased resistance to cellular stress, not only during leukemia development but also during treatment.

P-003

Acute Lymphoblastic Leukaemia

THE FREQUENCY OF HLA -A, B, DRB1 ALLELES ACCORDING TO RISK GROUPS IN CHILDREN WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Previous studies have demonstrated some significant differences in HLA allele frequencies in leukemic patients and normal subjects. The purpose of this study is to evaluate the frequencies of HLA class I (A, B) and class II (DRB1) alleles in patients with acute lymphoblastic leukemia and compare to unrelated healthy subjects in Central Anatolia of Turkey.

Methods

This study was performed in 90 children with ALL, whose ages were ranging between 1-18 years. Twenty nine of 90 patients had standard risk group (SRG) of ALL, 37 moderate risk group (MRG), and 24 high risk group (HRG) respectively according to Berlin Frankfurt Münster (BFM) standards. We have typed for HLA-A, B, DRB1* alleles in patients with ALL and 90 unrelated normal subjects in Central Anatolia of Turkey. PCR-SSO low resolution method (Luminex technology) was used for HLA typing.

Results

Allele frequencies of HLA-A*01,HLA-A*29 and DRB1*07 were higher in patients with ALL compared to the control group (p=0.008, p=0.032, and p=0.000, respectively). On the contrary, HLA-B*08 and DRB1*08 alleles frequencies in patients with ALL lower than controls (p=0.010, p=0.016, respectively). DRB1*04 allele was higher in HRG ALL and MRG ALL than in SRG ALL (p=0.009). DRB1*07 allele was higher in SRG ALL than in HRG and MRG ALL (p=0.007). The most observed haplotype was A*02, B*35, DRB1*13 (p=0.023) in patients with ALL. We could not find any haplotypes negatively associated with ALL. The most observed homozygous allele was A*24 (p=0.043) in the presented cohort.

Conclusions

These results suggest that HLA-A*01, A*29, DRB1*07 alleles may play a presumptive predisposing factor in ALL , whereas HLA-B*08 and DRB1*08 alleles have been found to be negatively associated with ALL. In addition, DRB1*04 allele has been found as associated with HRG and MRG ALL. Also, DRB1*07 allele may play a presumptive predisposing factor for SRG ALL.

P-004

Acute Lymphoblastic Leukaemia

PRECLINICAL IN VIVO EFFICACY OF PI3K PATHWAY INHIBITION IN PHILADELPHIA-LIKE ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Philadelphia-like B-precursor acute lymphoblastic leukemia (Ph-like ALL) is associated with various genomic alterations known or predicted to activate oncogenic signal transduction. We previously demonstrated constitutive phosphorylation of PI3K pathway proteins in Ph-like ALL, but therapeutic disruption of PI3K signaling in these leukemias has been minimally investigated. We hypothesized that PI3K isoform-selective or dual PI3K pathway protein inhibition would robustly inhibit Ph-like ALL proliferation *in vivo* and abrogate aberrant signaling.

Methods

Immunocompromised mice well-engrafted with pediatric Ph-like ALL were treated with the PI3Kα inhibitor BYL719, PI3Kδ inhibitor idelalisib, PI3K/mTOR inhibitor PKI-587, TORC1/TORC2 inhibitor AZD2014, or vehicle. Treated mice were assessed for (a) pharmacodynamic inhibition of phosphoproteins at 72 hours by phosphoflow cytometry and (b) residual ALL in murine spleens after 3-4 weeks of treatment by quantitative flow cytometry.

Results

7 of 7 Ph-like ALL xenograft models (5 *de novo* and 2 relapsed; Table) demonstrated potent *in vivo* inhibition of relevant phosphoproteins (phosphorylated PI3K, Akt^{T308}, mTOR, S6, 4EBP1, Akt^{S473}, and/or ERK) with PI3K pathway inhibition. PKI-587 treatment resulted in near-eradication of ALL in all models with mean 91.8% (range 86.0-99.4%) leukemia reduction versus vehicle treatment ($p<0.0001$ via ANOVA with Dunnett post-test for multiple comparisons). BYL719, idelalisib, or AZD2014 treatment inhibited ALL proliferation in all models with mean 56.8% (range 38.5-72.9%), 45.5% (range 40.2-53.1%), and 51.8% (range 37.4-69.4%) leukemia reduction, respectively ($p<0.001$ for all). Models with highest basal PI3K pathway phosphoprotein levels responded most robustly to PI3K pathway inhibitors.

Ph-like ALL genomic lesions
IGH@-CRLF2
IGH@-CRLF2, $JAK2_{R683G}$
IGH@-CRLF2, $JAK2_{GPinsR683}$
IGH@-CRLF2, $JAK2_{R867Q}$
$JAK1_{S646F}$
P2RY8-CRLF2, $JAK2_{R683G}$
IGH@-CRLF2, $JAK2_{R683G}$

Conclusions

PI3K pathway inhibition is an effective, biochemically relevant therapeutic approach for Ph-like ALL. Dual PI3K/mTOR inhibition was the most potent treatment strategy

evaluated in these models. These results will continue to inform development of clinical trials testing signal transduction inhibitors with chemotherapy in children with high-risk ALL.

P-005

Acute Lymphoblastic Leukaemia

IMPROVED THERAPEUTIC STRATEGIES USING PREDICTIVE BIOMARKERS IN PEDIATRIC ALL: AN ACTIVITY WITHIN THE EU NETWORK ENCCA TO INTRODUCE NEWLY DISCOVERED MOLECULAR INFORMATION INTO CLINICAL PRACTICE

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Objectives

Lately, major progress has been achieved in pediatric ALL by improved risk stratification of treatment based on the measurement of leukemic cell reduction by minimal residual disease (MRD) analysis. Outcome data clearly indicate, however, that a large proportion of recurrences cannot be predicted solely by their MRD response pattern. As part of the EU-funded network project ENCCA, a stepwise integrated approach by European clinical study groups on ALL was taken to molecularly characterize new risk groups and to systematically adapt existing trial infrastructures for associated common future treatment approaches.

Methods

First, a survey of diagnostics was conducted. Second, development of a harmonized pipeline for molecular diagnostics in a European virtual laboratory setting using very high-risk ALL (VHRL, characterized by molecular persistence under intensified treatment) as a model system was started. Third, the molecular diagnostic pipeline was integrated with preclinical model systems for molecularly targeted treatment and algorithms for identification and prioritisation of targets developed. Fourth, harmonization and integration of clinical platforms was promoted to practically pave the way for introduction of molecularly targeted treatment.

Results

So far, main achievements of this project were: a) implementation of coherent diagnostic strategies by developing recommendations for diagnostic approaches for pediatric ALL; b) implementation of a laboratory software system tailored to ALL and agreement on a shared dataset of ALL biospecimens to promote joint research activities including a meta-database for interfacing additional different laboratory systems; c) coordinated joint evaluation of molecularly defined prognostic entities (e.g., IKZF1-deleted, CRLF2+, ERG-deleted, TCF3/HLF+); d) implementation of a xenotransplant repository; and e) development of access to a functional clinical trial infrastructure (IntReALL).

Conclusions

Overall, this project exemplifies complexities, needs and solutions to adapt current fragmented infrastructures associated with different clinical trial groups to prepare for common future molecularly based treatment approaches of new pediatric ALL entities in Europe.

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P-006

Acute Lymphoblastic Leukaemia

REFINING RISK CLASSIFICATION OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA BASED ON GENETIC FEATURES AT PRESENTATION AND MINIMAL RESIDUAL DISEASE

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Objectives

To apply genetic characteristics and early response to therapy towards further refinement of ALL risk classification.

Methods

Study included precursor B-ALL patients presenting with low risk (LR) features [age 1-9.9 years and WBC<50x10^9/L, or DNA index ≥1.16 or TEL/AML1; with no CNS or testicular disease, or unfavorable genetic abnormalities] who were treated at Children's Cancer Hospital Egypt between July 2007 and December 2010 according to St Jude ALL Total Study XV (Pui et al., NEJM 2009; 360: 2730)

Results

Of 356 patients with provisional LR features, 290(81.5%) who had good early response and end of induction minimal residual disease (day42-MRD) ^{9}/L at presentation but treated on LR arm based on favorable genetic features and MRD response. Their 5-year RFS was 91.7±5.7%. LR patients with MRD day15

Conclusions

Therapy was successfully de-escalated based on favorable genetic features and MRD irrespective of age and WBC at presentation. MRD day15

P-007

Acute Lymphoblastic Leukaemia

IMPLEMENTATION OF AUTOMATED ELECTRONIC RISK ASSIGNMENT FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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Objectives

Risk-directed treatment has significantly improved survival in childhood ALL. The COG ALL Classification Study AALL08B1 and linked clinical trials require timely risk assignment for over 2,000 children annually according to a complex risk stratification scheme that integrates clinical information, laboratory data from the local site and three centralized reference laboratories that assess minimal residual disease, DNA ploidy, and central review of cytogenetic and fluorescent *in situ* hybridization data. The purpose of this study was to develop, implement and validate an automated risk assignment methodology.

Methods

An algorithm was implemented in the COG web-based remote data entry system (eRDEs) to automatically generate risk assignments for patients, after required data from all sources are entered. Individual sites review and validate the assignment, eliminating the need for manual centralized assignments. The algorithm was successfully modified during the study to accommodate new data on the prognostic impact of intrachromosomal amplification of chromosome 21 which refined the risk classification.

Results

Within 3.5 years, AALL08B1 has enrolled nearly 7,000 subjects. Patients with B-ALL are treated on three frontline studies (Infant-AALL0631, Standard Risk-AALL0932, High Risk-AALL1131) and are risk classified for post induction therapy. Comparison of programmatically generated risk assignments with automatic assignments in eRDEs, demonstrated discordance in only 109 of 4,776 evaluable cases (2.2%). Only one of these cases demonstrated discordant risk assignment between the two methods, due to alteration of a data entry after the site validated the risk assignment.

In the remainder, risk assignment was simply missing by one or the other method due to incomplete data, discontinuation of protocol therapy, or patient inevaluability for other reasons.

Conclusions

Automated web-based risk assignment, integrating multiple sources of data, is a rapid, accurate, and flexible mechanism that is well-suited for use in large-scale cooperative group clinical trials.

P-008

Acute Lymphoblastic Leukaemia

SIGNIFICANT CONCORDANCE OF EARLY TIME-POINTS MINIMAL RESIDUAL DISEASE (MRD) LEVELS, ASSASED BY EIGHT-COLOUR FLOW CYTOMETRY AND RQ-PCR IN PEDIATRIC T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Minimal residual disease (MRD), assessed by flow-cytometry(FC) or RQ-PCR-detection of rearranged immunoglobulin and T-cell receptor(Ig/TCR) genes, is the most significant prognostic factor in ALL.Compatibility of these methods has not been studied in pediatric T-ALL.

Objective: Comparative analysis of MRD levels in pediatric T-ALL, by 8-colour FC and (Ig/TCR)RQ-PCR aimed at assessment of MRD kinetics and concordance between FC-MRD and RQ-PCR-MRD results.

Methods

MRD was assessed in 30 T-ALL children,treated according to ALL-IC-BFM2002protocol, by RQ-PCR in 30 patients (77bone marrow mononuclear cell samples) and by FC in 26/30 patients (69bone marrow samples), on day15, day33 and before consolidation(week 12). MRD evaluation by RQ-PCR was according to ESG-MRD-ALL protocols, by FC-according to EuroFlow protocol,with informed consent of patients and approval of local review board. MRD results by both methods were available for comparison in 65/77 samples(84%). Spearman's rank correlation test was used to estimate the relation between FC-MRD and RQ-PCR-MRD. In 16/30 patients (53%) comparison of risk-group assignment, based on standard criteria (day15 FC-MRD; day33 & week12 RQ-PCR-MRD) was feasible.

Results

High MRD levels (>=0.001) were observed at early time-points:96% of results at day15 and 63%-at day33, equally for both methods. Before consolidation lower MRD levels were observed:82% of FC-MRD and 70% of RQ-PCR-MRD results were<0.001. Significant correlation between FC-MRD and RQ-PCR-MRD was observed at day15 (R=0.94;p=0.000) and day33 (R=0.87;p=0.000);before consolidation:R=0.66(p=0.002). Risk group assignment based on FC-MRD and RQ-PCR-MRD was concordant in 11/16 patients (69%).

Conclusions

Significant concordance, demonstrated for FC-MRD and RQ-PCR-MRD at day15 and day33, results from specific MRD kinetics in T-ALL: considerable proportion of high MRD levels at early time-points, lower-before consolidation. Longer follow-up is needed for prognostic significance of MRD measured by both methods to be assessed.

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P-009

Acute Lymphoblastic Leukaemia

ACUTE LYMPHOCYTIC LEUKEMIA (ALL) WITH NORMAL HEMATIMETRIC VALUES AT TIME OF DIAGNOSIS

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Objectives

ALL is the most frequent hematologic malignacy in childhood. Clinical suspicion allows diagnosis and opportune treatment. Abnormal blood count values are observed in 90% of cases. However, normal hematimetric values are detected in rare cases.

Our aim was to analyze the cause of consultation, signs and symptoms at time of diagnosis and time elapsed between the first symptom and ALL diagnosis and outcome in patients presenting normal blood count values .

Methods

Clinical records and laboratory data of patients with diagnosis of ALL who disclosed normal hematrimetric values at diagnosis. Blood counts were considered normal when WBC count was between 5,000-10,000/mm^3 (without neutropenia or blasts), appropriate haemoglobin levels for age and platelet count >150.000/mm^3. Reason for consultation, signs and symptoms, time elapsed since first symptom until diagnosis, ALL biologic characteristics and outcome of these cases were analyzed.

Results

From January-1990 to October-2013, 1572 cases of ALL were diagnosed and, 42 (2.7%) of them presented with an initial normal blood count. The average age was: 8.3 (range: 1-17) years. The average time elapsed between symptoms and diagnosis was 2 months (range: 15 days- 8 months). The signs and symptoms observed were: fever: 37%, bone pain: 34%, asthenia: 16%, weight loss: 16%, joint compromise: 13%, respiratory involvement: 16%, abdominal mass: 11%, pericardial compromise: 5%, testicular-ovarial compromise: 5%, renal compromise: 8%, skin: 3%, CNS: 10%. Immunophenotype was B-cell precursor in 79% of cases and T-ALL in 18%. Complete remission was achieved in 86% of cases and 4% relapsed.

Conclusions

Normal blood count values were observed in 2.7% of ALL patients. Fever and bone compromise were the most frequent clinical findings, showing extramedullar compromise of several localizations in >50% of cases. Thus, normal hematimetric values do not rule-out ALL diagnosis and thorough clinical examination is essential for reaching an accurate diagnosis.

P-010

Acute Lymphoblastic Leukaemia

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR INFANTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A RETROSPECTIVE STUDY FROM THE PEDIATRIC ALL WORKING GROUP OF THE JSHCT

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Objectives

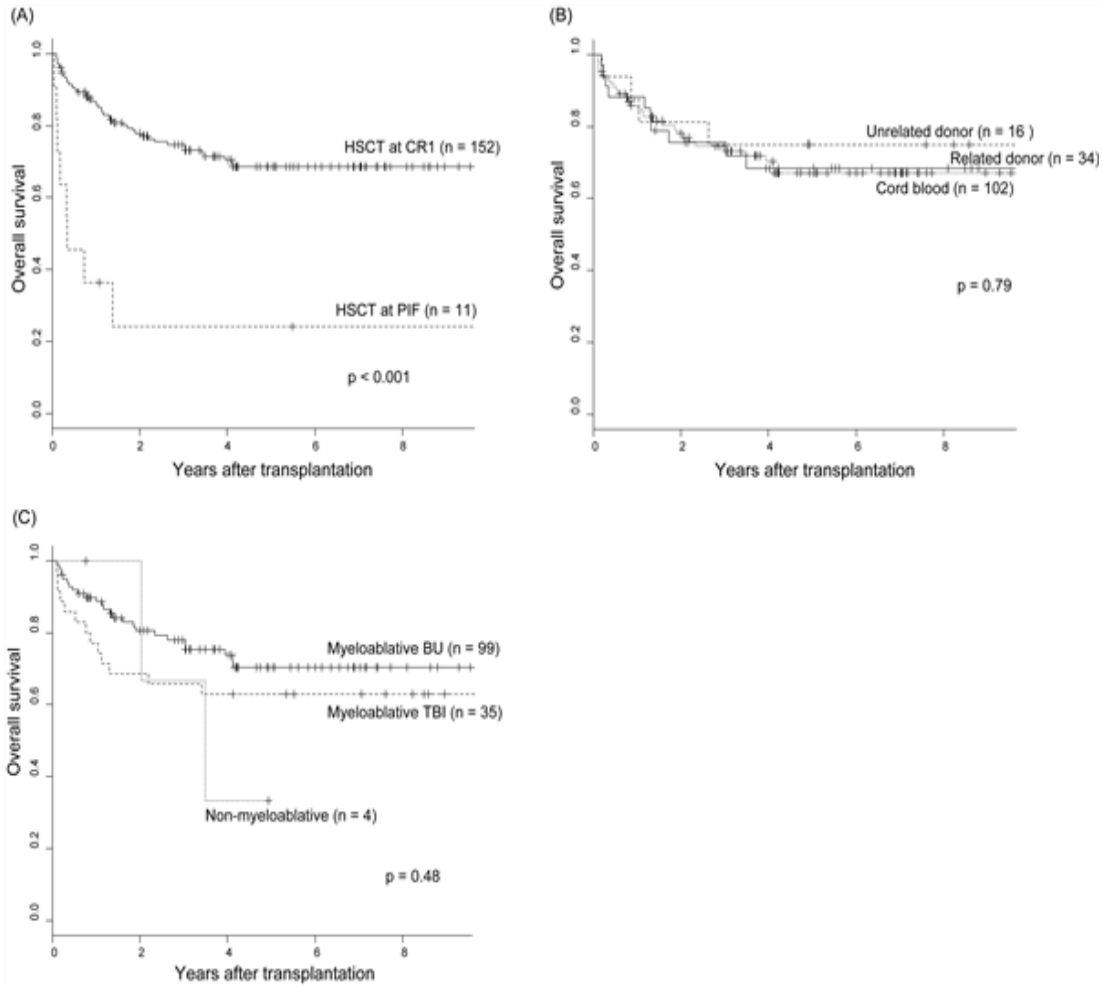
Infants with acute lymphoblastic leukemia (ALL) have worse outcomes than do older children, and recent clinical studies report improving results for infant ALL using intensified chemotherapy followed by hematopoietic stem cell transplantation (HSCT); however, the optimal role of HSCT as first line therapy for infant ALL is not defined. In this study, to obtain fundamental information for establishing a standard approach for infants with ALL, we retrospectively analyzed HSCT for infants ALL based which were reported to the Japan Society for Hematopoietic Cell Transplantation (JSHCT) registry.

Methods

A total of 163 infants with ALL were analyzed. The patients were selected according to the following criteria: (1) diagnosed as ALL at younger than 1 year old; (2) allogeneic HSCT was performed in first complete remission (1CR, n = 152); (3) HSCT was performed between 1996 and 2011. As a comparator, 11 infant ALL who undertook allogeneic HSCT in primary induction failure (PIF) during this period were also analyzed.

Results

Overall survival (OS) at 4 years was 70.5 ± 3.9% for 1CR group, and 24.2 ± 13.8% for those who received HSCT for PIF (Figure 1A, $p < 0.001$). There was no significant correlation between the outcomes and each factors including donor type (Figure 1B), conditioning of HSCT (Figure 1C), age at HSCT, initial leukocyte count, and cytogenetics.



Conclusions

Our results confirmed that HSCT was a valuable option for infants with ALL during the first CR, although it should be compared to the outcomes of chemotherapy and late complications should be assessed.

P-011

Acute Lymphoblastic Leukaemia

IN PATIENT INDUCTION MORTALITY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA: CAN WE COMBAT INFECTION? EXPERIENCE AT A TERTIARY CARE CENTRE

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Objectives

The main objective of the study is to determine the common causes of mortality during the treatment of acute lymphoblastic leukaemia (ALL) in children especially during induction remission.

Methods

We present a retrospective descriptive study conducted at in patient unit of Haematology/ Oncology Department at the Children's Hospital Lahore between November 2012 and October 2013. All newly registered patients of ALL between 1-15 years of age who expired over the one year period were included. Mortality data was collected and analyzed regarding age, gender, WBC count, risk categorization, timing of death with respect to treatment phase and cause of death. Lahore Group Protocol for acute lymphoblastic Leukemia LALL01 (Modified BFM and UKALLXI) was used for treatment.

Results

Out of 222 new patients of ALL registered in the study period, 40(18%) died during treatment. Majority 19/40(47.5%) were between1-5 years of age. Thirty (75%) patients belong to high risk group. During induction 11/40(27.5%) died, 10/40(25%) just after remission and 9/40(22.5%) died before initiation of therapy. Infection alone or in combination with other factors was responsible for deaths in 25/40 (62.5%) patients. Septicemia and pneumonia were documented in 14/40(35%) and 11/40(27.5%) patients respectively. Ten (25%) died due to hemorrhage and 5 (12.5%) due to progressive and resistant disease.

Conclusions

Infection is the leading cause of mortality in ALL patients in our study population. The only key to the solution is better supportive care and which can be improved by decreasing the patient load, increasing the no of nursing staff and educating the families regarding infection prevention and control measures.

P-012

Acute Lymphoblastic Leukaemia

ACUTE INFECTION OF CENTRAL NERVOUS SYSTEM (CNS) IN CHILDREN WITH ACUTE LEUKEMIA

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Objectives

Infections are the most frequent cause of morbidity in childhood acute leukemia (AL). However, CNS is a rare localization, with high mortality.

Our aim was to analyze cases with acute infection in CNS in patients with AL and to evaluate the causes of co-morbidity and immunocompromise status at the moment of this complication.

Methods

From January-1990 to February-2014, 2107 AL cases were diagnosed. Infection with CNS localization was detected in 20 cases (0.95%). We reviewed clinical records, biological-laboratory features and images of these patients.

Results

From the 20 observed cases, 17 (1.06%) were ALL (11 newly-diagnosed, 4 relapsed-ALL and 2 infants) and 3 (0.59%) AML. Etiology of infections was: **Bacterial** (n=10), fungal (n=6), parasitic (n=2), viral (n=1) and without germ isolation, but highly suspected bacterial (n=1). Patients disclosed neutropenia at the moment of this event in 67% (n=14) and 38% (n=8) did not have cause of co-morbidity. The infection occurred during induction in 7 patients (35%), 6 (30%) during high-risk blocks, 1 following HSCT, 3 receiving late-reinduction and 3 during maintenance or off therapy. Nine patients (45%) presented seizures and 45% also neurologic impairment. Only 20% presented showed meningeal syndrome. CSF cultures confirmed diagnosis in 62% of cases, 28% required a biopsy of lesions and 10% were confirmed by pathognomonic images and laboratory tests. Eight patients (40%) died due to CNS infection, 5 (20%) presented sequelae (2 severe) and 7 (35%) remained alive without sequelae.

Conclusions

1-CNS infections occurred with a low incidence (<1%) in AL. 2-Initial symptoms were mainly seizures and neurologic impairment. 3-Bacterial and fungal infections were the most frequent cause. 4- An increased risk was found during induction and consolidation phases. 5-Etiology was confirmed mainly by CSF culture or biopsy. 6-Most of patients either died or survived with sequelae. However, one third is alive with good performance status.

P-013

Acute Lymphoblastic Leukaemia

PREVALENCE OF INVASIVE FUNGAL INFECTIONS (IFI) IN CHILDREN WITH FEBRILE NEUTROPENIA BETWEEN 1- 12 YEARS TREATED FOR ACUTE LEUKEMIA- A PROSPECTIVE STUDY

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Objectives

The objective of our study was to ascertain the prevalence, determinants, etiological species of invasive fungal infections (IFI) and outcome (discharge/ death) during febrile neutropenic episodes in children with acute leukemia between 1-12 years age group during chemotherapy.

Methods

Episodes of febrile neutropenia of duration ≥96 hrs were enrolled and investigated for fungal infection. Blood investigations including Galactomannan antigen, aspergillus serology, Bactac fungal culture and radiological investigations were done. Serial monitoring of Galactomannan Ag was done to assess treatment response. Revised definitions of IFI from the European Organization for Research and Treatment of Cancer (EORTC) were used for analysis.

Results

Total 254 febrile neutropenic episodes were screened and 60 patients fulfilled the enrollment criteria. Out of 60, thirteen (21%) had IFI.As per EORTC out of thirteen, three (23%) classified as proven, seven (54%) probable and three (23%) as possible. Two (3%) patients died during same admission. Most common fungal isolate (n=3) from blood was Candida (67%) and one patient had trichosporon. Radiological findings suggestive of IFI was present in ten patients, nodular opacity in lung was most consistent findings. Galactomannan Antigen was positive in thirty patients.

Conclusions

This study is ongoing and preliminary analysis showed Candida is most common fungal agent causing proven IFI. Aspergillus was most commonly associated with radiological abnormalities. Galactomannan Ag was found to be useful in early diagnosis and monitoring of response to antifungal therapy. Prolonged neutropenia (> 14 days) was most consistently associated risk factor for IFI. EORTC guidelines for IFI has limitations as children with nasal/Oral swab or urine culture showing fungal growth, CT showing fungal ball in solid organs(Kidney) with positive Galactomannan Ag test also benefited with antifungal therapy suggesting likely systemic fungal infection although these were not included in criteria of IFI.

P-014

Acute Lymphoblastic Leukaemia

WHAT PLATELET COUNT AVOIDS A TRAUMATIC LUMBAR PUNCTURE?

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Objectives

The first diagnostic lumbar puncture has immense prognostic significance in acute lymphoblastic leukemia (ALL). This study assesses whether thrombocytopenia is associated with increased risk of traumatic lumbar puncture (TLP) in newly diagnosed ALL patients.

Methods

Children diagnosed with ALL between January 2010 and December 2012 were evaluated. Platelet count on the day of diagnostic lumbar puncture (LP) and cerebrospinal (CSF) status were noted. It is not our routine practice to transfuse platelets in otherwise well children prior to LP. Procedure is done under short sedation with Midazolam and Ketamine.

Results

310 children with ALL, median age 5 years (range 1-13 years), diagnosed to have ALL were evaluated. CSF status at the first diagnostic lumbar puncture (LP) was- 274: CNS1; 8: CNS3 and 28: TLP. Mean platelet count in patients with TLP was significantly lower than those with a non-traumatic LP (NTLP) (p=0.001). A platelet count (PC) of <50000/µL was observed in 93% of patients with a TLP, which was significantly higher than those who had a NTLP and a PC <50,000 (p=0.01). A platelet count of <10,000/µL was seen in 43% of patients with TLP and 13% with a NTLP (p=0.001). A receiver operator curve was constructed for predicting risk of TLP based on platelet count. Area under the curve was 0.74±0.05 [95% CI 0.64-0.85]. Platelet count <50500/µL at the time of LP had 93% sensitivity and 73% specificity in predicting a TLP.

Conclusions

Low platelet counts are significantly associated with risk of TLP. In a developing country with a high patient load and occasional inadequate infrastructure, platelet transfusions are not always given prior to performing a LP. Ensuring an adequate platelet count prior to the first LP in newly diagnosed ALL patients is necessary to avoid a TLP and subsequent associated morbidity and possible increased risk of relapse.

P-015

Acute Lymphoblastic Leukaemia

FEASIBILITY AND SAFETY OF FULL DOSE ANTICOAGULATION THERAPY (ACT) IN CHILDREN TREATED ACCORDING TO DANA-FARBER CANCER INSTITUTE (DFCI) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) CONSORTIUM THERAPY PROTOCOLS

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Objectives

There are no evidence-based guidelines for ACT with low molecular weight heparin (LMWH) in relation to platelet count. We examined the impact of thrombocytopenia on LMWH dosing and incidence of bleeding in children with ALL or lymphoblastic lymphoma (LL) who develop thromboembolism (TE) during therapy according to DFCI ALL protocols.

Methods

Patient records were reviewed for demographics, details of ALL/LL and TE diagnoses and therapy, platelet counts during ACT, LMWH dosing, and bleeding episodes. Institutional ACT policy is full dose LMWH for platelets >30x10^9/L, half-dose between 20-30x10^9/L and hold LMWH for platelets <20x10^9/L. Also, we hold LMWH for 24 hours prior to an invasive procedure.

Results

Twenty-two TEs (5 DVT, 2 PE, 4 CSVT and 11 Cardiac) were diagnosed in 19 patients (Mean age 6 years; M:F 9:10; Diagnosis: 17 ALL and 2 LL) over 4 years. One patient was diagnosed with TE during induction phase and 18 (95%) in consolidation II with mean time to TE 5.5 months from ALL/LL diagnosis. All patients received LMWH and mean duration of ACT was 5.8 months (range 3-11 months). Platelets were measured weekly with a mean count of 292X10^9/L. On 26 occasions, platelet nadir was <100x10^9/L and none <30x10^9/L. Hence no patient required LMWH dose adjustment for thrombocytopenia. Fifty-four procedures (49 LPs, 5 CVL insertion/revision) required withholding of LMWH. There were no bleeding episodes. Although asparaginase was held with TE diagnosis, all 19 patients completed all scheduled doses as per protocol.

Conclusions

In our cohort, thrombocytopenia did not interfere with LMWH dosing. The timing of TE diagnosis could be the likely explanation. Ability to administer full dose LMWH, lack of bleeding and completion of all asparaginase doses while on ACT suggest full-dose ACT is feasible and safe in children with ALL/LL who develop TE during DFCI ALL Consortium therapy protocols.

P-016

Acute Lymphoblastic Leukaemia

SIGNIFICANTLY HIGHER INCIDENCE OF ALLERGIC REACTIONS FOR INTRAVENOUS PEG-ASPARAGINASE AS COMPARED TO INTRAMUSCULAR PEG-ASPARAGINASE IN CHILDREN WITH HIGH RISK ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Peg-asparaginase (PEG-Asp) is a quintessential part of the treatment for Acute Lymphoblastic Leukemia (ALL). Historically PEG-Asp has been administered intramuscularly (IM) but Children's Oncology Group has introduced the intravenous (IV) administration of PEG-Asp in an effort to improve quality of life of ALL patients, and perhaps anti-leukemic efficacy. Those patients who experience an allergy require administration of IM Erwinase. However, there is paucity of published data on allergic reactions to IV PEG-Asp. The objective of this study was to determine the incidence of allergic reactions to IV compared to IM PEG-Asp in ALL patients.

Methods

The number of ALL patients who received IM PEG-Asp from January 2005 to May 2011 and those who received IV PEG-Asp from June 2011 to December 2013 was determined through the hospital database after ethics approval. The numbers of high risk (HR) and standard risk (SR) ALL patients were computed. The hospital drug database was utilized to determine the number of patients who received Erwinase, which was given to children who reacted to PEG. Comparison of incidence of allergic reactions in various patient groups was performed with Fisher's exact test.

Results

128 ALL patients (SR-ALL: 89, HR-ALL: 39) were managed at the authors' institution during the study period. Allergic reactions were seen in 3% (2/77) of ALL patients receiving IM PEG and 14% (7/51) receiving IV PEG-Asp (p=0.029). Allergic reactions occurred significantly more frequently in HR-ALL patients [24% (9/38)] versus SR-ALL [0%]; p= 0.0001. Allergic reactions to IV versus IM PEG occurred significantly more frequently in HR-ALL patients 44% (7/16) and 9% (2/22) respectively; p=0.021.

Conclusions

The present study demonstrates significantly increased incidence of allergic reactions in HR-ALL patients receiving IV PEG compared with IM PEG. Further studies are needed to confirm this observation and to consider change to the drug administration policy.

P-017

Acute Lymphoblastic Leukaemia

ANTI-CANCER NON STEROIDAL ANTI-INFLAMMATORY DRUG, TOLFENAMIC ACID ENHANCES THE EFFICACY OF CHEMOTHERAPEUTIC AGENTS IN LEUKEMIA CELL LINES

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Objectives

Leukemia is the most common malignancy affecting children. Current chemotherapy is effective but associated with many deleterious effects. The objective of this pre-clinical study was to test novel strategies to enhance the response of chemotherapy without additional morbidity. Recently, we demonstrated for the first time that Tolfenamic acid (TA), an anti-cancer NSAID inhibits leukemia cell proliferation by targeting Specificity protein (Sp) transcription factors, Sp1 and Sp3. Now, we evaluated the efficacy of TA in enhancing the chemotherapeutic response of Doxorubcin (DOX) and vincristine (VIN) in leukemia cells.

Methods

Jurkat, Reh, Molt and Nalm-6 cells were grown in the presence of TA (10-100μM) or DOX (10-100nM) or VIN (10-500nM) or TA (25μM) and DOX/VIN (25nM) and cell viability was measured at 24-72 h post-treatment using CellTiter Glo. The expression of Sp1, survivin was determined by Western blot analysis, Apoptosis was monitored by determining the expression of c-PARP by Western blot, caspase-3/7 activity by caspase-Glo kit and apoptotic cell population (Annexin-V staining) using flow cytometry.

Results

The combination of TA and DOX or VIN caused significantly higher cell growth inhibition when compared to individual agents. TA inhibited the expression of Sp1, survivin and up-regulated c-PARP. The chemotherapeutic agents had no effect on Sp1 and survivin. Confirmatory results show apoptotic markers (c-PARP expression, caspase-3/7 activity and Annexin V positive cells) were increased at 48 h post-treatment. The effect of proposed combinations on cell cycle phase distribution and markers of DNA damage and repair is under evaluation.

Conclusions

These results confirm that TA combined with Doxorubicin or Vincristine effectively inhibits leukemia cell growth. Further studies evaluating the mechanism of action of proposed combinations and in vivo assays are currently under investigation. This pre-clinical study suggests that by targeting Sp proteins, TA may enhance the anti-leukemic effect of standard chemotherapeutic agents.

P-018

Acute Lymphoblastic Leukaemia

IN VITRO DEXAMETHASONE SENSITIVITY OF ACUTE LYMPHOBLASTIC LEUKEMIA CELLS IS NOT INFLUENCED BY INTERVENING WITH HYDROCORTISONE

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Objectives

Based on recent studies, we hypothesized that dexamethasone induced neuropsychological side effects on mood, behavior and cognition in children with acute lymphoblastic leukemia (ALL) are caused by dexamethasone induced cortisol depletion of the mineralocorticoid receptor (MR) in the brain. Therefore it is feasible that these side effects could be ameliorated by an intervention with hydrocortisone. To exclude interference with the efficacy of glucocorticoids on ALL cells, we performed the current study.

Methods

To investigate responsiveness of leukemic cell lines and fresh patients' leukemic cells to dexamethasone and prednisolone in the presence of physiologic doses of hydrocortisone, a MTT-assay was performed. In addition the expression of the MR and the glucocorticoid receptor (GR) on leukemic cells of different ALL subtypes was studied with a microarray-based gene expression profiling and validated by quantitative real-time PCR.

Results

In vitro glucocorticoid sensitivity of both glucocorticoid resistant and sensitive leukemic cell lines and ALL patients' cells was independent of the added dose of hydrocortisone. MR expression levels on leukemic patient cells were very low compared to GR expression levels. MR expression had a wide variation between patients and was relatively higher in the TEL/AML-1 subtype. No difference in sensitivity to prednisolone or dexamethasone was found with addition of hydrocortisone between the TEL/AML-1 subtype patient cells and the other ALL subtypes.

Conclusions

This present study shows that it is not likely that MR activation with hydrocortisone interferes with the efficacy of glucocorticoids on ALL cells. These findings enable the currently ongoing clinical randomized study hypothesizing that hydrocortisone decreases neuropsychological side effects of dexamethasone in children with ALL.

P-019

Acute Lymphoblastic Leukaemia

FUNCTIONAL GENOME WIDE ENRICHMENT ASSOCIATION ANALYSIS OF VINCRISTINE NEUROPATHY

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Objectives

Vincristine is among the most commonly used anticancer agents, but little is known regarding its disposition and optimal dosing. Vincristine is associated with highly variable cumulative dose-dependent peripheral neuropathy (VIPN), which is often treated with pain medications and/or dose reductions which may compromise efficacy. In this study, we carried out a functional enrichment analysis using data from across the human genome to evaluate the association between genomic variation and VIPN in children with acute lymphoblastic leukemia.

Methods

Germline DNA from subjects enrolled to POG 9004 and 9005 was genotyped using the Affymetrix GeneChip Human Mapping 6 set. VIPN was captured using NCI CTCAE v3.0 and grade ≥ 2 was used as a cutoff for VIPN. GWAS analysis was completed and reported separately. Three functional analyses were conducted on GWAS results. The first focused on 101 genes targeted by 23 drugs, which treat pain as a manifestation of neuropathy. The second analysis focused on SNPs from gene regions that are differentially expressed in the fibrosarcoma cell line after vincristine treatment. The third analysis focused on SNPs from reported expression quantified trait loci (eQTLs) in cerebellar tissue from the Genotype Tissue Expression database.

Results

In the drug target analysis, SNPs were enriched in 8 genes: *CACNA1D, SLC29A4, CACNA1C, GRIK1, SCN8A, CACNB1, GRIN3A* and *SLC22A1* (p-value < 0.05). From the fibrosarcoma cell line expression experiments, 14 SNPs were associated with neuropathy ($p < 1x10^{-4}$), including SNPs in: *MICAL3, ERCC8*, (both identified in original GWAS) and *CANA1C*. The eQTL analysis from cerebellar tissue identified two additional SNPs associated with VIPN.

Conclusions

Functional enrichment analysis identified a number of genes across the human genome that may be associated with VIPN. This information has significant potential clinical relevance given the widespread use of this important drug in treating childhood cancers.

P-020

Acute Lymphoblastic Leukaemia

GENETIC DETERMINANTS OF VINCRISTINE NEUROPATHY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Vincristine is among the most commonly used anticancer agents, however little is known regarding its disposition and optimal dosing. This gap in knowledge can lead to negative clinical outcomes such as toxicity due to drug overdosing or lack of efficacy due to sub-therapeutic dosing. Vincristine is associated with highly variable cumulative dose-dependent peripheral neuropathy (VIPN). We carried out a genome-wide association analysis to explore the association between germline variants and VIPN in pediatric acute lymphoblastic leukemia patients.

Methods

Germline DNA from (n=1098) subjects enrolled to POG 9004 and 9005 was genotyped using the Affymetrix GeneChip Human Mapping 6 set. Quality control (QC) was performed to remove unreliable samples and markers. A population stratification approach was applied to adjust for potential ethnicity effects. VIPN was captured using CTCAE v3.0 for sensory and motor neuropathy. The primary outcome was defined as development of neuropathy (≥ grade 2); and secondary outcome was time to development of neuropathy or neuropathic pain. Each SNP association was evaluated in three genetic models: additive, dominant, and recessive. The SNP effect on VIPN was further adjusted by the clinical, demographic, and population stratification variables in the Cox regression analyses.

Results

After QC, a total of 587,014 SNPs and 1068 individuals remained in the analysis. Using COX model for association analysis, a total of 56 SNPs in 23 genes were identified across both primary and secondary outcomes (p-value < $1x10^{-4}$). Genes of most potential biologic relevance include, *CSNK1G3, Nek6, MICAL3*, and *ERCC8*. Validation in an independent cohort is ongoing.

Conclusions

A number of genes across the human genome may be associated with VIPN. This information has significant potential clinical relevance given the widespread use of this important drug in treating childhood cancers.

P-021

Acute Lymphoblastic Leukaemia

GENETIC VARIANTS IN VINCRISTINE TRANSPORTERS AS NEUROTOXICITY MARKERS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Acute lymphoblastic leukemia (B-ALL) is the most common pediatric malignancy. Therapeutic advances have increased survival, due in part to standardized treatment protocols. Vincristine is used in different phases of treatment (induction, intensification and reinductions). However, some individuals experience neurotoxicity and there are no markers to predict it. As vincristine has a narrow therapeutic range, pharmacogenetic studies may be useful for predicting toxicity.

Only few studies have been performed to date with conflicting results for CYP3A5 gene ABCB1 and MAPT. Recently, our group found new methotrexate toxicity markers, analyzing in depth genes involved in methotrexate transport. So, genes involved in vincristine transport, could also have a role in vincristine toxicity.

The aim of the present study was to analyze in depth the role of genetic variations in genes involved in vincristine transport as markers of neurotoxicity in a large cohort of children with B-ALL homogeneously treated.

Methods

DNA was extracted from remission blood samples of 200 pediatric ALL patients, all of them homogeneously treated with LAL/SHOP protocol. We studied 172 SNPs that cover 11 genes involved in vincristine transport with Illumina GoldenGate platform. The association between SNPs and neurotoxicity was analyzed using the Fisher exact test.

Results

Our results suggest that pharmacogenetic studies may be useful for neurotoxicity prediction and adjustment of vincristine treatment in pediatric ALL patients.

Conclusions

In conclusion, polymorphisms in the vincristine pathway genes may be useful for neurotoxicity prediction and adjustment of vincristine treatment in pediatric ALL patients.

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P-022

Acute Lymphoblastic Leukaemia

ASSOCIATION BETWEEN POLYMORPHISMS OF RFC1 GENE AND HIGH-DOSE METHOTREXATE THERAPY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

To investigate the association of the gene polymorphism of RFC1G80A and high-dose MTX (HD-MTX) related toxicity.

Methods

68 cases of ALL were enrolled in our department from February 2009 to January 2012. RFC1G80A gene polymorphism was detected before HD-MTX treatment. Plasma MTX concentration, liver and kidney function and peripheral blood cell count were detected on time after HD-MTX 24 to 42 hours. All data were analyzed by SPSS 16.0.

Results

RFC1 G80A gene polymorphism was associated with MTX toxicity. The risk of hepatotoxicity and myelosuppression in RFC1-AA genotype were 7.28 and 2.8 times higher than RFC1-GG(P=0.000?0.005). There were no significant differences between gene polymorphism of RFC1G80A and elimination delay of MTX and prognosis(P>0.05).

Conclusions

RFC1G80A genetic polymorphisms were associated with hepatotoxicity and myelosuppression after HDMTX chemotherapy and would be used as a risk indicators for HDMTX-related toxicity. No significant association was found among plasma MTX concentration, elimination delay and prognosis of childhood ALL with gene polymorphism of RFC1G80A.

P-023

Acute Lymphoblastic Leukaemia

THE EFFECT OF CRANIAL RADIATION THERAPY (CRT) ON BODY MASS INDEX (BMI) DURING TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN: AN EXPLORATORY ANALYSIS

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Objectives

CRT is shown to be associated with obesity in long-term survivors of childhood ALL. However, its impact on BMI during therapy is not well studied. The objective of this study was to determine the effects of CRT on BMI in children aged 2-18 receiving therapy according to Dana-Farber Cancer Institute ALL protocols from 1995-2010 at McMaster Children's Hospital.

Methods

Retrospective chart review was conducted to collect baseline demographic (age, gender, ALL risk category), therapy (steroid type and CRT) and anthropometric data at five time points during therapy (0,6,12,18 and 24 months). We studied the impact of above factors on BMI z scores (calculated according to the Centers for Disease Control and Prevention guidelines). Paired t-test and independent sample t-tests were used to compare BMI z-scores within and in-between groups respectively.

Results

A total of 159 children [mean age 78.4 months] were included. Of these 81(50.9%) were male, 105(66%) had standard-risk ALL, 91(57.2%) received dexamethasone and 60(37.7%) received CRT. There was a significant increase in BMI z-scores from 0 months to end of therapy (24 months) in the whole cohort (-0.076(0.12) vs 0.67(0.11) $p<0.001$). Patients receiving CRT had significantly lower BMI z-scores at 6 months (the first time point following CRT), compared to those without CRT (-0.58(0.29) vs.-0.06(0.16), $p<0.05$). Moreover, the rate of change in BMI z-scores from 0 to 6 months in these two groups (-0.54(0.23) vs. -0.048(0.15), $p=0.06$) was different. No other covariates significantly impacted BMI z-scores at six months. There was no difference in the BMI z scores at 12, 18 and 24 months in patients with or without CRT.

Conclusions

Patients receiving CRT tend to have significant reduction in BMI soon after administration, but this effect is transient. This observation suggests the need of different nutritional strategies in patients receiving CRT. Further research is needed to confirm these findings.

P-024

Acute Lymphoblastic Leukaemia

OUTCOMES OF YOUNG CHILDREN WITH CNS POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH AND WITHOUT CRANIAL RADIOTHERAPY: A SINGLE-CENTRE EXPERIENCE

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Objectives

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and is treated with a combination of intra-thecal (IT) and systemic chemotherapy +/- cranial radiotherapy (CRT). With increasing recognition of the long-term sequela of CRT, modern trials have largely omitted prophylactic CRT. For patients with CNS disease at diagnosis however, the decision to omit CRT is less clear. Children < 5 years of age are a particularly challenging subgroup, in whom the neuro-cognitive and endocrine consequences of CRT can be exceptionally devastating.

The primary aim of this study was to describe the outcome of young children (1-< 5years of age) with CNS positive ALL treated with and without CRT.

Methods

Retrospective cohort study of children age 1-<5years with ALL diagnosed between January 2000 - May 2013 at the Hospital for Sick Children. Data were abstracted through chart review. This study has been approved by the Institutional Review Board.

Results

468 children met inclusion criteria, 19 (4%) of whom presented with CNS involvement at diagnosis. Of these, only one child was treated with upfront CRT as part of bone marrow transplant (BMT) conditioning. Other forms of therapy intensification in this cohort included triple IT chemotherapy (16/19, 84%), dexamethasone (11/19, 58%) and high dose methotrexate (14/19, 74%). 16/19 (84%) patients are alive at last follow-up. Three children died from treatment related toxicity and one child had an isolated CNS relapse that was salvaged with BMT.

Conclusions

CNS leukemia in young children can be effectively treated with intensified IT and systemic chemotherapy and without CRT while maintaining favorable outcomes.This study adds to the growing body of literature supporting the omission of CRT from modern ALL protocols in an attempt to minimize acute and long term toxicities.

P-025

Acute Lymphoblastic Leukaemia

UNDERWEIGHT AND WEIGHT LOSS NEGATIVELY INFLUENCES OUTCOME IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Purpose: To study the influence of (change in) body mass index (BMI;kg/m^2) on outcome in pediatric ALL patients who were treated according to a dexamethasone-based protocol (Dutch Childhood Oncology Group [DCOG] ALL-9).

Patients and Methods: Data of body composition were prospectively selected from a national cohort of newly diagnosed Dutch pediatric ALL patients (n=762, age 2-17 years), treated from 1997-2004. BMI was expressed as standard deviation scores(SDS) and categorized into overweight (>1.1 SDS ≈ >25 kg/m^2) normal weight (–1.8 to 1.1 SDS ≈ > 18.5 to 25 kg/m^2) and underweight (<–1.8 SDS ≈ < 18.5 kg/m^2). Dual X-ray Absorptiometry (DXA) scans were performed in a nested single center cohort to assess the contribution of %fat and lean body mass to BMI. Body composition was reassessed after 32 weeks of treatment. Outcome measures were defined as 10-year event free survival(EFS), cumulative incidence of relapse(CIR) and overall survival(OS). Uni- and multivariable Cox-regression analysis were performed to examine the association between BMI and survival.

Results: Underweight patients (8%) at diagnosis had an increased risk of relapse (Hazard Ratio (HR) 1.86, 95% CI:[1.08-3.21] but not an increased mortality rate(HR 1.17 [0.61-2.24]). A BMI decrease during the first 32 weeks of treatment was associated with a higher mortality rate (HR 1.93 [1.04-3.58]), but not with a higher relapse rate (HR 1.18 [0.65-2.15]). DXA revealed that a BMI decrease consisted of a loss of lean body mass, while these patients showed an increase in their %fat.

Conclusion: Underweight at diagnosis influences the likelihood of relapse. A BMI decrease, which seems to consist of mainly muscle loss, is associated with a decreased overall survival in children with ALL.

P-026

Acute Lymphoblastic Leukaemia

OESTRADIOL AND DHEA BUT NOT TESTOSTERONE MODULATE OSTEOCYTE VEGF SECRETION IN VITRO: IMPLICATIONS FOR THE PATHOGENESIS OF CORTICOSTEROID-INDUCED OSTEONECROSIS

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Objectives

Interruption to VEGF signalling is a major pathological mechanism of corticosteroid-induced osteonecrosis, a disabling side effect of therapy for acute lymphoblastic leukaemia. Adolescent girls are at greatest risk but any relationship between sex steroids, puberty and VEGF signalling in osteocytes has not been previously documented. We have previously demonstrated that dexamethasone reduces osteocyte VEGF secretion and now hypothesise that sex steroids may influence osteocyte proliferation and/or VEGF secretion either via nuclear steroid receptors or via a non-genomic pathway.

Methods

MLO-Y4 osteocytes were incubated (24-72 hours) with oestradiol, DHEA or testosterone (10^{-11} – 10^{-8}M) in the presence or absence of dexamethasone (10^{-7}M). Cell number (MTS) and VEGF secretion (ELISA) were measured. Mechanisms were investigated by blockade of oestrogen receptors (ERs) with selective oestrogen receptor modulators (SERMs) tamoxifen and fulvestrant (both 10^{-7}M) and inhibition of the conversion of DHEA to oestradiol with the aromatase inhibitor anastrozole (10^{-7}M). The effect of dexamethasone on ER as well as the non-genomic G-coupled protein receptor 30 expression was also measured (qRTPCR).

Results

Oestradiol and DHEA significantly reduced osteocyte cell number (8-13% and 12-16% reduction respectively, $p<0.001$). When SERMS were co-incubated with oestradiol and anastrozole with DHEA, these effects were abolished. Both oestradiol significantly increased VEGF secretion (by 24%; $P=0.002$ and 43%; $p<0.001$ respectively). Co-incubation with SERMs or anastrozole did not ameliorate this increase suggesting firstly that oestradiol acts via a non- genomic pathway and secondly that DHEA exerts independent activity rather than by conversion to oestradiol. Dexamethasone prevented the oestradiol-induced increase in VEGF secretion and caused a 2.3 fold reduction ($p<0.001$) in ER alpha gene expression. No effect of testosterone on cell number or VEGF secretion was demonstrated.

Conclusions

This study reveals novel interactions between sex steroids and dexamethasone on osteocyte angiogenesis which may contribute to the understanding of the high incidence of osteonecrosis in adolescent patients.

P-027

Acute Lymphoblastic Leukaemia

DO PARENTAL OCCUPATION AND AREA REMOTENESS LEAD TO SOCIAL DISPARITIES IN SURVIVAL FROM CHILDHOOD LEUKEMIA? RE-ANALYSIS OF DATABASES AND A META-ANALYSIS

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Objectives

Advances in treatment have greatly improved survival of children suffering leukemia during the last decades. Concerns have been raised, however, regarding social disparities in survival due to potential interference of socio-economic status (SES) and health care access components with treatment. This re-analysis of available primary data in two databases along with meta-analyses following a systematic review of the literatures aims to shed light into the effects of parental occupation and area remoteness in terms of rural/urban status upon survival from childhood leukemia.

Methods

The National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER) 1973-2010 data were critically re-analyzed along with the Greek Nationwide Registry of Childhood Hematological Malignancies (NARECHEM, 1996-2011) data, whereas a systematic review of the literature contributed to the subsequent meta-analyses additional study arms from published evidence. Overall survival was the main outcome; random-effects (DerSimonian-Laird) models were appropriately used to calculate pooled effect estimates.

Results

In the largest ever analyses (>27,000 acute lymphoblastic leukemia, ALL and >3,000 acute myeloid leukemia, AML cases), less privileged parental occupation predicted considerably poorer survival from ALL (pooled RR=1.51, 95%CI: 1.22-1.87), whereas the respective finding for childhood AML did not reach significance. No statistically significant association was observed regarding rural vs. urban place of residence with survival from either ALL (pooled RR=1.06, 95%CI: 0.89-1.26) or AML (pooled RR=1.19, 95%CI: 0.92-1.55).

Conclusions

Lower occupation related SES may unfavorably impact on survival, at least from the less aggressive ALL, through a variety of functions, such as poor compliance, refusal or abandonment of treatment, modified attitudes by health care providers, inadequate

health insurance and access to quality health care. Contemporary satisfactory transport infrastructure, may underlie, the minimal, non significant association with residence remoteness.

P-028

Acute Lymphoblastic Leukaemia

COMPARISON OF THE EFFICACY, SAFETY AND ECONOMIC COST OF VINDESINE AND VINCRISTINE FOR NEWLY DIAGNOSED PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA: A RETROSPECTIVE ANALYSIS

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Objectives

The anti-tumor botanicals Vincaal kaloidsm, vindesine (VDS) and vincristine (VCR), are worldwide used components of chemotherapy, although associated with serious adverse effects. We compared the efficacy, toxicity and economic cost of VDS to VCR during induction and intensification in children with newly diagnosed acute lymphoblastic leukemia (ALL) on the Chinese Children's Leukemia Group (CCLG)- ALL 2008 protocol in a hospital.

Methods

Archived medical records were reviewed for 105 children diagnosed in our hospital in the trial CCLG-2008 who had received VDS administered as 3 mg/m2 or VCR 1.5 mg/m2 per week during induction and Intensification.

Results

Between May 2009 and October 2013,105 children (1 to 18 years of age, 48 VDS vs. 57 VCR) with newly diagnosed ALL (excluding mature B-cell ALL) were included. Complete-remission (CR) rates were similar with VDS and VCR (91.7% and 94.7%, respectively; P = 0.53). Three-year results in both treatment groups were similar (overall survival 91.7%± 4.4% for VDS vs. 91.2%± 4.3 for VCR, P=0.94, event-free survival 89.6%±4% vs. 82.5%± 4%, P=0.14). Treatment-related mortality (TRM) in continuous complete remission children was lower in the presence of VDS than VCR (2.2% vs. 14.2%, P=0.04). A total of 199 cases (including 113 cases/times for VDS group, 86 cases/times for VCR group), were recorded for adverse events' statistics. VDS had lower rates of Grade 3/4 decreased hemoglobin (P<0.001) and thrombocytopenia (P=0.01) than VCR, and total neurotoxicity (P=0.008). Three cases of VCR group occurred unbearable paresthesia or significant movement disorders, which disappeared with VDS. The expenses of hospitalization were lower with VDS than VCR (25,996 RMB vs. 34,244 RMB, P = 0.002).

Conclusions

At the given dose, VDS has similar antileukemic activity compared to VCR, causes less treatment-related mortality in continuous complete remission children, decreases the rates of neurotoxicity and hematotoxicity and reduces the expenses of hospitalization, worthy of further clinical studies and use.

P-029

Acute Lymphoblastic Leukaemia

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA IN THE MIDDLE EAST AND NEIGHBORING COUNTRIES: A PROSPECTIVE MULTI-INSTITUTIONAL INTERNATIONAL COLLABORATIVE STUDY BY THE MIDDLE EAST CHILDHOOD CANCER ALLIANCE (MECCA)

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Objectives

The Middle East Childhood Cancer Alliance (MECCA) was established in 2000 and is comprised of member institutions in 16 countries in the Middle East and surrounding area. Little is known about childhood ALL in the Middle East. This study, funded by Qatar National Research Fund, was undertaken by MECCA as initial efforts in collaborative data collection to provide clinical, laboratory, molecular genetic characterization, induction toxicity and outcome data on children with ALL in the Middle East.

Methods

Clinical, laboratory, molecular genetic characterization, induction toxicity and outcome for patients with ALL between January 2008-April 2012 were prospectively collected from institutions in 14 Middle East countries and entered into a custom-built-database during induction phase. All laboratory studies including cytogenetics were done at local institutions.

Results

The 1,171 voluntarily enrolled patients had a mean age of 6.1±3.9 years and 59.2% were boys. T-ALL represented 14.8% and 84.2% had B-precursor ALL. At diagnosis, 5.6% had CNS disease. The distribution of common genetic abnormalities reflected a similar percentage of hyperdiploidy (25.6%), but a lower percentage of *ETV6-RUNX1* translocation (14.7%) compared to large series reported from Western populations. By clinical criteria, 49.1% were low/standard risk, 16.9% were intermediate risk and 36% were high-risk. The majority of patients (96.9%) received care at their local or regional hospitals. Patients had excellent induction response to chemotherapy with an overall complete remission rate of 96%. Induction toxicities were acceptable.

Conclusions

In conclusion, we believe that this study provides proof of principle that collaborative clinical research with a centralized data repository is feasible in the Middle East. Despite the limitations of an incomplete population-based study, it provides the first comprehensive baseline data on clinical characteristics, laboratory evaluation, molecular genetic characterization, induction outcome and toxicity. Further work is planned to uncover possible biologic differences of ALL in the region and to improve diagnosis and management.

P-030

Acute Lymphoblastic Leukaemia

SURVIVAL OF CHILDREN WITH LEUKEMIA IN SOUTH AFRICA AND LESOTHO

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Objectives

Leukemia remains the most common childhood cancer in South Africa and Lesotho. The cure rates of acute lymphoblastic leukemia (ALL) in developed countries reach 90%. In Africa there is a paucity of data regarding the survival of children with leukemia. The aim of the study was to calculate the survival rates of children diagnosed and treated for ALL in South Africa and Lesotho.

Methods

This was a retrospective study including all children <15 years diagnosed and treated for ALL between 1 January 1995 to 31 December 2009 in 2 centres in South Africa (Tygerberg Hospital in Cape Town and Universitas Hospital in Bloemfontein) and and all the patients from Lesotho.

All diagnoses were confirmed by the certified National Health Laboratory Services in South Africa

Results

There were 307 patients treated for ALL (27 from Lesotho and 280 from SA)., males 55% and females 45%. The average age at diagnosis was 78.9 months (range 2 -181 months). The black children were the most 128, followed by the colored population ,100 patients and finally the white 79 patients.

The overall survival for the group was 55% (the 2 South African centres 46.8 % and 67.7%) and Lesotho 44.4%.

The follow up time was 66 months. The survival of the black children was the lowest at 45.3% followed by the white children 59.5% . The colored children had the best survival rate at 64%. All patients were treated with the same protocols.

Conclusions

The survival rates of children diagnosed with ALL in South Africa and Lesotho are low and showed significant differences in corelation with the ethnic group. Further clinical and genetic research is required.

P-031

Acute Lymphoblastic Leukaemia

STANDARD RISK CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN MOROCCO: EXPERIENCE OF 170 CASES TREATED IN A SINGLE CENTER

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Objectives

The event free survival of childhood acute lymphoblastic leukemia (ALL) was < 34% in Morocco. The main causes of failure were abandonment (15%) and non-availability of drugs for almost 80% of patients. A national therapy protocol (MARALL 2006) was developed based on the French protocol FRALLE 2000. Herein we report the results of the Standard Risk (SR) group.

Methods

Treatment included Induction, consolidation, intensification and interphase courses (11 months) followed by maintenance (2 years). Chemotherapy consisted of Vincristine, Doxorubicin, L-Asparaiginase, corticosteroids, high and low-dose Methotrexate, Cyclophosphamide, Cytarabine, 6-mercaptopurine, and 18 doses of triple intrathecal therapy. Children (≥ 2and ≤9 yrs) diagnosed with *de novo* precursor-B ALL with WBC < 50,000/mm^3 and absence of central nervous system disease were categorized as SR. A dedicated team of physicians, nurses, social worker and data manager supervised the ambulatory ALL therapy. All patients had free access to medication through NGOs, Hospital and health insurance. Weekly team meetings reviewed patient management, data, problems and arrangement for aid to patients.

Results

From 2006 to 2013, a total of 389 patients were diagnosed with ALL; 170 (44%) were SR . The median age was 4 years and M:F ratio was 1.29. FAB classification was L1 in 74% and L2 in 26% of cases. Remission rate was 97% and 1% had refractory ALL. Therapy abandonment rate was 2%. Overall mortality was 2% and 11% patients relapsed with a median time of 18 months from diagnosis. With a median follow-up of 49 months, the event free and overall survivals were 66% and 72% respectively.

Conclusions

Compared to historical data, MARALL 2006 protocol resulted 50% increase in survival of children with SR ALL and low abandonment rate. This was achieved with a close follow-up by a dedicated ALL team, commitment to drug procurement and social support for patients.

P-032

Acute Lymphoblastic Leukaemia

DEVELOPMENT OF THE EVALUATING QUALITY OF LIFE IN ACUTE LYMPHOBLASTIC LEUKAEMIA (EQUALL) QUESTIONNAIRE: A TREATMENT-SPECIFIC MEASURE FOR THE EFFECTS OF CORTICOSTEROIDS ON QUALITY OF LIFE

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Objectives

The use of corticosteroids (particularly dexamethasone) within acute lymphoblastic leukaemia (ALL) protocols has contributed greatly to the excellent survival rates. However this is not without cost – in addition to physical side effects, corticosteroids influence behaviour, mood and cognitive functioning leading to an impaired quality of life (QoL) for patients. The UKALL 2011 randomisation to maintenance therapy with or without dexamethasone pulses has both survival and QoL as primary outcome measures. The aim of this study was to develop a QoL measure sensitive to the effects of corticosteroids that may detect potential differences in QoL in patients receiving dexamethasone.

Methods

Patients aged 8-24 years and parents of children aged 1-15 years receiving maintenance therapy for ALL from 4 UK centres, were invited to participate. The study comprised 3 stages: A) focus groups and interviews asked participants to describe their experience of dexamethasone, and the themes identified formulated Version 1 of EQuALL. B) Version 1 was emailed electronically to healthcare professionals and patients to evaluate the importance and relevance of questions. Amendments were made to create Version 2. C) Cognitive interviewing confirmed face validity and explored question interpretation. Further modifications were made to define Version 3.

Results

Six parents and eight patients attended focus groups/interviews. Interpretative phenomenological analysis of transcripts identified that patients feel dexamethasone has adverse effects on behaviour, appetite, body image, mood and family relationships. 121 healthcare professionals and 36 patients/parents completed the electronic survey leading to further amendment of the questions. Face validity was confirmed by cognitive interviewing of 21 patients. EQuALL comprises 35 questions within 4 domains and has age-specific versions.

Conclusions

EQuALL is the first treatment-specific QoL measure for corticosteroids. It can be completed in 10-15 minutes by children aged 8 years and above. Further validity and reliability testing will be undertaken within UKALL 2011.

P-033

Acute Lymphoblastic Leukaemia

OUTCOME OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS UNDERGOING CHEMOTHERAPY USING LOW-INCOME-COUNTRY REGIMEN 1 PROTOCOL AT THE UNIVERSITY OF THE PHILIPPINES - PHILIPPINE GENERAL HOSPITAL (2009-2013)

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Purpose: To determine the impact on survival rate, toxicity and abandonment of treatment among childhood Acute Lymphoblastic Leukemia (ALL) patients using the Low Income Country (LIC) Regimen 1 Chemotherapy Protocol at the University of the Philippines - Philippine General Hospital (UP-PGH).

Methods: Medical records of newly diagnosed ALL patients from June 2009 to September 2011, ages 0-18 years, were reviewed. Demographic data were collected. Treatment outcome was evaluated at study endpoint, December 31, 2013, and included death, treatment refusal, abandonment, relapse, and phase of treatment.

Results: 173 patients were diagnosed from June 2009 to September 2011. Diagnosis was by immunophenotyping in 86% and morphology in 14%. Seventy-five patients (43.40%) refused treatment; while 86 patients underwent LIC regimen 1 (without radiation). Male to Female ratio was 2.4:1. Age ranged from 17 months-18 years (mean=6 years). 60% were NCI standard risk, and 40% high risk. One had CNS involvement at diagnosis. None had testicular involvement at start of therapy. Remission induction was 75.58% (n=65). Ten patients (10.47%) died during Induction. At study endpoint, 20 (23.5%) completed therapy, 9 (10.6%) were on maintenance. Relapses occurred in 18 patients: CNS (n=10; 11.8%) and bone marrow (n=8; 9.4%). Fifteen (17.6%) abandoned treatment. Seventeen patients died during treatment (19.77) due to sepsis and intracranial bleeding. At end of study period, 39.53% of the patients were alive (n=34) and 30.23% (n=26) were in remission.

Conclusion: In LIC, the choice of ALL therapy should consider available supportive care. Aside from good infection control, accessibility of blood products, database, financial and social work support are imperative. The survival rate among our ALL patients is still low, however the use of LIC Regimen 1, was associated with an improvement in the survival rate and reduction in toxic death and abandonment.

P-034

Acute Lymphoblastic Leukaemia

BIOIMPEDANCE ANALYSIS (BIA) AND ANTHROPOMETRY IN PROGNOSIS OF COMPLICATIONS AND GRAFT FUNCTION AFTER HEMATOPOIETIC STEM CELLS TRANSPLANTATION (HSCT) IN CANCER CHILDREN

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Objectives

HSCT has become an established treatment for malignant hematological diseases, solid malignancies and autoimmune diseases. Our goal is to assess the value of some BIA and anthropometric indicators as prognostic factors for severe complications (steroid diabetes; erosive or ulcerative duodenitis/enterocolitis with bleeding; gastro/enterocolitis more than 30 days; destructive pancreatitis (pancreanecrosis); veno-occlusive disease; hemorrhagic cystitis more than 14 days; renal insufficiency; toxicodermia more than 30 days; toxic or infectious encephalopathy; heavy toxic polyneuropathy; mukositis 2nd or higher degree; septic shock) after HSCT.

Methods

101 patients were examined at a period started before conditioning till day +100 after HSCT. Both BIA and anthropometry were used in 50 children aged 5 to 17; anthropometry without BIA was used in 61 children aged 6 months to 4 years old.

Results

In patients with the following indexes before conditioning: phase angle (PA) ≤ 4°, the ratio of active cell mass/lean body mass (ACM/LBM) < 0.45 and shoulder muscles circumference (SMC) ≤ 10 percentiles the risk of severe complications was significantly higher in the early period after HSCT ($P < 0.05$). Similarly, in patients with PA ≤ 4 and ACM/LBM < 0.45 the risk of graft hypofunction was considerably higher in compare with patients with PA>4 and ACM/LBM≥0.45 ($P < 0.05$).

Conclusions

Low PA, ACM/LBM and SMC before conditioning are prognostic factors of severe complications and graft hypofunction after HSCT. Low PA, ACM/LBM and SMC are symptoms of malnutrition, so malnutrition before conditioning is a significant factor of high risks of severe complications and graft hypofunction after HSCT. Thus, nutritional status correction should be included as a mandatory component of children preparation for HSCT. BIA is a good method to assess the nutritional status and prognose risks of severe complications and graft hypofunction after HSCT.

P-035

Bone Tumours

QUANTIFICATION OF CIRCULATING TUMOR DNA FROM PLASMA OF SARCOMA PATIENTS

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Objectives

Quantification of tumor specific molecular markers is a well-established diagnostic tool for therapy monitoring in acute and chronic leukemia. Response assessment in solid tumors is mainly based on imaging studies, particularly in sarcomas, lacking secretion of tumor associated protein markers or release of metabolites to the blood stream. However, the majority of sarcomas is characterized by specific chromosomal translocations, representing a potential marker not only for diagnostic purposes but also for assessment of therapy response by the quantification of circulating tumor DNA (ctDNA) from patient's blood samples.

Methods

Correlation of ctDNA-quantity and Ewing sarcoma (ES) volume was evaluated in a NOD scid gamma mouse xenotransplantation model. ES cells were injected intravenously and blood samples were taken once a week during tumor growth. ctDNA was quantified in plasma with *EWS-FLI1* fusion sequence spanning probe sets using high sensitivity droplet digital PCR. After optimization of the assay, plasma samples from ES patients under treatment were collected and analyzed in comparison to the tumor regression assessed by MRT and PET-CT.

Results

We were able to document the tumor growth by quantification of tumor-specific *EWS-FLI1* fusion sequences in the plasma of xenotransplanted mice. Tumor growth was correlated with increasing ctDNA levels. The percentage of fusion gene-specific DNA fragments of all circulating DNA molecules reached up to 10%. In serum samples of patients under ES treatment, initial tumor size and regression during induction therapy could be monitored with ctDNA copy numbers.

Conclusions

Chromosomal translocations represent genomic markers enabling highly sensitive DNA quantification. Their unique sequence composition at the fusion sites enabled a superior specificity compared to single nucleotide mutations predominantly identified in common epithelial cancers. Conventional blood sample volumes are sufficient to allow the detection and quantification of circulating tumor DNA both in experimental xenotransplant mouse models and ES patients under treatment.

P-036

Bone Tumours

IS THE MONITORING OF ANGIOGENIC FACTORS RELEVANT IN PATIENTS WITH OSTEOSARCOMA?

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Objectives

Osteosarcoma is the most common malignant bone tumour in adolescents and young adults. Angiogenesis is essential for the progression and metastasis of solid tumors, but the relevance of monitoring angiogenic factors in patients with osteosarcoma still needs to be addressed. The aim of this study was to determine the levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in patients with osteosarcoma and to investigate whether these biomarkers at diagnosis as well as their kinetic under treatment were associated with disease characteristics and provide prognostic information.

Methods

Patients with localized or metastatic osteosarcoma registered between 2005 and 2011 in OS 2005/2006 clinical trials were prospectively included. Levels of VEGF and bFGF in serum and plasma, and of bFGF in urine were measured by ELISA at diagnosis, before surgery and at the end of treatment.

Results

Samples at diagnosis were available in 269 patients (54% males; 73% $\leq$18 years; 68% with a localized disease, 17% with lung doubtful lesions and 15% with metastases). Median follow-up was 3.3 years, 3-year progression-free survival was 62% (se=3%). High values of serum (>402 pg/ml) and plasma (>115 pg/ml) VEGF were observed in 55% and 39% of patients respectively. Serum and plasma VEGF levels correlated ($r=0.53$; $p< 0.0001$). High VEGF levels were more frequent in large tumors ($\geq$10 cm, $p= 0.003$). We observed a significant VEGF decreased during pre-operative chemotherapy ($p<0.0001$), but the variation was not associated with the histological response, nor with the outcome. No significant association was found between blood or urine levels of bFGF and clinical characteristics, histological response or outcome.

Conclusions

High levels of angiogenic factors can be detected in body fluids of osteosarcoma patients, but the clinical utility of these measurements was not demonstrated.

P-037

Bone Tumours

THE RECEPTOR TYROSINE KINASE RON: A THERAPEUTIC TARGET IN METASTATIC EWING SARCOMA?

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Objectives

Novel treatment options for Ewing sarcoma patients with metastatic disease are urgently needed. Yet, while therapeutic targeting of receptor tyrosine kinases (RTK) in cell proliferation has improved prognosis in many cancers, and a role for RTKs in cell migration and metastasis is undisputed, it remains less well understood. Also, the emerging RTK networks by-passing targeted inhibition remain to be elucidated. Our previous work suggested the “pro-metastatic” RTK RON as possible resistance factor in IGF1R-targeted therapies in paediatric sarcomas. Objective therefore is to elucidate and target RON function in paediatric sarcoma metastases.

Methods

see below

Results

RON is expressed in Ewing sarcomas and mRNA expression levels (TaqMan-PCR) in primary tumours of 6 patients with metastases were significantly higher than in 15 patients with localized disease, supporting a role in metastasis. RON protein was phosphorylated (i.e. activated) in the presence of serum or specific MSP ligand, as were downstream signalling elements AKT and ERK. Also, RON knockdown impaired cellular migration in wound-healing assays. 3D-spheroid formation is being investigated.

To evaluate RON as therapeutic target, sarcoma cell lines were treated with anti-RON antibody in monolayer and 3D cultures. Surprisingly, no activity was observed, either alone or in addition to an IGF1R antibody, and independent of baseline IGF1R antibody sensitivity. This prompted us to investigate for RON variants, including a short-form (sfRON) lacking the extracellular (antibody binding) domain. First experiments found sfRON in Ewing sarcoma cell lines; and in keeping, some activity for the BMS-777607 inhibitor targeting the RON tyrosine kinase domain.

Conclusions

RON is expressed and activated in Ewing sarcomas, with evidence for pro-metastatic cellular functions. Experimental and therapeutic targeting is challenging, possibly due to RON short-form or splicing variants. Given the clinical impact of metastasis and an ongoing development of multi-tyrosine kinase inhibitors, further studies are warranted.

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P-038

Bone Tumours

THE ROLE OF MEGATHERAPY (MGT) AND STEM CELL TRANSPLANTATION (SCT) IN HIGH RISK EWING TUMORS (ET): MORE THAN 30 YEARS OF EBMT ACTIVITY

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Objectives

Registry data of the European Group for Blood and Marrow Transplantation (EBMT) on ET helps to explore indications and outcomes.

Methods

Since 1980, 3695 patients (pts) with ET (2186 males) were registered (142 centers/24 countries). MGT indications were primary multifocal &high-risk local disease (2411pts) or relapse (719pts). Median age is 15 years (yrs); range, 1 to 65; 2568pts <18yrs. The median survival time is 0.5 yrs after allogeneic (70 pts) and 2.8yrs after autologous (A)SCTs. Peripheral blood stem cells were used in 3143 pts.

Results

The 5-year overall survival rates (%) are: 44% with ASCT (3521pts) (49% for primary treatments [for localized disease: 53%; for multifocal 41%]; 31% after relapse) and 12% for alloSCT ($p<0.001$). Age has significant impact: 48% for ≤10yrs, 43% for >10 to ≤ 18yrs and 38% >18yrs ($p<0.001$). The preSCT remission status is of importance (ASCT only): 58% in first complete remission (CR1) (1343pts), 40% in partial remission (836pts), only 20% in stable disease (144pts) or primary refractory (146pts); ($p<0.001$). The second complete remission (CR2) results in 46%; all others do significantly worse with< 20% (p<.000). During primary treatment total body irradiation (TBI) regimens are inferior to non-TBI MGT with 38% vs. 50% ($p<0.026$). A significant influence of MGT type > year 2000 is observed: busulphan based (684 pts) 60%, melphalan based (148 pts) 37%, treosulfan based (95pts) 19% and others (133pts): 55% ($p<0.01$). A Cox proportional hazards regression model identified age, response status, stem cell source and MGT regimens as independent risk factors.

Conclusions

EBMT Ewing data shows improved results in high-risk pts and favours busulphan based MGT and suggests exploring in more depth the results and roles of Busulphan versus Treosulfan in front line trials.

P-039

Bone Tumours

RISK STRATIFICATION BY NUMBER OF METASTATIC SITES IN NON-LOCALIZED EWING SARCOMAS

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Objectives

The outcome variation in subgroups of Ewing sarcoma patients with metastases at initial diagnosis is high. A major current criterion is to stratify Ewing sarcoma patients according to the site of metastases, e.g., patients with pulmonary metastases only are distinguished from patients with bone metastases and other metastatic sites. In this project outcome in non-localized Ewing sarcomas was analyzed according to the number of metastatic sites.

Methods

Five-hundred Ewing sarcoma patients with metastases at diagnosis were retrospectively analyzed. All patients were included in the GPOH (German Society of Pediatric Oncology and Hematology) Ewing sarcoma registry from 1998-2009 and received similar treatment strategies with standard and/or high-dose chemotherapy in accordance with the appropriate GPOH protocols*. The median follow-up was 2.62 years (range 0.20-14). Outcome by event-free-survival (EFS) was analyzed by univariate and multivariate analyses.

Results

3y-EFS in patients with isolated pulmonary metastatic disease was 0.46 (SE=.03; n=268), compared to 0.27 (SE=.03; n=232) in patients with dissemination to sites other than lung alone, primarily bone metastases (R3) (p<.001). In R3 patients, 3y-EFS with one metastatic site was 0.39 (SE=.07; n=52), compared to 0.28 (SE=.04; n=120) with two, and 0.14 (SE=.05; n=60) with three or more metastatic sites (p<.001). Overall outcome in non-localized patients with one metastatic site, also including patients with isolated pulmonary metastatic disease, was 0.45 (SE=.03; n=320). In multivariate analysis, the number of metastatic sites persisted as the major significant risk factor (Hazard ratio (HR): 1.45 (2 vs. 1); 2.38 (>2 vs. 1); p<.001), whereas the risk group affiliation did not (HR: 1.21; p=.302), even if the model was controlled for treatment intensification with high-dose chemotherapy (HR: 1.82-2.70; p<.001 vs. 1.63; p=.025; n=432).

Conclusions

Stratification by virtue of the quantity of metastatic sites appears to discriminate for prognosis in non-localized Ewing sarcoma patients.

*supported by Deutsche Krebshilfe

P-040

Bone Tumours

MAINTENANCE THERAPY WITH ORAL CYCLOPHOSPHAMIDE + CELECOXIB IN PATIENTS WITH METASTATIC EWING SARCOMA: PRELIMINARY RESULTS OF THE ITALIAN SARCOMA GROUP/AIEOP EW-2 STUDY

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Objectives

To ameliorate the prognosis of patients with metastatic Ewing sarcoma at onset, ISG and AIEOP designed a phase II treatment protocol including a maintenance phase with oral low-dose cyclophosphamide + celecoxib (ISG/AIEOP EW-2, Eudract 2009-011197-15).

Methods

ISG/AIEOP EW-2 was opened on April 2009. Inclusion criteria are: histologically proven previously untreated Ewing sarcoma, synchronous metastases at lungs or solitary skeletal metastasis, age < 40 years. ISG/AIEOP EW-2 consists of 8 courses chemotherapy, radiotherapy and/or surgery on the primary tumor, high-dose busulphan/melphalan+autologous stem cell rescue, radiotherapy on the lungs; responsive patients receive a continuous 180-days maintenance phase with cyclophosphamide 50 mg/d + celecoxib 400 mgx2/d (200 mgx2/d for pts <14 years of age). Exclusion criteria from the maintenance phase are progression of the disease, cardiovascular or gastrointestinal co-morbidity. Aims of the study were to evaluate the feasibility of the maintenance phase and the 3-year survival probability.

Results

From 1 April 2009, 47 consecutive patients (36 males, 11 females; median age 15 years, range 1-37) have been enrolled. 16/47 concluded the maintenance phase, 14/47 were ineligible for previous progression of the disease (n=11) or for concomitant co-morbidities (n=3), 17/47 are on treatment. One pt interrupted the maintenance at day 101 for progression of the disease. A temporary suspension of maintenance occurred in 9% of days of maintenance scheduled up to now and occurred in 6 patients, with a range of 1-20 days suspension (median 9 days), due to the following reasons: HZV infection-2, grade 3 hematological toxicity-2, fluid retention-2, diarrhoea-1, pulmonitis-1, febrile episode-3. The 3-year EFS probability for patients who entered the maintenance phase is 0.63 (±0.11).

Conclusions

This schedule of maintenance phase is feasible, with encouraging results. The enrolment is ongoing, and a longer follow-up is needed to evaluate efficacy and to monitor side effects and late sequelae

P-041

Bone Tumours

LOCAL CONTROL IN EWING SARCOMA OF THE CHEST WALL- THE VALUE OF COMBINED MODALITY LOCAL TREATMENT

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Objectives

Primary Ewing sarcoma (ES) may present as chest-wall tumor. Multidisciplinary management including systemic treatment and local treatment consisting of surgery, radiotherapy, or both has improved the survival of patients with localized ES. The best approach to achieve local control, however, remains controversial.

Methods

We retrospectively analyzed data from 198 patients registered in the database of the German Society of Pediatric Hematology and Oncology who had histologically confirmed non-metastatic ES of the chest wall and were treated between July 1998 and April 2009. Median age was 13,9 (0.5-60) years. 119 patients were male. Surgical resection was performed in 191 patients. 85 patients underwent only surgery (group 1) and 106 patients were treated with surgery in combination with radiotherapy (group 2). Seven patients received only radiotherapy (group 3).

Results

Overall survival (OS) for all patients was 78 % and 71 % at 3 and 5 years. The event-free survival (EFS) at 5 years was 73 % in group 1, 63 % in group 2 and 57 % in group 3. Multivariate analysis including tumor size (</>=200ml), local therapy modality (OP vs OP&RT), surgical margins (R0 vs R1&R2) and pleural effusion (no vs yes) showed that poor histological response (HR=2.74; 95%CI 1.54-4.89) and initial pleural effusion (HR=1.87; 95%CI 1.02-3.44) remained as significant risk factors. Seventeen patients showed late complications (3 secondary malignancy, 3 thoracic bone hypoplasia, 1 myelopathy, 3 valvular disease, 7 lung function reduction).

Conclusions

An additional benefit of radiotherapy in terms of survival could not be demonstrated. This was also true for patients with additional risk factors such as large tumors, inadequate surgical margins, poor histological response. The main limitation of the current analysis consists in the very nature of a retrospective analysis. A prospective evaluation on the role of radiotherapy in chest wall Ewing sarcomas is warranted.

P-042

Bone Tumours

IS NON-HIGH DOSE–METHOTREXATE (HD-MTX) BASED, DOSE-DENSE, COMBINATION CHEMOTHERAPY (CT) A VALID CHOICE IN HIGH TUMOR BURDEN AND NUTRITIONALLY CHALLENGED OSTEOSARCOMA?

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Objectives

Standard treatment of osteosarcoma includes HD-MTX; however considering significant toxicity, and need of complex pharmacokinetic monitoring, other non HD-MTX based CT regimens are worth exploring.

Methods

This prospective study evaluated the efficacy & toxicity of dose-dense CT regimen comprising Doxorubicin, Ifosfamide, & Cisplatin. CT response was evaluated with histological-necrosis (HN) grading. Good responders (GR) were defined as those with ≥ 90% HN.Baseline tumor burden and nutritional parameters were correlated with outcomes and toxicity. Survival analysis was performed using the Kaplan–Meier method and compared with Log-rank test.

Results

239 eligible patients were enrolled (median age 17yrs) between December 2011 and December 2013. At presentation, 48% were malnourished, 31% anemic, 50% iron deficient, and 39% were B12 deficient. Mean lesion size was 11cm, 24 % had metastasis, 46% had high LDH and 85% had high SAP. Post CT, 194 underwent surgery till analysis; 56 % had GR. At a mean follow-up of 16 months, median overall survival (OS) is not reached in nonmetastatic(NM) patients while in metastatic patients it was 25.36 months(p=0.008).Estimated 2-year-OS is 87 % in NM and 67% in metastatic patients.

Grade III/IV chemotoxicity like febrile-neutropenia (FN) (20%), thrombocytopenia(7%) & GI-toxicity(11%) were managed successfully.Compliance to chemotherapy was 81%.

In multivariate analysis HN, low albumin & FN were identified as independent variables for OS; ECOG-PS and transferrin-saturation (TS) were identified as independent variables for FN.

Conclusions

Non-HD-MTX based dose-dense CT regimen produces outcomes comparable to those of HDMTX-containing regimens with acceptable toxicity and compliance even in nurtitionally challanged and high tumor burden osteosarcoma cases.

Albumin & FN are identified as nonconventional potential prognostic markers while ECOG-PS and transferrin-saturation as noval markers for toxicity prediction at baseline, and merits further exploration.

P-043

Bone Tumours

SELF-REPORTED FUNCTIONAL OUTCOMES AND QUALITY OF LIFE ASSESSMENTS IN LONG-TERM SURVIVORS OF PEDIATRIC EWING SARCOMA

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Objectives

To collect long-term patient-reported functional outcomes and quality of life assessments from pediatric patients treated for Ewing Sarcoma at Mayo Clinic and assess the impact of disease characteristics and primary tumor treatment modality.

Methods

Surviving patients treated at Mayo Clinic for Ewing Sarcoma between 1977 and 2009 were eligible to complete a self-reported quality of life questionnaire. Assessment tools included the Toronto Extremity Salvage Score (TESS) and the age appropriate PEDSQL™4.0 Generic Core instruments. Inventory scores were calculated according to the published TESS and PEDSQL guidelines, with higher scores indicating better outcomes for each instrument (range 0-100). Univariate analysis of TESS and PEDSQL score with patient clinical characteristics was assessed using a Chi square for discrete variables and the ANOVA method for continuous variables.

Results

33 patients (20 male) completed the self-assessment. Median age at diagnosis was 14.9 years (range 3.5-17.9) and median age at survey completion was 31.5 years (range 12.2-52.8). The median TESS scores and PEDSQL total scores for all patients were 99.2 (IQR=96.9-100) and 89.1(IQR=78.4-98.4), respectively. Within the PEDSQL instrument, scores were highest in the social domain (median=100) and lowest in the physical domain (median=87.5). PEDSQL total scores correlated strongly with TESS scores with a Pearson correlation coefficient of 0.72. Median TESS scores did not differ significantly based on primary tumor location (axial=100, extremity=98.8, pelvis=97.9, p=0.84). Local therapy did not affect TESS scores significantly, with mean scores of 99.2(RT), 100.0(S), and 98.3(RT+S), p=0.78.

Conclusions

This study is the largest single institutional assessment of quality of life in long-term survivors of pediatric Ewing Sarcoma. Self-reported functional outcomes in our series were excellent relative to published values for healthy subjects and do not appear to be influenced by tumor location or mode of local therapy. These data will provide a benchmark for comparison in future studies.

P-044

Bone Tumours

METHYLENE TETRAHYDROFOLATE REDUCTASE POLYMORPHISMS AND TOXIC EFFECTS AFTER HIGH-DOSE METHOTREXATE IN CHILDREN WITH OSTEOSARCOMA

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Objectives

Methotrexate is a dihydrofolate reductase inhibitor. High-dose methotrexat (HD-MTX) is one of the most important agents in therapy of high-grade osteosarcoma in children. The major side effects of HD-MTX include mucositis, nephrotoxicity and hepatotoxicity. Delayed MTX clearance followed by toxic effects (acute and delayed) still represent clinical problems. Methylene tetrahydrofolate reductase (MTHFR) has a key role in the folate cycle. Usual polymorphism of MTHFR gene is represented by replacement of citozin(C) with timine (T) on position 677 . The result is C677T allele with 60% of enzyme activity or T677T allele with 30% of enzyme activity. Consequence of lower MTHFR enzyme activity is reduced folate pools witch may cause additional toxicity and delayed MTX clearance .

Methods

During 2010 we evaluated 15 patients (pts) with high-grade osteosarcoma, which had delayed MTX clearance and toxic effects after administration of HD-MTX in dose of 12g/m^2. The median age was 15 years (10,5 to 16,5 years). We used PCR-RFLP method and analyzed peripheral blood to detect polymorphism of 677 MTHFR allele. Prior to HD MTX infusion all pts had normal laboratory findings.

Results

All 15 evaluated pts had delayed MTX clereance from 144 to 192 hours and hepatotoxicity grade 3-4. Three pts had nausea and vomiting. Eight out of fifteen pts had C677T polymorphism with 60% of enzyme activity, one patient had 30% of enzyme activity (T677T). One patient with C677T allele had developed mucositis/stomatitis grade 3/4.

Conclusions

MTX toxicity and delayed MTX clearance can be explained by MTHFR polymorphism on position 677 and prolonged MTX exposure. Polymorphism C677T on MTHFR gene is related to lower level of folate pools caused by loss of catalitic function of MTHFR.Carriers of MTHFR polymorphism receving HD-MTX chemotherapy protocols could be in grater risk for toxic effects .

P-045

Bone Tumours

RESPONSE TO CHEMOTHERAPY ESTIMATED BY FDG PET AS AN IMPORTANT PROGNOSTIC FACTOR IN PATIENTS WITH EWING SARCOMA

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Objectives

Response to the neoadiuvant chemotherapy is a prognostic factor in patients with Ewing sarcoma (ES). The role of FDG PET to predict response to neoadjuvant chemotherapy in these patients has not been thoroughly investigated. We evaluated the diagnostic accuracy and the potential of F-18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) to compare chemotherapy (CHT) response with the degree of necrosis defined histologically.

Methods

We analyzed data of 50 patients with ES (median age 12,6 years). All patients were treated with neoadiuvant CHT, and underwent surgery excision. All patients had ^{18}F-FDG PET/CT at diagnosis and after induction CHT, prior to local control. We compared response assessed by histopathology with FDG PET using standard uptake values (SUV). We also analyzed FDG PET uptake with other diagnostic imaging studies.

Results

Forty-three patients (86%) are alive with a median follow-up of 25.63 months from diagnosis. Median SUV at diagnosis was 5 (range 0-17). Median SUV after initial chemotherapy was 1.95range 0-8.4). Histologically, 38 (76%) patients were classified as having good responses (≥90% necrosis) and 12 (24%) as having poor responses (<90% necrosis). SUV after CHT was significantly lower in patients with good histological response than in patients with poor histological response (median 1.8 vs. 3.1). Additionally, FDG PET was more sensitive than bone scintigraphy to detect bone metastases; however, its sensitivity for detection of lung disease was low.

Conclusions

^{18}F-FDG PET demonstrates high diagnostic accuracy for response to initial chemotherapy and it is more sensitive than bone scintigraphy for the detection of bone metastases. FDG PET may be a useful tool in the estimation of histological response in patients with ES.

P-046

Brain Tumours

OUTCOMES FOR PEDIATRIC MEDULLOBLASTOMA IN CANADA FROM 1990 TO 2010: A REPORT FROM THE CANADIAN PEDIATRIC BRAIN TUMOR CONSORTIUM.

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Objectives

The Canadian Pediatric Brain Tumor Consortium (CPBTC) examined the incidence of medulloblastoma from 1990 to 2010. The outcomes by treatment type, especially use of radiotherapy, are presented.

Methods

Treatment of children with brain tumors is centralised in 16 institutions in Canada forming the CPBTC. In order to assess if there was a change in incidence from 1990-2010, data was collected. The outcomes according to treatment, 5-year groups (1990-94, 95-99...) M status, gender, age, and use of radiotherapy in first line treatment are presented.

Results

669 patients were treated over 20 years, 406 male and 255 female. 443 patients had M0 disease and 226 had metastatic disease. There were 304 patients under age 5 with a greater proportion having M+ disease: 42% vs. 30% for those older. First line therapy was chemotherapy only in 9.6% of patients, radiotherapy only in 11.4%, with a decrease from 16.4% in the first decade to 6.8% in the latter decade, and combined chemotherapy and radiotherapy in 60.8% of patients. In the 2005-2010 period, high dose chemotherapy was used alone in 8.7% and with radiotherapy in 23.1%. Survival at 5 years was 80% for patients receiving radiotherapy and 40% for those not receiving radiotherapy (p= 0.0001). Stage M0 vs. M+, and age under 5 years were also significantly related to survival (both p=0.038) in the COX Hazard model. There was no difference in survival by gender or 5-year periods.

Conclusions

There was no improvement in survival over the study time period, and the use of radiotherapy as first line was the most important prognostic factor. Younger children, under 5 years, presented with a worse stage. There was an independent effect of young age and stage on prognosis, but to a much lower extent than the use of radiotherapy as first line therapy.

P-047

Brain Tumours

LONG TERM FOLLOW UP OF INFANTS WITH MEDULLOBLASTOMA TREATED WITH SEQUENTIAL HIGH DOSE CHEMOTHERAPY

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Objectives

High dose chemotherapy strategies were developed to avoid craniospinal irradiation and prevent unacceptable neurotoxicity in young children. However, long-term outcome, including neurocognitive outcome, of this approach has not been widely described.

Methods

This retrospective study collected data from 6 institutions, on young children with medulloblastoma who received high-dose Carboplatin, Thiotepa according to the protocol CCG99703 between 1998-2012. Data on pathology, molecular subgrouping, chemotherapeutic, radiation, ototoxicity , neurognitive evaluations and survival were collected.

Results

There were 47(25 males) patients diagnosed at a median age of 24.5 months(2.9-63.2). Nineteen(39.6%) had metastatic disease and 30(62.5%) underwent gross total resection(GTR). Fifteen(31.3%) had nodular desmoplastic(ND) subtype. Three patients received intrathecal chemotherapy, 6 received HD MTX during induction and 7 underwent maintenance chemotherapy post HDC. Fifteen patients received radiation, including 9(18.7%) in an adjuvant setting. Complete continuous remission(CCR) rates after induction and consolidation were respectively 66.7% and 75 %. Two patients died of treatment related toxicity. Thirty seven patients are alive at a median follow-up of 3.7 years from diagnosis with a projected 5-year PFS and OS of respectively 68.4%(±7.5)and 76.4%(±6.6). GTR, M0&M1 stage, ND histology, and CCR were significantly associated better PFS, but only CCR post consolidation and M0&M1 stage remained significant for better OS. Non irradiated children had a better PFS compare to those who received radiation(5y PFS 82.3% versus 45%p=0.017). Outcome by molecular subgrouping is pending. Severe ototoxicity (≥ Brock grade 3) was present in 23.3% of 30 evaluable patients. Nine required hearing support. Neurocognitive assessements were available in 19 patients (51%). Mean FSIQ for the cohort was 91(range 67-119).

Conclusions

Young children with MB treated with this strategy have an encouraging OS(76.4 %). Less than 20% of the patients received adjuvant radiation. Although the ototoxicity of this regimen was significant, neurocognitive profile of the survivors appears to be within normal range.

P-048

Brain Tumours

ACUTE TOXICITIES AND TREATMENT OUTCOMES FOR PEDIATRIC MEDULLOBLASTOMA PATIENTS TREATED WITH PROTON-BASED CRANIOSPINAL IRRADIATION

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Objectives

CSI was delivered using cranial photon fields and spinal posterior-anterior proton fields to allow for field size limitations at our institution. We report the acute toxicities and outcomes with this technique.

Methods

From September 2011-August 2013, 19 patients were treated. Standard-risk patients received 23.4Gy(RBE) CSI and tumor bed proton boost to 54Gy(RBE); high-risk (HR) 36Gy(RBE) and 55.8Gy(RBE), respectively (2 with spine boosts of 5.4Gy(RBE) and 12.6 Gy(RBE)). All patients received vincristine. 3 HR patients received additional daily carboplatin. Toxicities were documented according to CTCAEv4.

Results

Median age was 10.3 years (range 3.7-17.4). 11 were female, 11 required daily anesthesia during radiation, 14 were standard-risk. At baseline, mean neuropsychological abilities across a broad range of performance based measures and parent reported functioning were in the average range (Wechsler IQ Mean=101.86, SD=13.18, Range 76-115). Most toxicities were grade 1-2(G1-2). The only G3+ toxicities were: nausea/vomiting (G3, n=3), anorexia (G3, n=9, max weight loss G2), decreased hemoglobin (G3, n=3), leukopenia (G3, n=3; G4, n=1) and thrombocytopenia (G3, n=1). The patient with G4 leukopenia also had G3 thrombocytopenia; she had high-risk medulloblastoma, treated with spine boost, vincristine and carboplatin. G3+ bone marrow toxicity occurred in 4/5 HR patients and all patients receiving carboplatin. Hepatic and renal toxicities were mild. Of 8 patients with available audiograms, at median 11.3 months from end of RT (range 6.6-26.6), 5 had mild-moderate hearing loss, 3 had none. Of 8 patients for whom detailed post-radiotherapy imaging was available, none had radiation necrosis. Follow-up data were available for 16 patients. At median follow up of 13.8 months (range 3.8-24.5), 14 are alive without disease, 1 is alive with cerebellar and thecal sac recurrences, and 1 is alive with ventricular recurrence.

Conclusions

This CSI technique is safe and well-tolerated. Proton CSI may decrease GI, bone marrow, hepatic, and renal toxicities depending on chemotherapy regimen.

P-049

Brain Tumours

CLINICAL OUTCOME BY REDUSED-DOSE IRRADIATION PLUS ADJUVANT CHEMOTHERAPY AND PROGNOSIS AFTER RECURRENCE IN MOLECULAR SUBGROUPING OF MEDULLOBLASTOMAS

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Objectives

Therapeutic challenges against recurrence of medulloblastomas have difficult problems, although prognosis of medulloblastomas has been improved by craniospinal irradiation and adjuvant chemotherapy. We retrospectively analysed recurrent patterns and differences of clinical outcome based on molecular subgrouping for medulloblastomas treated by redused-dose irradiation and high-dose chemotherapy.

Methods

Twenty-one patients with medulloblastomas treated in our institution from 1994 to 2013 were classified into four subgroup by nanoStrings assay using frozen specimens. Age distribution was one to twenty-two years old. The subgroup distribution was four SHH, five group 3 and eleven group 4 without WNT case. In all cases older than 3 years old, redused-dose craniospinal or cranial irradiation (18 Gy) plus adjuvant chemotherapy was done after tumor removal. High-dose chemotherapy was performed in high-risk group.

Results

No recurrence was seen in SHH. Of five group 3 cases, four had recurrent medulloblastomas and the period between initial treatment and recurrence was within 16 months. 5 year progression-free survival (5y-PFS) was 20.0%. Recurrent cells were rapidly and extensively disseminated and progressive despite of many therapeutic chanllenges. The period between recurrence and death was 4 to 7 months and 5 year overall survival (5y-OS) was 26.6%. Of eleven group 4, slow-growing and asymptomatic recurrences were shown in four cases. The period between initial treatment and recurrence was 18 to 70 months. Both 5y-PFS and 5y-OS were 70%. Although high-dose chemotherapy or intrathecal injection of chemotherapeutic agents had little effect, the conditions of partial response or stable disease were maintained by stereotactic radiotherapies and metronomic chemotherapies using oral etoposide and temozolomide.

Conclusions

By therapeutic regimen including redused-dose irradiation, 5y-PFS, 5y-OS and survival time after recurrence in group 4 are significant longer than those in group 3. Molecular subgrouping may predict recurrent patterns, response against treatment and prognosis in each group.

P-050

Brain Tumours

A FUNCTIONAL GENOMICS APPROACH TO IDENTIFY MECHANISMS OF DRUG RESISTANCE IN SHH MEDULLOBLASTOMA MURINE MODELS

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Objectives

Despite improvements in survival, Medulloblastoma (MB) patients face a multitude of long-term neurocognitive sequelae due to aggressive chemo- and radio- therapy. Many novel MB targeted therapies are emerging, however these are likely to reveal drug resistance pathways that are present or acquired in response to therapy. Previous work from our group has demonstrated that Foretinib, an inhibitor of cMET activity, is an effective treatment of Sonic Hedgehog (SHH) subgroup MB. Currently we seek to identify pathways that may lead to Foretinib resistance in SHH MB, such that informed up-front combinatorial therapies could be uncovered and evaluated.

Methods

A MB Sleeping Beauty transposon mutagenesis murine model (Ptch+/-/SB11/T2Onc) was used which frequently and spontaneously develops primary and metastatic MB. Mice were treated with vehicle or Foretinib, via Alzet osmotic pump slow-infusion into the cerebrospinal fluid for 28 days at a rate of 0.25ul/hour. Transposon common insertion sites were identified by SPLINK PCR of tumour DNA, followed by paired-end Illumina next-generation sequencing (HiSeq 2500). This data identified different insertions in control mice versus Foretinib treated mice, relating to different pathways that had been selected in response to treatment.

Results

We demonstrate that Sleeping Beauty MB mice have a statistically greater survival upon treatment with continuous CSF infusion of the cMET inhibitor Foretinib. Despite an improvement in survival, Foretinib treated mice eventually succumb to tumour formation and metastasis. Using an unbiased functional genomics screen, we have identified novel mechanisms and pathways of resistance to cMET inhibition. The targets identified converge upon regulators of cell cycle, apoptosis, and tumour invasion, and reveal pathways that may be leveraged for combinatorial treatment with Foretinib.

Conclusions

Our study has identified potential pathways that SHH MB cells may co-opt to overcome Foretinib inhibition, and provides a system for which drug resistance pathways to other MB targeted therapies may be identified.

P-051

Brain Tumours

TSP-1 peptidomimetics as novel therapeutics in Medulloblastoma

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Survival of localized medulloblastoma (MB) has improved significantly with intensified chemo-radiotherapeutic regimens in recent years, however, treatment and/or prevention of craniospinal metastases remains a major obstacle in clinical management of MB. In prior studies, we generated MYC driven xenograft models of metastatic MB and identified thrombospondin-1 (TSP-1), an anti-angiogenic factor, as a robustly repressed target in metastatic MB. In this study we sought to determine whether expression of TSP-1 or TSP-1 peptidomimetics alters metastatic behavior and conventional treatment responses of MB.

Immuno-histochemical analyses revealed that TSP-1 is often down-regulated in primary human MB especially in non-WNT tumours, and correlates with clinical metastases. Orthotopic xenograft studies revealed that stable TSP-1 expression significantly prolonged mice survival (p

Our collective findings further underscore the critical tumor suppressive role of TSP-1 in MB and highlight TSP-1 peptidomimetics as important novel therapeutics for Myc-associated MB, one of the most lethal of MB variants.

Document not received

P-052

Brain Tumours

LONGITUDINAL CHILD AND PARENT REPORTED HEALTH RELATED QUALITY OF LIFE IN CHILDREN ENROLLED ON A PROTON RADIOTHERAPY PHASE II MEDULLOBLASTOMA STUDY

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Objectives

To describe the longitudinal HRQoL in patients treated on a prospective phase II trial for pediatric medulloblastoma with proton radiotherapy (PRT).

Methods

59 medulloblastoma patients (enrolled 2003-2009) were assessed with PedsQL during PRT and annually thereafter. 38 had evaluable PedsQL surveys at follow-up (FU). Patients received PRT (median dose: 23.4 GyE CSI (18-36)), and tumor bed (TB) or posterior fossa (PF) boost (54 GyE, (54-59.4GyE)). We compared HRQoL by risk group (SR/HR), age, SES (address-derived median income, >=vs < $60,000), and boost volume (TBv.PF) using ANOVA and paired t-tests.

Results

Median HRQoL follow up (FU) among those with baseline evaluations was 4.0 years (n=38). Parent Proxy Report (PPR) were non-significantly less than Child Self-Reported (CSR) at baseline for Total Core Score (TCS) 57.8 vs. 69.2, Physical Score (PS) 51.6 vs.66.5, and Psychosocial Score (SS) scores 62.8 vs. 72.7. The mean TCS, PS, and SS at last FU were similar across PPR & CSR; [n=29] 73.6 vs. 78.4, [n=29] 76.4 vs. 81.3, and [n=35] 71.3 vs. 76.6 (p's=NS).

Both PPR & CSR HRQoL measures improved following treatment although this difference was significant for only TCS and PS and among PPR. Across HRQoL domains, SS minimally improved with time. FU HRQoL scores improved differentially across age (<=7 vs.>=8) in TCS (+9.6 [95% CL 0.3-18.8] vs. 23.7 [95% CI 13.3-34.1], p=0.04) and PS (17.1 vs. 34.6, p=0.05) among PPR but not CSR. There was no difference in change over time in TCS, PS or SS across gender, risk category, SES or boost volume.

Conclusions

PPR/CSR HRQoL domains improved over time across all domains but SS, with the largest improvement in PPR of TCS and PS. SES was not correlated to HRQoL scores at baseline, FU or the change over time.

P-053

Brain Tumours

SIOP PODC: ADAPTED REGIMENS TO MANAGE CHILDREN WITH STANDARD RISK MEDULLOBLASTOMA IN LOW- AND MIDDLE-INCOME SETTINGS.

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Objectives

Effective treatment of children with medulloblastoma requires a functioning multi-disciplinary team with adequate neurosurgical, neuroradiological, pathological, radiotherapy and chemotherapy facilities and personnel. The treating center should also have the capacity to effectively screen and manage any treatment associated toxicity. These requirements have made it difficult for many low and middle-income countries (LMIC) centres to offer curative treatment. This presentation describes management recommendations for children with standard risk medulloblastoma according to the level of facilities (settings) available.

Methods

Under the auspices of the SIOP PODC group, a multidisciplinary writing group composed of doctors from the LMIC and developed countries was established to produce guidelines to assist professionals working in LMIC to treat children with standard risk medulloblastoma. To start, a survey was conducted amongst doctors in LMIC to establish what difficulties they encountered in treating children with medulloblastoma. There were 104 respondents from 47 countries. Following a number of web conferences, guidelines based on the best available evidence and appropriate for the different settings (graded 0-4) were drawn up. These were then circulated to professionals in LMIC for comments on its usefulness. Further enhancements were made following these comments.

Results

The guideline used standard settings developed by the overall SIOP PODC group with modifications appropriate to treatment of medulloblastoma. Those in settings 0 and 1 are not recommended to treat children with medulloblastoma. Surgical, radiotherapy and chemotherapy options appropriate to the settings are included in the guideline. In addition, suggestions for investigation and management of potential toxicities are included. The importance of a functioning multidisciplinary team is emphasised.

Conclusions

Guidelines such as these may be useful for those working in LMIC . However, it is important that appropriate consultation with the potential users of such documents is conducted.

P-054

Brain Tumours

TREATMENT OF MEDULLOBLASTOMA AND PNET CHILDREN ABOVE THREE YEARS OF AGE IN SAUDI ARABIA: A PROSPECTIVE MULTICENTER STUDY

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Objectives

Treatment for children with medulloblastoma in Saudi has been heterogeneous and essentially institution-based. A cooperative protocol was launched in 2009 between 4 tertiary centers

Methods

Patient above 3 years with medulloblastoma and PNET received postoperative craniospinal radiation according to their risk group with concurrent oral etoposide 35mg/M2/days. They then received six cycles of chemotherapy alternating cycle A(Cisplatin 90 mg/m2/day, day 1 and Etoposide 35 mg/m2/day P.O. days 1-21 of a 4-week cycle) and Cycle B (Cyclophosphamide 1.5 g/m2/day, days 1-2 with Vincristine 1.5 mg/m2, days 1,8,15 for each 4weeks cycle). Post-chemotherapy, maintenance with Isotretinoin 160mg/M2/day1-14 was given for 6 months.

Results

62 patients (36males/ 26 female) were enrolled from 09/2009 to 02/2014. 56 patients had Medulloblastoma, 2 SPNET, and 4 pinealoblastoma . Median age was 7.1 years; 35 patients (56%) underwent gross total resection, 8 near-total, 12 subtotal, 2 partial and 5 patients underwent a biopsy only. 22 patients had M2/3 disease. 26 patients were treated as average-risk (AR,42%) and 36 treated as high-risk (HR,58%). Radiation started at a median interval of 35 days post-surgery (18-105). Etoposide was well tolerated during radiation, but most patients experienced grade3-4 hematological toxicity during post-radiation chemotherapy. Only 50% of the patients received isotretinoin. No toxic death occurred on treatment. Hearing assessment (Brock scale) was available for 51 patients and showed gr0 toxicity in 30 patients(48.4%), gr1-2 in 16, and gr3-4 in 5. At a median follow-up of 23 months, 56 patients are alive and 6 have died (3/26 AR patients, and 3/36 HR patients). The 2 year overall survival (OS) is 91.5$\pm$5% and the projected 5 year OS 80.7$\pm$8%.

Conclusions

Although it is still too early to draw conclusions on survival with this approach, initial results are encouraging showing mild toxicity, in particular in terms of hearing loss.

P-055

Brain Tumours

MEDULLOBLASTOMA IN CHILDREN ABOVE 3 YEARS; REPORTING TREATMENT RESULTS FROM KING FAISAL SPECIALIST HOSPITAL & RESEARCH CENTRE, RIYADH, SAUDI ARABIA

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Objectives

Medulloblastoma is the most common malignant brain tumor seen in childhood. Long term survival of medulloblastoma has improved over the past few decades. We analyzed data from our institution on children above 3 with medulloblastoma

Methods

From 2005 until 2012, 89 eligible patients were identified

Results

66 were male (64.1%), median age at diagnosis was 6 years (range, 0.81-13.21 years), boys: 5.9years, girls: 6.2years). Tumor was confined to the posterior fossa in 50 patients (56.2%), 30 (33.7%) spine metastases (mets), and 9 (10%) disseminated disease within the brain. CSF metastases in 11 pts who had spine mets (36.6%). Symptoms at presentation were headache (74.2%), vomiting (70.8%), and ataxia (31.5%). One patient had neurofibromatosis. Surgical intervention was performed on all patients; 59 gross total resection, 20 had subtotal resection, 7 had debulking and 3 had biopsy only. 58 pts (65.2%) were high risk disease (>1.5 cm^2 residual tumor and/or M1- M4) and 31 (34.8%) standard risk. The therapeutic regimen consisted of full dose craniospinal for high risk pts and reduced neuro-axis dose for standard risk pts with concurrent weekly vincristine followed by 8 cycles of cisplatinum, lomustine and vincristine.The 5-year OS for all pts was 79%±5%.The 5-year overall survival for standard risk vs high risk pts was 84.1% (± 7.6) vs. 76.3% (± 6.5), (P=0.380) and for non-metastatic versus metastatic disease was 85.9 %(± 5.5) vs. 69.6 %(± 8.8),(P=0.114). The 5-year event free survival for standard risk vs high risk was 73.5% (± 8.8) vs. 61.2% (± 7.5),(P=0.331) and for non-metastatic vs. metastatic 70.95% (± 7.5) vs. 57.9% (± 9.2), (P=0.1).

Conclusions

The outcome analysis for high risk patients was very good and comparable to standard risk pts. It may be possible to further refine stratification of patients utilizing molecular markers thereby minimizing use of potentially harmful therapeutic modalities

P-056

Brain Tumours

RELAPSE AND OUTCOME PATTERNS OF CENTRAL NERVOUS SYSTEM (CNS) 'SECRETING' GERM CELL TUMORS (GCT) TREATED WITHOUT IRRADIATION: FINDINGS FROM THE THIRD INTERNATIONAL CNS GCT STUDY

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Objectives

To evaluate patterns of relapse and outcome in patients newly-diagnosed with CNS 'secreting' (or Mixed Malignant) GCT treated initially with chemotherapy without irradiation on the International CNS GCT Study III.

Methods

A retrospective chart review was conducted using all 25 patients enrolled on the International CNS GCT Study III, with at least 7 years follow-up for all patients. Details of the chemotherapy regimen have been published previously (DaSilva *et al*: Pediatric Blood & Cancer, 54:337-383, 2010).

Results

Thirteen patients at diagnosis had 'secreting' CNS GCT by pathology and tumor markers (n=11) or tumor markers alone (n=2). Twelve were treated with chemotherapy alone, one receiving focal irradiation following chemotherapy prior to relapse. Six patients (46%) relapsed (mean of 30.5 months; range 6 to 59 months), two beyond and 4 within the primary site alone. Three patients relapsed 'early' (between 6 and 23 months from diagnosis), 2 with alpha-fetoprotein (AFP) elevations and one without tumor markers assessed; all 3 expired of progressive disease at 2-10 months following initial relapse. Three patients relapsed 'late' (between 37 and 59 months), all without AFP elevations, one with pathologically-pure germinoma, two with mild beta-human chorionic gonadotropin elevations (<20mIU/mL in serum/cerebro-spinal fluid); these patients survive disease-free at 86+, 94+ and 126+ months following additional chemotherapy and irradiation.

Conclusions

Patients with CNS 'secreting' tumors who relapse following chemotherapy-only regimens display two distinct patterns of recurrence and outcome; patients relapsing 'early' appear to possess 'secreting' elements and have a dismal prognosis, while patients relapsing 'late' appear to do so with pure germinomatous elements and have an excellent outcome. Current international cooperative group studies utilizing more localized fields of irradiation should evaluate closely the patterns of relapse and outcome; late recurrences with germinomatous elements might be avoided by initial use of low-dose larger field irradiation (whole ventricular or craniospinal).

P-057

Brain Tumours

TUMOR VOLUME OF PRIMARY INTRACRANIAL GERMINOMAS IS CHANGING DYNAMICALLY BEFORE CHEMORADIOTHERAPY

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Objectives

Spontaneous regressions in intracranial germinomas have been reported in some cases, but the natural history of them has not been well known. To answer a part of that question, we retrospectively measured the tumor volume before and after chemo-radiotherapy and analyzed volumetric changes and the correlation with other clinical parameters.

Methods

Twenty-nine cases with primary intracranial germinomas and HCG-producing germinomas were treated in our hospital from 1994 to 2013. In eight of them, plural MRI scans were done before the first course of chemotherapy regimen. Their age ranged from 16 to 26 years. Endoscopic or open biopsies were performed in all. Two were bifocal type. Tumor volume of ten lesions was analyzed by volumetric assessment based on MRI. Ratio of volumetric change between the first MRI on admission and the scan immediately before chemotherapy was defined as shrinking rate (%). Ratio of volumetric change influenced by the first course of chemotherapy was defined as response rate (%). Period between disease onset and the first chemotherapy was 22 to 47 days.

Results

Initial tumor volume ranged from 0.962 to 24.15 cubic centimeter (mean: 6.39). Diagnostic radiation dose was estimated to be from 52.2 to 910.1 mSv. Shrinking rate ranged from -57.8 to 85.3% (mean: 29.1). Only in 3 cases, shrinking rate was within ±30%. There is no significant relationship between diagnostic radiation dose and shrinking rate. Shrinking rate had no correlation with age, sex and response rate. Shrinking rate was negatively influenced by initial volume ($p=0.049$).

Conclusions

This study shows the possibility that the volume of intracranial germinomas are changing dynamically for a short time before chemoradiotherapy in most cases and spontaneous regression is a part of volumetric changes. More information about large-scale study is needed to give light on the biological nature of them.

P-058

Brain Tumours

INTEGRATIVE ANALYSES OF PEDIATRIC HIGH GRADE ASTROCYTOMAS REVEAL SIMILARITIES BETWEEN ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA

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Objectives

Brain tumors are the leading cause of cancer-related mortality in children. Pediatric high-grade astrocytomas (HGA), including grade III (anaplastic astrocytomas, pAA) and grade IV (glioblastoma, pGBM), are rare but devastating brain tumors accounting for 15% of brain tumors in children. pAA are rare and consequently have not been investigated as a separate entity. pGBM have been well-characterized and, to date, several subgroups of this tumor have been found including those related to mutations in *H3F3A* or *IDH1*. In the literature, HGA are often studied together and as such, no molecular data is available for pAA.

Methods

To identify genetic differences based on tumor grade in children, we investigated pediatric HGA by integrating data from whole exome sequencing, DNA methylation and gene expression analyses.

Results

Our results demonstrate that there is no significant segregation between these two tumor groups, neither at a genomic nor at an epigenomic level. At the RNA expression level, genes related to cell cycle progression, DNA repair, or apoptosis inhibition are upregulated in pGBM compared to pAA (ex. *KIAA0101, PRR11, BIRC5, GTSE1*). In addition, *GAS7*, a gene responsible for the growth and morphological differentiation of cerebellar neurons is downregulated 2.5 fold in pGBM relative to pAA. pGBM segregate into molecular subgroups based on underlying mutations, and our data indicates that the same molecular subgroups apply to pAA. Kaplan Meier analyses show no significant difference in overall survival (p=0.8622) between the two groups emphasizing a similar clinical course between both tumor types.

Conclusions

Our integrative analysis not only indicates that pAA may not be a distinct entity from pGBM, but also highlights the need for molecular diagnostic criteria in pediatric HGA. We propose that pAA and pGBM be grouped together in the hope that molecular-based treatment of this tumor group can improve the clinical outcome of these patients.

P-059

Brain Tumours

MULTIDISCIPLINARY TREATMENT AND ROLE OF SYSTEMIC CHEMOTHERAPY IN LOW GRADE GLIOMA

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Objectives

The aim of this study was to evaluate the role of multidisciplinary therapeutic approach including surgery and systemic chemotherapy, and the outcome in pediatric patients with different low grade glioma (LGG) subtypes.

Methods

Study patients were prospectively included. All patients were diagnosed as LGG between July 2007 and June 2012. Upfront surgical resection was attempted in all tumors of other than optic pathway sites. Systemic chemotherapy was given according to CCG- A9952 protocol.

Results

Total of 225 patients were enrolled onto study with male to female ratio of 1.2:1. The median age was at 1 year (range: 1-18 yr) with only 9 patients (4%) above 14 years old. Grade-I pilocytic astrocytoma (PA) was the most frequently encountered histologic subtype (43%) with cerebellar site predominance (43.1%), while optic pathway glioma constituted 5.8% of cases. Gross total/near total resection was feasible in 40.8% of the study patients while 26.7% underwent subtotal resection followed by adjuvant chemotherapy because of big residual size and/or symptomatic disease. The 5 year OS and EFS of the entire group were 87.3% and 65.5% respectively. Compared to chemotherapy patients underwent surgical tumor resection had OS and EFS of at 89.9% and 65.1% versus 86.1% and 59.9% for chemotherapy patients. Tumor site, histological subtype, and extent of residual tumor were significantly associated with OS.

Conclusions

Although GTR remains the standard initial treatment in LGG, yet systemic chemotherapy can be a comparable alternative when surgery can not be safely accomplished or being not technically feasible.

P-060

Brain Tumours

ACTUAL TREATMENT STRATEGIES IN INFANTS WITH PROGRESSIVE HYPOTHALAMIC CHIASMATIC GLIOMA

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Objectives

Treatment of infant hypothalamic chiasmatic glioma (iHCG) is challenging, since about 30% of the children progress during chemotherapy and despite subsequent treatments the 5 year overall survival rate is only 70%. This study investigates the treatment strategies as currently applied for iHCG.

Methods

A webbased questionnaire about the dillemma in the treatment of iHCG was sent out to the members of the SIOP Brain tumor group as well as the Low Grade Glioma group.

Results

The questionnaire was answered by 48 respondents (44 paediatric oncologists, 4 other professionals). Progressive disease during first line therapy with carboplatin-vincristine would be treated with (intensified) chemotherapy by 16 (33%) and with surgery plus changed chemotherapy by 24 respondents (50%). Components suggested for this second line chemotherapy were 72% vinblastine, 40% cisplatin, 30% cyclophosphamide and 25% etoposide. As components for third line therapy bevacizumab was considered as suitable by respondents in 62%, irinotecan 47% and vinblastine by 40% respectively. Experience with bevacizumab in iHCG is quite common (median treated 1-5 patients at any age) for 57% mostly in combination with irinotecan with a 12 month duration. Effect was reported for all patients with at least stable disease while severe complications were rarely mentioned (1 proteinuria & hypertension, 1 bleeding). Bevacizumab would be available for future protocols for patients of 86% of respondents. Radiotherapy was considered as treatment option after failure of two or three treatment lines with a wide range 3-18 years for lower age limit (median 8 years).

Conclusions

Multiple different cytostatic drug regimens are applied for progressive iHCG often combined with surgery, while bevacizumab is often used at a satisfactory level in third line in combination with irinotecan.

P-061

Brain Tumours

UNRAVELING THE BIOLOGICAL ROLE OF SPINT2 IN GLIOMAS

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Objectives

SPINT2 is a tumor suppressor gene that codifies protein SPINT2, a serine protease involved in the HGF/MET signaling pathway. *SPINT2* has been demonstrated to be hypermethylated in a variety of cancers, including medulloblastomas. Herein, we intent to determine the clinical relevance of SPINT2 expression/hypermethylation in pediatric and adult high-grade gliomas (HGG), as well as to elucidate the functional role of the different transcripts of *SPINT2* in pediatric glioma cell lines.

Methods

A cohort of 410 adult and 78 pediatric primary HGG samples was used to characterize protein expression (immunohistochemistry) and methylation status (methylation-specific PCR) of SPINT2. Moreover, 424 glioblastoma patients from TCGA were used to evaluate *SPINT2* mRNA expression and methylation levels. Plasmids containing SPINT2a and SPINT2b transcripts were constructed and the role of each transcript in cell migration and viability were evaluated by wound-healing and MTS assay.

Results

We observed that SPINT2 protein is frequently absent in adult HGG (88%), and in all (100%) pediatric cases. These results together with *in silico* analysis demonstrate that down-regulation of *SPINT2* is a common event of brain tumors. We found that down-regulation of *SPINT2* is associated with methylated status of *SPINT2* promoter, *In vitro* analysis showed that ectopic expression of each *SPINT2* transcripts reduced cell migration capacity and cell metabolic viability. Furthermore, we revealed for the first time that SPINT2b has a more pronounced effect in migration while SPINT2a has a stronger effect on cell viability.

Conclusions

We concluded that low expression of SPINT2 and gene hypermethylation are common events in both pediatric and adult HGG, which are associated with higher tumor aggressiveness.

P-062

Brain Tumours

CHROMATIN ARCHITECTURE IN PEDIATRIC GLIOMAS

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Objectives

The epigenome has emerged as one of the core elements de-regulated in pediatric gliomas. A key facet that has not been investigated in this context and is only beginning to be understood in human cancer, is the spatial organization of chromatin and its influence on the regulation of gene expression in cancer cells. The chromatin landscape can influence gene regulation and even promote oncogenic alterations by virtue of geographic proximity in the nucleus.

Methods

To this effect we decided to explore the spatial organization of chromatin in pediatric gliomas with a focus on the *BRAF* locus in pilocytic astrocytoma (PA) utilizing genome-wide chromosome conformation capture (Hi-C) technology in freshly-resected patient tumors.

Results

BRAF is altered in a significant proportion of PA tumors, in the form of tandem duplication at chromosome 7q34 leading to in-frame fusions of *KIAA1549-BRAF,* with a notable predilection to tumors arising in the cerebellum. Interestingly, Hi-C analyses reveal a putative topologically-associated domain (TAD) consistent across tumors within the cerebellum in the study; bordered strikingly by *KIAA1549* and *BRAF* regions. This TAD appears to be consistent across other cell types originating from hematological, fibroblast and other sources from publically available datasets.

Conclusions

To best confirm this TAD we intend to profile heterochromatin H3K9me3 marks, and integrate this data with gene expression. In this way, we may be able to elucidate structural determinants that may favor *BRAF* fusion in PA that may originate from inherent DNA conformation.

P-063

Brain Tumours

MOLECULAR CHARACTERIZATION OF MAPK PATHWAY AND ONCOGENE-INDUCED SENESCENCE IN A BRAZILIAN COHORT OF PILOCYTIC ASTROCYTOMA PATIENTS

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Objective:

Pilocytic astrocytoma (PA) is an indolent glioma, with up to 10% of cases progressing poorly. Activation of MAPK, its main molecular pathway, may trigger Oncogene-induced senescence (Ois). Loss of expression of *MTAP* has been described in aggressive neoplasms, including gliomas, but no data concerning PAs has been published. Conversely, its overexpression has been related to senescence in neurodegenerative diseases. Our aim was to assess the relationship between the expression of Mtap by immunohistochemistry (IHC) and molecular markers of MAPK activation (FGFR1 mutation and *KIAA-BRAF* [*K:B*] fusion).

Methods:

In this retrospective study, IHC was performed with an antibody against Mtap in the FFPE in tissue microarray platforms (TMAs). In the available samples, *FGFR1* mutation was evaluated by Sanger sequencing and *K:B* fusion by a customized dual-target, dual-color fluorescence in situ hybridization (FISH) probe set in samples in the TMAs validated in Agilent 8x60K aCGH and RT-PCR assays in 5 cases.

Results

Overall 75 samples from 69 patients were evaluated (1.2 M/F - median age of 11.6 years). Cerebellum was the main location (53.6%). There was overexpression of Mtap in 66/69 patients, significantly related to: cerebellar location (p=0.025); point mutation of *FGFR1* (p=0.022), which was noted in 2/44 cases; and *K-B* fusion (p=0.028) that was detected in 38/64 samples. In adjacent cortex (9 cases) astrocytes had weak expression of Mtap, while Purkinje neurons had strong reaction.

Conclusions

As far as we are concerned, this is the first study to show overexpression of *MTAP* in PAs. This seems to reinforce a positive relationship between constitutive activation of MAPK pathway and the Ois phenomenon, which is one of the mechanisms responsible for the indolent behavior of PAs. Further studies with larger cohorts are necessary to confirm this relationship.

P-064

Brain Tumours

RESULTS OF VARIOUS METHODS OF TREATMENT FOR CHILDHOOD ANAPLASTIC EPENDYMOMA

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Objectives

Presently there are no standards treatment for anaplastic ependymoma.

Methods

We evaluated the treatment results for 169 children with AE. Median age was 4 y.o. Most patients were over 3 y.o (119; 70.4%). There were 104 boys (61.5%) and 65 girls (38.5%). Infratentorial tumors were in 81 pts (48%); supratentorial, in 82 (48.5%), and 6 pts (3.5%) had the tumor in the spinal cord. 118 pts (70%) had stage M0; 14 (8%) had metastases or detected tumor cells; for 37 patients (22%), the stage was not known. 78 pts (46%) received chemo- and radiotherapy according to protocol HIT 2000/2008; 57 (34%) received only radiotherapy after the surgical operation; 25 (15%) patients got chemotherapy; and 9 (5%) pts were treated using only surgical intervention. Most patients underwent total (*n*=70) or subtotal (*n*=91) tumor resection; for 8 (5%) patients, the extent of the resection was not evaluated.

Results

3-year PFS 0.47±0.05, 5-year PFS 0.32±0.05, median PFS 32 months (2 to 34 months). 3-year survival was better in children over 3 in comparison with younger than 3 y.o: 0.50 and 0.36, respectively. 3-year survival among girls was 0.36; among boys, 0.22 (*?*=0.19). 3-year PFS were better for supratentorial tumors in comparison with intratentorial: 0.54 and 0.39, respectively (*?*=0.19). Survival results were better among patients with stage M0 in comparison with stage M+: 0.50 and 0.39, respectively. In the case of total tumor resection, the 3-year survival was better than in the case of subtotal

resection: 0.42 and 0.22, respectively (p=0.44). PFS were the same among patients who received chemoradiotherapy or only radiotherapy: 0.53 and 0.50, respectively. Among patients who got chemotherapy after tumor resection, the 3-year PFS were 0.19; after surgery only, all patients had recurrence (*?*=0.0002).

Conclusions

Chemotherapy does not improve the results of treatment for anaplastic ependymoma.

P-065

Brain Tumours

TWO SUBSEQUENT AIEOP PROTOCOL FOR CHILDHOOD AND ADOLESCENT EPENDYMOMA: LOOKING AT PROGNOSTIC IMPROVEMENT

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Objectives

Ameliorating ependymoma patients prognosis throuh two subsequent Italian protocols.

Methods

In first protocol, patients were given: focal radiotherapy(HFRT) if with no evidence of disease (NED), or 4 VEC chemotherapy HFRT for residual disease(ED). HFRT dose was 70.4 Gy; VEC was VCR 1.5 mg/m2 1/w, VP16 100 mg/m2/day 1-3, CTX 3 g/m surgery was recommended. The 2nd study stratified pts according to the two prognostic factors found: surgical results and histology was upfront centrally reviewed as in previously. Children/adolescents aged over 1 yr/below 21 if with NED/gr2 tumors were focally 1.8Gy/d up to 59.4Gy, while if with NED/gr3 tumors also received 4 VEC after irradiation. ED pts received 4VEC, second-look possible, 59.4Gy irradiation plus a 8Gy boost into 2 fractions on surgical residue.

Results

Between 1994/December 2012, 60+141 patients, respectively in the 1st and 2nd protocol, were treated and actively followed. At of 10 and 5 years, 5 years-PFS/OS were 53%/72% and 69%/84%, for the first and second protocol, respectively, showing improvement for EFS (P=0.009) and OS (P=0.02). We analyzed the two populations: first series (1994-2001) contained significantly whose tumor aroused in posterior fossa, while the second contained more patients with grade 3 tumors and younger ones (cut-off of 6 years of the first series); surgical results and hydrocephalus needing shunts were not different. At multivariate analysis, posterior fossa origin confirmed to be risk factors for both EFS and OS while treatment according to the second protocol was better EFS (P 0.0003) and OS (P 0.0007).

Conclusions

The aim at improveing treatment strategies seems to have been satisfied even if a longer 2nd series follow-up is needed to confirm this benefit .

P-066

Brain Tumours

CRIBRIFORM NEUROEPITHELIAL TUMOR (CRINET): A SMARCB1-DEFICIENT NON-RHABDOID TUMOR WITH FAVORABLE PROGNOSIS.

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Objectives

The majority of atypical teratoid/rhabdoid tumors (AT/RT) is characterized by inactivation of the SMARCB1/INI1 gene and dismal prognosis. Few children harboring unusual non-rhabdoid SMARCB1-deficient tumors, for which the term *cribriform neuroepithelial tumor* (CRINET) has been coined, are on record. Anecdotal evidence suggests a relatively favorable prognosis of CRINET. We therefore aimed to investigate clinical features and prognosis in a first series of these rare tumors.

Methods

Clinical details, neuropathological and molecular genetic data as well as information on outcome were collected for 9 children harboring CRINET. Data on survival and recurrence-free survival were compared to 59 SMARCB1-deficient AT/RT from the European Rhabdoid Tumor Registry EURHAB.

Results

Median age of the 6 boys and 3 girls was 20 months (range: 10-27 months). The majority of CRINET was located supratentorially, often in the midline. Neuropathologically, all tumors were characterized by cribriform strands and ribbons and well-defined epithelial membrane antigen-immunopositive surfaces. Tumoral staining for SMARCB1/INI1 was lost. After a mean observation time of 54 months, only one child had died due to respiratory failure in the early postoperative phase. On Kaplan-Meyer analysis, children with CRINET experienced significantly longer progression-free survival as compared to AT/RT [103 months (95% confidence interval: 61-146 months) vs. 18 months (12-23 months), P=0.009] and overall survival [124 (95-152) months vs. 25 (18-32) months; P=0.005].

Conclusions

CRINET is a rare non-rhabdoid SMARCB1-negative tumor with favorable prognosis as compared to AT/RT.

P-067

Brain Tumours

PROGNOSTIC FACTORS IN PATIENTS OF AT/RT OF THE CENTRAL NERVOUS SYSTEM

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Objectives

AT/RT is a malignant tumor with an agressive behavior.

Methods

We have evaluated the prognostic factors in 43 patients with AT/RT. Most patients were younger than 3 years old (28, 65%), and 15 patients (35%) were above 3. The boys and girls were 20 and 23, respectively. The tumor was infratentorial in 21 patients (48.8%); 2 patients (4.7%) had infratentorial and renal tumors; and 20 patients (46.5%) had supratentorial tumors. Stage M0 was in 24 patients (55.8%); 11 patients (25.6%) had metastases or detected tumor cells at diagnosis; and the stage was not precisely determined for 8 patients (18.6%).Treatment according to protocol ATRT-2006 was administered to 24 patients (55.8%); protocol CWS, to 8 patients (18.6%); HIT-SKK, to 4 patients (9.3%); and 7 patients (16.3%) got off-protocol treatment.

Results

13 patients (30.2%) are alive, and 30 (69.8%) have died: 26 due to disease progression, 4 due to chemotherapy toxicity. The PFS was 30%±0.06, and the OS was 38%±0.06. The median survival time was 18 months; and the median observation time was 14 months (range 2 to 89 months). The survival rate was significantly higher among patients over 3 y.o in comparison with younger patients: 53 and 14%, respectively (p=0.004); among patients after total tumor resection in comparison with subtotal or partial resection: 55%, 31%, and 12%, respectively (p=0.015); among patients who got radiotherapy in comparison with those who did not: local radiotherapy, 50%; craniospinal radiation, 35%; no radiotherapy, 0% (*?*=0.033); among patients with stage M0 in comparison with stage M+: 37% and 0%, respectively (*?*=0.007). Therapy according to the ATRT-2006 protocol led to better survival rate (43%) in comparison with protocols CWS (12%) and HIT-SKK (18%), p=0.01.

Conclusions

The factors that affected the prognosis were the patient's age, the extent of the surgical resection, the chemotherapy program, the use of radiotherapy, and the presence of metastases.

P-068

Brain Tumours

PROSPECTIVE STUDY ON PEDIATRIC PATIENTS WITH ATYPICAL TERATOID RHABDOID TUMORS (ATRT) OF THE CENTRAL NERVOUS SYSTEM (CNS)

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Objectives

ATRT is a rare and aggressive CNS tumor usually presenting in very young children. Aggressive treatments have improved outcomes. Such strategies have included radiation therapy. However, at such a young age, short and long term radiation toxicities are prevalent. We prospectively enrolled pediatric CNS ATRT patients onto the Proton Collaborative Group registry protocol to evaluate the efficacy and toxicities of proton radiation therapy in this population.

Methods

13 consecutive pediatric ATRT patients were treated with at the Central DuPage Hospital Proton Center and the Oklahoma City Procure Proton Therapy Center between March 2010 – December 2013 utilizing 3D Conformal Proton Therapy.

Results

13 patients were evaluated. They were all 3 years of age or younger (4.4 – 37.7 months). Eight patients had gross total resections, while 4 had subtotal resections along with another 1 not documented. Nine patients received multiagent intensive chemotherapy per the Dana Farber Cancer Institute regimen while 4 had treatment either on or per ACNS 0333 protocol with intensive multiagent chemotherapy along with stem cell transplants. Radiation was to local fields for 10 patients, while 3 had craniospinal irradiation. The mean follow up was 14.9 months (range of 1-43 months) and median follow up 14.2 months. At last follow up, 11 patients were alive without evidence of disease. Only 4 children had grade 3 toxicities (all acute nausea, vomiting and anorexia during radiation therapy that responded to steroids). Proton therapy was able to reduce the dose to the cochlea, optic chiasm, hippocampus, temporal lobes and integral whole brain.

Conclusions

The initial results on the largest prospective series of CNS ATRT patients treated with proton therapy seem to be favorable. The aggressive treatment regimens utilizing proton beam therapy yield proven efficacy and improved toxicity profiles, which is critically important in this young patient population with such an aggressive disease.

P-069

Brain Tumours

PROGRESSIVE DECLINE IN HEALTH-RELATED QUALITY OF LIFE AMONG LONG-TERM SURVIVORS OF BRAIN TUMOURS IN CHILDHOOD AND ADOLESCENCE.

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Objectives

The trajectory of health-related quality of life (HRQL) was assessed in survivors of brain tumours in childhood and adolescence during a longitudinal study over a decade

Methods

An inception cohort of 40 patients comprised the study sample in 2000/ 2001. All were at least 2 years from completion of therapy with no evidence of progressive or relapsed disease; aged 5 years or more; and able to communicate in English. Children and parental proxy respondents were interviewed using 40 item questionnaires for Health Utilities Index (HUI) Mark 2 (HUI2) and Mark 3 (HUI3). The HUI utility scores for single attribute (domains/ dimensions) morbidity and for multi-attribute HRQL have an upper limit of 1.00. Negative scores for HRQL represent states of health considered worse than being dead. The subjects were re-assessed 5 and 10 years later

Results

Medians and ranges for HUI2 scores of HRQL at the 3 time points were: 0.93 (0.49 to 1.00); 0.90 (0.36 to 1.00); 0.88 (0.16 to 1.00). Corresponding HUI3 scores were 0.88 (0.13 to 1.00); 0.85 (0.01 to 1.00); and 0.77 (-0.19 to 1.00). The differences over time are statistically significant and clinically important. Main burdens of morbidity were in attributes of HUI2 sensation, emotion, cognition; and HUI3 vision, cognition and pain. For comparison, median HUI2/HUI3 scores were 1.00/1.00 for survivors of Wilms' tumour (n=52), 1.00/0.97 for acute lymphoblastic leukemia (n=194) and 0.92/0.90 for neuroblastoma treated by myeloablative chemotherapy with stem cell rescue (n=99).

Conclusions

Over the 10 year study period, survivors of brain tumours in childhood and adolescence exhibited a progressive decline in overall HRQL with important burdens of morbidity in numerous attributes, especially cognition. These findings identify the need for interventions to minimize these deteriorations in health.

P-070

Brain Tumours

A CROSS-SECTIONAL COHORT STUDY OF CEREBROVASCULAR DISEASE AFTER RADIATION THERAPY FOR CRANIOPHARYNGIOMA

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Objectives

To determine the prevalence and characteristics of cerebrovascular disease in craniopharyngioma patients treated with radiotherapy (RT).

Methods

Craniopharyngioma survivors, who were diagnosed at age ≤21 and treated with RT in British Columbia between 1971-2007, were eligible for the study. Of the 35 eligible patients, 20 patients were recruited to participate. Patients underwent a clinical assessment, blood work, and a magnetic resonance angiogram (MRA) if possible. Two patients had computed tomography angiograms (CTAs) because of metal implants that precluded them from MRAs. One patient exceeded equipment weight limitations and could not have imaging. Fasting lipid profiles were obtained on 18 patients, and fasting glucose or hemoglobin A1c tests on 20 patients.

Results

Median age was 10 years at diagnosis (range: 2-21) and 29 years at the time of the study (range: 17-62). Vascular abnormalities were detected in 6 of the 19 (32%) patients' angiograms. Five of 20 patients (25%) had a history of CVA, of whom 4 had abnormalities on angiogram, and the remaining patient was the one who could not be imaged. Two patients with no history of CVA had abnormalities on MRA. The remaining 13 patients had normal angiography and no history of CVA.

Table 1: Description of CVAs and MRA or CTA abnormalities

Patient Number	Type of previous CVA	Timing of CVA	Age at CVA (years)	Type of Imaging	MRA or CTA findings
1	Ischemic	Post-operative setting, before RT	10	MRA	Small supraclinoid right internal carotid artery (ICA) and M1 segment
2	Ischemic	7 years after RT	12	MRA	Irregularity and narrowing of the right middle cerebral artery
3	Ischemic	25 years after RT	38	MRA	Possible short segment stenosis of the right P1 segment
4	Hemorrhagic	2 years after RT	22	CTA	Stable clipped aneurysm, mature right anterior frontal lobe infarct, and mature small lacunar infarct
5	Ischemic	3 years after RT	15	None – could not be imaged due to weight	Not applicable (N/A)
6	None	N/A	N/A	MRA	Left ICA stenosis and a small left posterior cerebral artery
7	None	N/A	N/A	MRA	Cavernous malformation or a remote focus of hemorrhage in the periventricular white matter

At the time of the study, 12 of 18 (67%) patients had hyperlipidemia, 1 of 20 (5%) had diabetes, and 1 of 20 (5%) had pre-diabetes. Five patients (25%) had a body mass index (BMI) >30 and 8 patients (27%) had a BMI of 25-30.

Conclusions

Young patients treated with RT for craniopharyngioma have a high prevalence of hyperlipidemia, CVA, and cerebrovascular abnormalities on imaging. These patients should undergo careful monitoring and aggressive modification of stroke risk factors.

P-071

Brain Tumours

IMPACT OF AGE AT DIAGNOSIS ON OBESITY IN PEDIATRIC BRAIN TUMOR SURVIVORS

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Objectives

Obesity is a long-term morbidity for children diagnosed with CNS tumors. Body Mass Index (BMI) normally declines until the age of adiposity rebound (AR), after which it increases. Tumor location, radiation therapy, or surgery near the hypothalamus increases the risk of obesity. We hypothesized hypothalamic involvement would result in a greater BMI, and diagnosis/treatment before AR would lead to the greatest BMI.

Methods

Retrospective cohort of brain tumor survivors diagnosed from 2001-2011 at Children's Hospital of Wisconsin: chart review extracted BMI (recorded as BMI z-score) at diagnosis and two-year follow-up. Children were categorized into six groups, based on age at diagnosis and hypothalamic involvement (HI). Consistent with CDC growth curves, ages were classified as 'before AR' (0-41.99 months), 'during AR' (42-83.99 months) and 'after AR' (84.00 – 120 months old). BMI z-scores were compared using Wilcoxon signed ranks tests.

Results

116 children had two-year follow-up. BMI z score at diagnosis was similar across groups. Children pre-AR and post-AR with HI had higher two-year follow up BMI z scores than at diagnosis (before AR 0.466 to 1.589 p=0.004 N=12, after AR 0.519 to 1.268 p=0.001 N=18). No group without HI had increased BMI z score at two year follow up (before AR 0.663 to 0.518 N=24, during AR 0.279 to 0.278 N=18, after AR 0.658 to 0.793 N=24). The before AR and during AR cohort with HI had a higher BMI z score at two-year follow up then those without HI (p=0.004 and 0.015). The after AR cohort did not significantly differ from those without HI at two-year follow up.

Conclusions

Children with CNS tumors with hypothalamic involvement have increased BMI compared to those without hypothalamic involvement. Diagnosis before adiposity rebound is associated with a greater BMI than diagnosis at later age. Future studies can help elucidate the endocrine causes of these changes.

P-072

Brain Tumours

ASSESSING THE ACCURACY OF DEATH RECORDS AND PRE-MORTEM CLINICAL DIAGNOSES: A RETROSPECTIVE CHART REVIEW OF DECEASED CHILDREN DIAGNOSED WITH BRAIN TUMOURS IN BRITISH COLUMBIA, CANADA

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Objectives

Despite advances in diagnostic and imaging techniques, disparities exist between pre-mortem and post-mortem diagnoses. To the best of our knowledge, there are currently no studies investigating the relationship of pre-mortem diagnoses with post-mortem autopsy findings in children diagnosed with a pediatric brain tumour (PBT). The purpose of this study was to determine whether discrepancies exist in pre-mortem diagnoses and provincial cancer registry death records when compared to post-mortem autopsy findings in deceased children diagnosed with a PBT.

Methods

A retrospective review of medical records and autopsy reports of all deceased children (0-14 years) diagnosed with PBT in British Columbia, Canada who had an autopsy from 1980 to 2012 was performed. Pre-mortem diagnoses were compared to post-mortem diagnoses and classified based on major or minor discrepancies according to the Goldman criteria and concordance.

Results

In total 238 deaths occurred during the study period, of which 33 (13.9%) had autopsies. Of the 33 patients that had autopsies, 24 patients had an autopsy available for review. Analysis of pre-mortem and post-mortem clinical diagnoses in these 24 cases, revealed 5 (20.8%) had minor discrepancies, 9 (37.5%) had major discrepancies, and 10 (41.7%) had no discrepancies. Analysis of cause of death from the British Columbia Cancer Registry and post-mortem autopsy findings determined 13 (54.2%) cases were discordant, 9 (37.5%) were concordant, and 2 (8.3%) could not be determined due to missing cause of death information

Conclusions

In deceased children diagnosed with a PBT who had an autopsy, there were discrepancies between pre-mortem and post-mortem findings in a significant proportion of cases. Autopsies provide valuable information that serves to educate clinicians and are an invaluable tool for providing feedback regarding the accuracy of diagnostics and appropriateness of patient management. A very small proportion of deceased PBT patients have autopsies and efforts should be made to increase this number.

P-073

Brain Tumours

AVOIDING DELAYS IN THE DIAGNOSIS OF UK PAEDIATRIC CNS TUMOUR PATIENTS: A RETROSPECTIVE MULTICENTRE AUDIT OF THE SOUTH WEST REGION

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Objectives

Prompt recognition of paediatric central nervous system (CNS) tumours is uncommon in the United Kingdom (UK). The median symptom interval (SI) - from first symptom onset to diagnosis - has been measured at 3.3 months, comparing poorly with similar nations. This retrospective multicentre audit aimed to establish the common clinical presentation with the SI achieved most recently in the South West region, outlining strategies to limit systematic delays.

Methods

From 15 hospitals, 131 paediatric patients newly diagnosed with a primary CNS tumour between 01 January 2006 and 01 November 2012 were identified. On approval from the local review board, the following data were retrieved from clinical notes: date of birth, gender, ethnicity, social deprivation, age at symptom onset and diagnosis, clinical features at onset and diagnosis, date and location of first presentation, date and modality of first imaging, tumour pathology, tumour grade, tumour location and available referral pathway data until treatment.

Results

Regardless of tumour pathology, grade or location, the most common features at onset were: headache, motor system abnormalities, nausea and/or vomiting and seizures. At diagnosis, these were: visual system abnormalities, motor system abnormalities, headache, nausea and/or vomiting and behavioural change. Signs and symptoms increased from a median of 1 at onset to a median of 4 at diagnosis. Median SI was 3.3 months. High-grade tumours were significantly associated with a reduced SI ($p=0.005$). There was no significant association between SI and patient gender, social deprivation or first presentation in the community or in hospital.

Conclusions

Visual and motor system abnormalities and behavioural change commonly emerged during the SI; typically bilateral papilloedema, diplopia, reduced visual acuity, reduced coordination and new onset lethargy. These features, within an otherwise non-specific symptom profile, should prompt urgent clinical reassessment. SI was consistent with reports from other regions. Measures to restrict SI in the UK are recommended.

P-074

Brain Tumours

COMBAT (COMBINED ORAL METRONOMIC BIODIFFERENTIATING ANTIANGIOGENIC TREATMENT) THERAPY IN POOR PROGNOSIS PEDIATRIC MALIGNANT BRAIN TUMORS-IS THERE A ROLE?

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Objectives

The outcome of children with recurrent/high risk malignant brain tumors continues to be poor with conventional modalities of therapy. Metronomic therapy (COMBAT) has been found to be beneficial in many disseminated and aggressive pediatric solid tumors. We evaluated the impact (efficacy and toxicity) of this strategy in children with poor prognosis malignant brain tumors.

Methods

Children deemed to have a poor risk malignant brain tumor (by histology, site, metastatic status) were started on COMBAT regimen after completion of conventional therapy. Relapsed high grade tumors were also included. The treatment strategy consisted of the COMBAT regimen which includes low dose temozolomide, etoposide, sodium valproate and 13-cisretinoic acid administered in 12-weekly cycles. All children were followed up at 3 monthly intervals with clinical evaluation and MR imaging.

Results

Thirty four children were started on COMBAT therapy between the year 2010-2013 and 32 were available for evaluation. The median age of the study population is 10 years with a male:female ratio being 2:1. Among the 32 patients, 13(40.6%) had relapsed/progressive medulloblastoma, 7(21.9%) had metastatic/recurrent PNET(supratentorial), 7(21.9%) had recurrent anaplastic ependymoma and 5(15.6%) were diagnosed with diffuse pontine glioma. 23/32 (71%) of patients showed a response(SD/PR/CR) to therapy while 9(28%) of patients continued to progress with no response documented. Toxicity included grade III/IV cytopenia in 2 patients and 1 patient developed myelodysplastic syndrome. Isotretinoin skin toxicity was noted in majority and was manageable with topical interventions. In the final analysis 62.5%(20) of patients had progressed with median time to progression being 9 months (2-44 months) while 37.5%(12) patients had shown a positive sustained response.

Conclusions

COMBAT regimen is a feasible, well tolerated and effective treatment option for children with high risk or metastatic brain tumours. The data is a retrospective analysis and hence a prospective study to evaluate this strategy systematically is warranted.

P-075

Brain Tumours

TUMOR CELLS IN THE CEREBROSPINAL FLUID IN LOW GRADE CHOROID PLEXUS TUMOR: DO NOT OVERTREAT!

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Objectives

Cytomorphology of cerebrospinal fluid (CSF) remains essential for treatment stratification in many embryonal brain tumors. However, incidence and significance of positive CSF in choroid plexus tumors (CPT) is not well understood. Therefore CSF was evaluated in the CPT-SIOP-2000 study (01/2001-03/2010) and the CPT-SIOP registry (03/2010-04/2014).

Methods

Chart review and central review of cytology from lumbar and or ventricular CSF.

Results

Cytospin preparations of 18 patients (7 males, 11 females; median age at diagnosis 0.55 years) with low grade CPT (choroid plexus papilloma [CPP], n=9; atypical choroid plexus papilloma [APP], n=9) were positive (n=13) or highly suspicious (n=5) for tumor cells. Positive CSF was detected for a median of 17 days after tumor resection (range from pre-operative day -1 to post-operative day 288). Complete resection of the primary tumor was achieved in all patients. MRI showed leptomeningeal dissemination in 3/12 patients. No patient was irradiated. Nine patients were observed, nine patients diagnosed before 2011 received a mean of six chemotherapy cycles: Two patients with APP and postoperative residual tumor, one patient with primarily unresectable CPP, three patients with positive CSF, three patients prior to down-grading from CPC to APP or CPP by reference histology; one patient with APP was treated by systemic and intrathecal chemotherapy because of M1 stage. All patients are alive without relapse or progression at a median of 5.4 years.

Conclusions

Cytomorphological examination of CSF is required for complete staging of CPT. Differentiation between plexus papilloma cells and normal choroid plexus or ependymal cells can be challenging. Persistence of tumor cells longer than 14 day after tumor resection can be an innocuous finding in low grade CPT and may reflect the unique properties of cells derived from the choroid plexus. Deferral of chemotherapy is justified for CPP and completely resected APP with positive CSF cytology.

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P-076

Brain Tumours

DECREASED MORBIDITY AND MORTALITY OF POST-INDUCTION MARROW-ABLATIVE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOETIC RESCUE FOR CHILDREN WITH NEWLY-DIAGNOSED MALIGNANT BRAIN TUMORS: THE "HEAD START" CONSORTIUM TRIALS, 1991-2009

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Objectives

Since 1991, three sequential prospective multi-national clinical trials (including 39 participating institutions) have been conducted by the 'Head Start' Consortium for young children newly-diagnosed with malignant brain tumors, to improve their cure rate and quality of survival through avoidance (

Methods

Overall treatment design has remained unchanged throughout the 3 prospective trials, and has been previously reported; five 21-28 day cycles of induction chemotherapy [cisplatin, vincristine, cyclophosphamide, etoposide (HSI) with/without high-dose methotrexate (HSII-III), oral etoposide and oral temozolomide (HSIII)] were followed – for patients with minimal residual, non-progressive tumor - by a single marrow-ablative cycle with thiotepa and etoposide days -5 to -3, preceded by carboplatin days -8 to -6. Bone Marrow (HSI) or leukapheresed peripheral hematopoietic cells under Neupogen stimulation (HSII-III) were obtained following recovery from the first and/or second induction cycles. Radiotherapy was reserved for patients with residual tumor following completion of induction or >6yo.

Results

A total of 226 children were enrolled on 3 consecutive HS trials with primary malignant brain or spinal cord tumors *and* underwent marrow-ablative chemotherapy, the 100 day toxic mortality for whom steadily declined from HSI (3/47=6.4%) through HSII (1/48=2.1%) to HSIII (1/131 = 0.8%). Grade IV transplant-related oropharyngeal mucositis/stomatitis/pain declined from 14.9% (HSI) to 5.3% (HSIII) and grade IV infection declined from 8.5% (HSI) to 0.8% (HSIII).

Conclusions

Increasing experience with the marrow-ablative chemotherapy regimen, combined with improved leukapheresis and post-reinfusion supportive care techniques, have likely contributed to the steady decline in transplant-related morbidity and mortality in this patient population, contributing towards improved overall survival.

P-077

Brain Tumours

MANAGEMENT OF PEDIATRIC BRAIN TUMORS: REPORT FROM THE MOROCCAN SOCIETY OF PEDIATRIC HEMATOLOGY AND ONCOLOGY

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Objectives

Brain tumors (BT) are the most frequent solid tumor in children, but information about its management in low income countries is lacking.

Methods

A national multidisciplinary group for children with BT was implemented on February 2011 in Morocco to improve communication among healthcare providers, develop adapted protocols, decrease referral time and treatment delays, and improving data collection. The group included the four pediatric oncology centers of Morocco (Rabat, Marrakech, Fez and Casablanca) and international experts from ST Jude Children Research Hospital and Sick Children Hospital in Toronto. E-mail communications and online meetings via www.cure4kids.org web site were used to discuss patient care, develop protocols, administrative issues, and plan two brain tumors workshops in Morocco.

Results

From January 2012 till December 2013, data on 84 pediatric BT cases from 3 centers estimated to treat 75% of all pediatric cancers in Morocco were available. These 84 cases represent approximately 5% (range, 2% - 7.5%) of all pediatric cancers treated at these three centers for the study period. The male/female ratio was 1.1 and median age 7 years (range, 4 months - 16 years). 53/63 patients had fossa posterior lesions. The histological types according to WHO 2007 classification were reported for 75 patients (30 astrocytoma, 29 medulloblastoma/PNET, 12 ependymoma, 2 plexus choroid carcinoma, one pineoblastoma and one oligodendroglial tumor). Follow up data were available for 66 patients: 7 were alive in complete remission, 31 alive with residual disease 2 had progressive disease, 12 died. Status was unknown for 14 (7 Lost of follow up, 5 abandonment, 2 referral abroad).

Conclusions

Low accrual rate, poor survival, and abandonment are still major obstacles facing BT management in Morocco. We hope that the national BT group, the multidisciplinary approach and collaboration with international experts will overcome such obstacles.

P-078

Brain Tumours

CAN-COL-BRAIN-KIDS: WORK IN PROGRESS...WHAT HAVE WE LEARNED?

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Objectives

A collaboration between Canada and Colombia to improve the management of Central Nervous System (CNS) tumors was started at the beginning of 2013. Colombia, a middle-income country, has an estimated 400 brain tumors diagnosed per year. Health insurance is the individual's responsibility in most cases, which brings intrinsic challenges to the timely diagnosis and treatment of brain tumors.

Methods

A monthly teleconference tumor board using the cure4kids platform has been held since March 2013. The only requirement is a computer with internet access in each participating center.

Results

Over the last 12 months 9 tumor boards have been held and 25 cases have been reviewed with an average of 2.7 cases per session. The average number of attendees was 11. Up to 5 centers have been present for the tumor boards with 2 centers present at all 9 sessions held. Centers in multiple cities in Colombia (Bogota, Cartagena and Neiva) have participated. Diagnoses reviewed included Low-grade astrocytomas (8), medulloblastoma (4), ependymomas (3), PNETs (3), CNS Sarcomas (2) and others (5). Some areas of improvement have been identified. It is not uncommon to identify delays in referral to a tertiary center for adjuvant treatment after initial surgical intervention. Unfortunately, administrative healthcare issues negatively impact the timely management of patients with brain tumors; delays in the acquisition of appropriate imaging for intervention or follow-up are frequent. No national guidelines for management have been developed.

Conclusions

A collaboration project has been established and needs widespread participation of multiple centers for appropriate impact. Development of national and institutional treatment guidelines are crucial to improving timely work-up, treatment and follow-up. Guideline development will be a priority moving forward in the management of CNS tumors in Colombia.

P-079

Brain Tumours

METASTATIC RHABDOID PAPILLARY MENINGIOMA WITH BRAF V600E MUTATION AND GOOD RESPONSE TO PERSONALIZED THERAPY

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Objectives

Papillary rhabdoid meningioma is an agressive histological variant of meningioma which accounts for 1-2.5% of all meningiomas. The clinical course is very agressive and in most of the time the disease disseminates through the CSF after frequent local recurrences.

Methods

We describe the case of a 6 years old girl with a history of headache, phonophobia and photophobia. Brain MRI demonstrated a right temporal extra-axial tumor. Frontotemporal craniotomy was performed with tumor macroscopic excision. Histopathological examination demonstrated the diagnosis of papillary rhabdoid meningioma. Spine MRI and CSF cytology excluded metastasis; external involved-field radiation therapy was delivered (5400 cGy). Three months later, she developed recurrent headache with photophobia, CNS imaging revealed massive right hemisphere recurrence with leptomeningeal spread. The child's neurological status deteriorated rapidly with left hemiplegia, anisocoria and grade II coma despite urgent craniospinal irradiation.

Results

A specimen from the tumor was sent for comprehensive genomic profiling. The assay revealed activating BRAF mutation (V600E). Therapy with a BRAF inhibitor (Dabrafenib) was initiated at a dose of 30 mg bid for one month and then 35 mg bid. The clinical condition of the child improved progressively and 6 months later, she started to walk without any help. We added a MEK inhibitor (Trametinib) at a dose of 0.45 mg daily and then 0.9 mg according to PK values.

Our patient, one year from the start of targeted therapy is now going school with complete recuperation of the right hemiplegy and normal neurological functions.

Conclusions

An effective strategy to build upon the successes seen with Dabrafenib and Trabetinib monotherapies in melanoma has been to combine these agents with the goal of further improving response rates and delaying resistance. The role of BRAF rearrangements and tailoring therapies for pediatric malignancies needs further researches in a larger pediatric population.

Conflict of interest

P-080

Brain Tumours

NEUROCYTOMA: THE CLEVELAND CLINIC EXPERIENCE

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Objectives

Neurocytoma is an uncommon tumor and the need for postoperative therapy is controversial. We reviewed the Cleveland Clinic experience.

Methods

Patients with histologic diagnosis of neurocytoma between 1994 and 2011 were identified through an IRB-approved database. Clinical, tumor, and treatment factors were evaluated. Survival times were calculated using the Kaplan-Meier method.

Results

Seventeen patients with neurocytoma were treated, age at diagnosis 16.8 - 66.8 years; (median 35.3 years). Thirteen patients were male, all were Caucasian. Most common presenting symptoms: headaches (n=12) and gait disturbance (n=3). Sixteen patients had intraventricular lesions. All patients underwent surgery (gross total resection, GTR: 5, subtotal resection, STR: 10). Three patients (2 with STR and 1 with a biopsy) underwent adjuvant radiation; 2 with fractionated RT and one with stereotactic radiosurgery. Median event free survival (EFS) was 6.3 years and the projected 10 year EFS was 23%. Overall survival (OS) was 92%. The degree of resection did not correlate with EFS. After median follow-up of 8.4 years, 5 patients are without evidence of disease, 4 of which had developed recurrent disease and subsequently underwent GTR. Patients treated with adjuvant radiation did not experience disease recurrence (n=3). Twelve patients had Ki-67 results available from diagnosis (median 1.3 %,), 4 had Ki-67 results at recurrence which was invariably higher than at presentation (median 10.5%) Ki-67 was not predictive for EFS or OS.

Conclusions

In this cohort of patients, median EFS was only 6.3 years, and suggested a possible benefit to adjuvant radiotherapy in select cases. The excellent OS of 94% suggests that these patients benefit from salvage therapy with a combination of surgery and radiation. Prospective and molecular analyses of these tumors may identify risk factors for disease recurrence and help determine who would benefit from more aggressive upfront therapy.

P-081

Brain Tumours

NO RADIATION FOR CHOROID PLEXUS CARCINOMA PATIENTS WITH LI-FRAUMENI SYNDROME?

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Objectives

Choroid plexus carcinomas (CPC's) are rare pediatric tumors often associated with Li-Fraumeni Syndrome (LFS), a germ line mutation in the TP53 tumor suppressor gene, predisposing to cancer. The standard of care is controversial. Some studies recommend radiation therapy as a treatment modality. We used a literature analysis to evaluate the hypothesis that radiation therapy should be avoided in patients with CPC and LFS.

Methods

Expanding a preexisting CPC literature database, we added all cases of CPC with LFS identified in PubMed through the end of 2013 and compared survival using Kaplan Meier curves and log rank tests. We restricted the analysis to CPC patients identified by the presence of TP53 dysfunction or phenotypic characteristics of LFS. We compared overall survival between patients who received radiation therapy and patients treated without radiation therapy.

Results

25 patients were documented with CPC and LFS. Ten of those had received radiation and fifteen did not receive radiation therapy. The median overall survival of all LFS CPC patients was 0.83 years $\pm$ 0.58 standard error. The survival of patients receiving radiation was inferior to those without radiation (mOS 3.25 years versus 0.16). Kaplan Meier curves did not cross and the log rank tests suggested the difference to be statistically significant (p=0.04).

Conclusions

Different from previous analyses we find a survival disadvantage for patients with LFS and CPC, who received radiation versus those that did not. This does not simply suggest that radiation shortened the lives of these patients, since the chemotherapy was very different in the two patient groups. However, the finding does provide evidence to pursue treatment approaches that do not include radiation in these patients and to continue developing them.

P-082

Brain Tumours

A NATIONAL BRAIN TUMOUR CONSORTIUM- THE CANADIAN PAEDIATRIC EXPERIENCE 2002-2014

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Objectives

In 2003 Canadian paediatric oncologists recognized the benefit to establish protocols for central nervous system (CNS) tumours where no open international studies were available. This spearheaded the formation of the Canadian Paediatric Brain Tumour Consortium (CPBTC). CPBTC included all 17 Paediatric oncology centers in Canada in the development and collaborative conduct of clinical and pre-clinical studies aimed at improving knowledge of brain tumours, developing more effective therapies and maximizing quality of life. It was also established to foster research, support and encourage young investigators. We reviewed the development, challenges and successes of the group over the past 12 years.

Methods

The CPBTC meetings, minutes and publications were reviewed.

Results

The first CPBTC teleconference was held in November 2002 with 5 centers in attendance. The number of centers participating in the teleconferences peaked at 15 in February 2004. The collaborative studies faced challenges with multiple ethics review board submissions and development of contracts between institutions. Funding was limited and allocated preferentially to pathology reviews and data collection. The Principal Investigators of active studies were representative of the 17 participating centers. There have been 20 publications, 6 abstracts at international meetings, 3 completed clinical trials and 4 prospective research papers with consortium collaboration. A neuro-oncology handbook is in press. Participation in the consortium is comprehensive, reflecting the multidisciplinary approach in managing paediatric brain tumour patients. Preclinical and clinical studies complement Children's Oncology Group (COG), International Society of Paediatric Oncology (SIOP) and other cooperative group trials.

Conclusions

The CPBTC has facilitated the completion of several nationally based projects and is recognized as a vehicle for collaborative research. Future goals include the development of a national virtual tumour bank, advocacy for a Canadian national ethics review board, academic recognition of participation and contribution, and a website. Success in grant applications will be key to funding future collaboration.

P-083

Brain Tumours

THE USE OF POSITRON EMISSION TOMOGRAPHY IN PAEDIATRIC BRAIN TUMOURS

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Objective:

Magnetic resonance imaging is conventionally used to image central nervous system (CNS) tumours. There are significant limitations in evaluating response to treatment with MR imaging, and positron emission tomography (PET) is now widely utilised in imaging cancers. However, ^{18}F-fluoro-deoxy-glucose (FDG) - the main tracer in clinical use - is unsuitable for brain imaging as glucose is the primary substrate for brain metabolism. We investigated whether simultaneous ^{18}F-fluoroethylcholine (FECH) PET/MRI with functional semi-quantitative parameters; Maximal **S**tandardized **U**ptake **V**alue (SUVmax/mean) and **A**pparent **D**iffusion **C**oefficient (ADC) max and mean is a viable option for diagnosis, and treatment response assessment, in children with histologically confirmed astrocytic tumours.

Methods:

Eleven patients with biopsy proven astrocytomas were injected with 250 MBq 18 F-Choline. Imaging was performed 40 minutes later using a hybrid PET/MRI scanner. PET data were acquired simultaneously with MR sequences. SUVmax and SUVmean and ADC max and mean of the whole tumoural Region of Interest were recorded.

Results:

At baseline the areas of ^{18}F-choline up-take matched areas of contrast enhancement and restricted diffusion. There was a negative correlation trend between SUV_{max} and ADC_{mean}, and a positive correlation trend between SUV_{max} and tumour size. There was concordance between reduction in tumour size and reductions in SUV_{max} and SUV_{mean} in four children, in three of whom, ADC_{mean} values were increased. In two patients, although anatomical tumour size remained stable, SUV_{max} and SUVmean values were increased and there was a reduction in the ADC_{mean} values. Additionally, in two children cross-sectional MRI showed an increase both in tumour size as well as increased SUV_{max} but a reduction in ADC values.

Conclusion:

The results suggest that fluoroethylcholine PET combined with functional MRI has a high degree of sensitivity and specificity, and may be a better tool for response assessment when compared to conventional cross sectional MRI alone.

Document not received

P-084

CNS/Brain

MULTI-SEGMENTS INTRAMEDULLARY SPINAL CORD TUMORS IN ADOLESCENT PATIENTS

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Objectives

To prospectively analyze the clinical features and characteristics of multi-segments intramedullary spinal cord tumors in adolescent patients.

Methods

In our study, 30 consecutive adolescent patients with multi-segments intramedullary spinal cord tumors were recruited, who underwent microsurgery for the tumor using a posterior approach and were hospitalized in Peking University Third Hospital within a period of 10 years. The tumor was exposed through dorsal myelotomy. Preoperative and postoperative neurological functions were scored using the Improved JOA (IJOA) grading system. The functional outcome was defined as postoperative IJOA score minus preoperative IJOA score. All the patients were followed-up until Jan. 30, 2014.

Results

There were 20 male and 15 female adolescent patients younger than 25 years. Their mean age was (15.3±6.83) years. The most common initial symptom was sensory disturbance (including pain and/or numbness, 51.4%, 18/35), followed by motor disturbance (including limbs weakness and gait deterioration, 25.7%, 9/35), pain and motor disturbance (22.9%, 8/35), as well as fever, limbs deformities, and sphincter dysfunction, respectively. The preoperative IJOA scores of the patients were (14.4±3.38). The postoperative IJOA scores of the patients were (15.5±3.31). The most commonly involved location was the cervicothoracic segments (37.1%, 13/35), followed by the conus terminalis (25.7%, 9/35), the cervical region(17.1%, 6/35), the thoracic region (14.3%, 5/35),and the lumbus region (5.7%, 2/35). The average involved segments were (4.4±1.38). The most frequent tumors were neurodevelopmental tumors (including lipoma, epidermoid cyst and teratoma) (34.3%, 12/35), followed by astrocytomas (28.6%, 10/35),ependymomas (20%, 7/35), hemangioblastomas (11.4%, 4/35), and glioblastomas and schwannomas, respectively.

Conclusions

In adolescent patients with multi-segments intramedullary spinal cord tumors, the most commonly involved locations are the cervicothoracic segments and the conus terminalis, while the most frequent tumors are neurodevelopmental tumors and astrocytomas. Good prognosis in adolescent patients is observed in a long-term follow-up.

P-085

CNS/Brain

CHILDHOOD MALIGNANT DISEASES ASSOCIATED WITH NEUROFIBROMATOSIS TYPE 1: HACETTEPE EXPERIENCE

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Objectives

To evaluate clinical characteristics and prognosis of patients with NF 1 and malignancy excluding optic glioma.

Methods

Between 1975 and 2013, 92 of 473 patients (19%) with NF 1 who were followed up at our center were found to have malignant disease. 67 (14%) of them had optic glioma and in 25 (5%) of them there were other malignant disorders. Files of these 25 patients were analyzed retrospectively in terms of clinical features and treatment results.

Results

The male to female ratio of these 25 patients was 16/9. The age of diagnosis of NF 1 was between 3 months-16 years (median 5.5 years) and diagnosis of malignancy at age between was 1.5 - 33 years (median 8), respectively. Sixteen patients were diagnosed with NF1 and malignancy simultaneously. Histological subtypes were 12 soft tissue tumors (6 malignant peripheral nerve sheath tumor (MPNST), five rhabdomyosarcoma and one malignant fibrous histiocytoma), 10 brain tumors (three grade 3-4 astrocytoma or glioblastoma, four astrocytoma, two medulloblastoma and one cervical pilocytic astrocytoma), two neuroblastoma and one non-Hodgkin's lymphoma. Disease was located in the posterior fossa in three patients with brain tumors. Three patients with high grade glioma, one with non-Hodgkin’s lymphoma, one with medulloblastoma, two with rhabdomyosarcoma, and one with astrocytoma have died with disease progression despite treatment. Five of 6 patients with a diagnosis of MPNST died with disease, one patient diagnosed at age 1.5 years is being followed up in remission during 32 months. Twelve out of 25 patients are still alive.

Conclusions

Five percent of the patients with NF1 have developed malignant diseases. The prognosis is poor despite the treatment. Close and regular follow-up is crucial for early detection of malignancy for NF 1.

P-086

Epidemiology

ESTIMATING THE INCIDENCE OF ACUTE LEUKEMIA IN CHILDREN IN WESTERN KENYA BY REVIEW OF MALARIA BLOOD SMEARS: A PILOT AND FEASIBILITY STUDY

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Objectives

A retrospective review of malaria slides was undertaken as an epidemiology study to estimate the incidence of acute leukemia in Kenya, and to determine the feasibility of utilizing malaria slides to improve detection of acute leukemia.

Methods

Over one year, 22,000 malaria slides were collected at Kitale District Hospital in Kenya for secondary review. A trained technologist performed the review of all slides. On first screening, potential positive slides were identified using the following criteria: (1) estimated white blood cell (WBC) count over 50,000/mm3 or (2) Less than 10% neutrophils seen on the blood smear. Once identified, two authors reviewed and photographed each of the positive slides. 100 cell count differentials were done on each of the positive slides, and clinical data about the slides were obtained from hospital records.

Results

299 slides were identified as showing signs of possible leukemia, including leukocytosis or severe neutropenia. On further review of slides and clinical data, 9 slides showed a combination of findings making them highly probable as indicating leukemia. Of the slides not showing definitive signs of leukemia, many (~25%) had neutrophilia suggesting acute infection. Other slides with neutropenia were from infants, under one year of age with malaria. A third group of slides were screened as showing neutropenia, but on review, the neutrophils were distorted such that neutropenia was not present.

Conclusions

This study demonstrates the feasibility of using a slide made to screen for malaria, to also screen for leukemia. Based on the numbers of likely positive slides we identified, our estimate of the incidence of acute leukemia, 4.2 cases/100,000 children/year, is similar to that in high-income countries. We are planning a prospective trial to screen slides and identify patients for earlier referral for diagnosis and treatment.

Acknowledgements: supported by Alex's Lemonade Stand Foundation.

P-087

Epidemiology

THE LANDSCAPE OF PEDIATRIC, ADOLESCENT AND YOUNG ADULT THYROID CANCER IN ONTARIO: 1992-2010

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Objectives

To describe the current landscape of Thyroid Carcinoma (TC) diagnoses and demographics in Ontario among children, adolescents and young adults over an eighteen year period.

Methods

A retrospective cohort was assembled from data extracted from the provincial cancer registry and administrative health-care databases. Direct age-adjusted incidence rates were calculated.

Results

A total of 2,552 children and youth less than 30 years of age were diagnosed with thyroid cancer between 1992 and 2010 in the province of Ontario, Canada. The overall age-adjusted thyroid cancer incidence rate per 100,000 increased from 2.00 [95% CI 1.80-2.22] in 1992-1995 to 4.10 [95% CI 3.84-4.36] in 2006-2010. The sex specific age-adjusted incidence rate of TC between 1992-1995 and 2006-2010 has nearly doubled for both females and males: 3.23 [95% CI 2.85-3.60] to 6.77 [95% CI 6.29-7.25] and 0.81 [95% CI 0.63-0.99] to 1.42 [95% CI 1.21-3.65], respectively. The most common histologic types are papillary-93.4% (including the follicular variant-28.9%), follicular-4.6%, and medullary-1.9%. There were no documented cases of anaplastic thyroid carcinoma in this cohort. TC was a second primary malignancy for 47 individuals, and of those patients that had a primary thyroid cancer, 22 developed a subsequent malignant neoplasm. The majority of all TC cases (92%) resided in urban area, and there were 12 deaths among all diagnosed TC cases during this period.

Conclusions

As reported in other populations, there is a rising incidence in TC diagnoses over time, though the extent of this increase appears more limited than elsewhere. Explanation for this rising incidence, as well as the observed association with multiple primary malignancies and well as long-term outcomes merit further investigation

P-088

Epidemiology

CHILDHOOD LEUKEMIA INCIDENCE AND SURVIVAL IN SOUTHERN THAILAND FROM 1989-2011

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Objectives

Disparities exist in childhood leukemia detection, diagnosis and treatment between developing and developed countries. We analyzed childhood acute myeloid (AML) and acute lymphoblastic (ALL) leukemia incidence and survival trends from 1989-2011 in Songkhla, Thailand. For a point of reference, we compared these results to childhood leukemia incidence in the United States (US) using Surveillance, Epidemiology, and End Results (SEER) data.

Methods

Using population-based registry data from Songkhla, 324 cases of leukemia were diagnosed in children age 0-19 from 1989-2011. Among those, 87% had vital status and follow-up time. Leukemia subgroups were classified using International Classification of Childhood Cancer definitions. SEER data was obtained from SEER*Stat. Age-adjusted two-year incidences were computed and standardized using WHO 2000 standard population. Incidence trends were analyzed using joinpoint regression. Percent survival was computed for 1,3, and 5 years for each year of diagnosis from 1989-2006 and analyzed using univariate linear regression.

Results

AML and ALL composed 22% and 56% of leukemia cases from Songkhla, respectively. The overall age-adjusted incidence of ALL and AML was 1.85 and 0.70 cases per 100,000, respectively. ALL incidence increased 1.3% per year in Songkhla (p=.057), but was lower compared to the US (p=.002) from 1989-2010. AML incidence increased 4.0% per year (p=.096) in Songhkla while it decreased 1.7% (p=.005) in the US from 1989-2010. AML incidence was higher in Songkhla compared to US (p=.034). In Songkhla, the median survival was 1.00 year for AML and 7.53 years for ALL. Five-year percent survival for ALL improved 2.2% annually (p=.022) from 40.0% in 1989 to 71.4% in 2006.

Conclusions

The incidence of leukemia is increasing in Songkhla. The proportion of AML cases is higher compared to the US. While survival is improving for ALL, it is lower than the US. These temporal changes in leukemia incidence and survival warrant investigating novel risk factors throughout Thailand.

P-089

Epidemiology

TRENDS IN HEPATOBLASTOMA INCIDENCE AMONG CHILDREN AND ADOLESCENTS IN THE UNITED STATES, 1999-2010: RACIAL AND ETHNIC DISPARITIES

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Objectives

Low birth weight (LBW) is associated with a high risk of developing hepatoblastoma. Prevalence of very low (VLBW) and LBW have significantly increased in the United States in the last decades, particularly among Hispanics, due to increased specialization in delivering pre-, peri- and neonatal health care. The aim of our study was to evaluate trends in hepatoblastoma incidence according to sex, race, and ethnicity.

Methods

We retrieved data from the National Program Cancer Registries (NPCR) database (49 states and the District of Columbia, 1999-2010). All children ages 0-19 years diagnosed with hepatoblastoma (ICCC group VIIa) were included in the study. Age-standardized incidence rates (ASIR) were calculated according to sex, race, and ethnicity using Segi population. Trends over time and average annual percent changes (AAPC) were assessed using Joinpoint Regression Model.

Results

1409 new hepatoblastoma cases were registered in the period Incidence was significantly higher among males (Rate Ratio=1.47, 95%CI 1.32-1.64). Highest and lowest incidence rates were observed among Asians (ASIR=2.42/million) and blacks (ASIR=1.18/million), respectively. Hispanics showed a higher incidence (ASIR=2.03/million) compared to non-Hispanics (ASIR=1.80/million), but difference was not statistically significant (RR=1.13, 95%CI 0.99-1.28). Overall, a significant increase in the incidence of hepatoblastoma was observed in the period 1999-2010 (AAPC=2.80, 95%CI 1.05-4.59). However, trend was statistically significant only for males (AAPC=4.11, 95%CI 1.72-6.55). Stratified analysis by ethnicity has shown a 2% per year increase for non-Hispanics (AAPC=1.96, 95%CI 0.49-3.46), while a larger increase has been observed for Hispanics, although not statistically significant (AAPC=4.39, 95%CI -0.42-9.43). The largest increasing trend in hepatoblastoma incidence was observed among Blacks (AAPC=6.04, 95%CI 0.11-12.32).

Conclusions

We have documented substantial differences in the incidence of hepatoblastoma among different ethnic and racial groups. Given the known correlation between hepatoblastoma and LBW, whether these differences represent ethnic and racial variations or barriers in prenatal and neonatal care needs to be determined.

P-090

Epidemiology

USE OF TREND ANALYSIS TO ILLUSTRATE RESIDUAL CANCER DISPARITIES IN SURVIVAL FROM CHILDHOOD NON-CNS EMBRYONAL TUMORS

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Objectives

Trends in survival from childhood non-CNS embryonal tumors have not been fully explored from the perspective of cancer disparities. In this study we aimed to assess these trends and identify residual disparities.

Methods

Cases of neuroblastoma, retinoblastoma, nephroblastoma, hepatoblastoma, rhabdomyosarcoma , and non-CNS germ cell tumors (GCT) among children 0-19 years old diagnosed 1/1/1993-12/31/2010 were retrieved from SEER-13 for data from 1993-1999 and SEER-18 for data from 2000-2010. Race/ethnicity categories included: White-non-Hispanic, Black-non-Hispanic, Hispanics, American Pacific Islander (API), and American Indian/Alaska Native. Three-year overall survival was obtained using the Kaplan Meier Methods. Annual percentage change (APC) was obtained using Jointpoint.

Results

Inclusion criteria retrieved 8,188 cases. Pairwise comparison between race/ethnicity categories for the most recent analyzable period (2005-2007) showed significant difference in 3-year survival only for neuroblastoma (Blacks vs. Whites 73% vs. 84%, p=0.035) and rhabdomyosarcoma (API vs. Whites 52% vs. 78%, p=0.025). Trend analysis for the cohort showed significant increase in APC for Whites (+0.43) and although positive, not significant for the other minorities (Hispanics +0.55, Blacks +0.22, API +0.06). Positive trends achieving significance were found in neuroblastoma for Whites (+1.26), Hispanics (+1.44) and API (+12.4 since 2003), but not for Blacks (-2.49). Hispanics with hepatoblastoma or nephroblastoma showed negative survival trends achieving significance (-2.66 and -0.82, respectively), while Whites showed significant improvement in survival for hepatoblastoma (+3.41), but not for nephroblastoma (+0.02). Relatively flat or converging trends were noted for retinoblastoma, rhabdomyosarcoma, and germ cell tumors. Possibly diverging trends were noted in neuroblastoma, nephroblastoma and hepatoblastoma.

Conclusions

Standard survival analysis using pairwise comparison of magnitude at a specific recent time interval would have missed the disparities identified. Although the number of cases is relatively low in pediatric oncology non-CNS solid tumors, trend analysis using Jointpoint allowed better illustration of possible residual pediatric cancer survival disparities.

P-091

Epidemiology

SPATIAL CLUSTERING OF CANCER IN CHILDREN AND YOUNG PEOPLE FROM NORTHERN ENGLAND

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Objectives

The aetiology of childhood cancer is not well understood. Both genetic and environmental factors are likely to be involved. 'Spatial clustering' occurs if the cases display an irregular geographical distribution, with a small numbers of localised areas with large excesses or a large number of areas with modest excesses. To assess whether localised environmental factors may play a role in aetiology we tested for spatial clustering of both address at birth and diagnosis using population-based data from northern England.

Methods

We extracted all 5612 cases of cancer diagnosed in children and young people aged 0-24 years during the period 1968-2003 from the Northern Region Young Persons' Malignant Disease Registry. This is a population-based registry and includes all cases of cancer in children and young adults who were resident at time of diagnosis in northern England (population aged 0-24 years = 898,000; area = 15727 km^2). Overall clustering analysis was performed using point process methods, testing the null hypothesis that disease risk does not vary spatially and cases occur independently. Kulldorff's scan statistic, based on a Bernoulli model was used to test for individual clusters.

Results

Based on both address at birth and diagnosis there was evidence of overall clustering for leukaemia, lymphomas, central nervous system (CNS) tumours, sympathetic nervous system tumours, retinoblastoma, germ cell tumours and carcinomas (all $P < 0.05$). Based on address at birth there was evidence of overall spatial clustering for soft tissue sarcomas ($P = 0.03$). Based on address at birth, Kulldorff's scan statistic detected individual spatial clusters for CNS, renal and bone tumours ($P < 0.05$). Based on address at diagnosis, there was an individual spatial cluster for all carcinomas ($P = 0.01$).

Conclusions

This study suggests that spatially varying environmental factors may be implicated in the aetiology of a number of different cancers.

P-092

Epidemiology

RACIAL AND ETHNIC DISPARITIES IN PEDIATRIC NON-CNS EMBRYONAL TUMORS INCIDENCE IN THE UNITED STATES: TRUE EFFECT OR CONFOUNDING BY SOCIOECONOMIC STATUS?

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Objectives

Racial and ethnic disparities in the incidence of non-CNS embryonal tumors have not been fully explored. Existing studies often address racial disparities, but fail to incorporate ethnicity or control for socioeconomic status (SES).

Methods

Cases of neuroblastoma, retinoblastoma, nephroblastoma , hepatoblastoma, rhabdomyosarcoma , and non-CNS germ cell tumors (GCT) among children 0-19 years old diagnosed 1/1/2000-12/31/2010 were retrieved from SEER-18 database. Race/ethnicity categories included: White-non-Hispanic, Black-non-Hispanic, Hispanics, American Pacific Islander (API), and American Indian/Alaska Native. Age-adjusted incidence rates and rate ratios (RR) were obtained. County data on poverty level was used to stratify analysis by SES.

Results

Hispanics presented a lower incidence of neuroblastoma compared to Whites (RR=0.53; p<0.001) and effect remained significant after adjusting for SES. Higher incidence of retinoblastoma was observed among Hispanics (RR=1.26; p=0.005) and for bilateral disease in particular (RR=1.4, p=0.02), but effect dissipated when controlling for SES. Compared to Whites, Hispanics (RR=0.80; p<0.001) and API (RR=0.43; p=0.001) had a lower risk of nephroblastoma, although for Hispanics association lost significance in the low SES group. Risk of hepatoblastoma was lower among Blacks (RR=0.44; p<0.001) and effect remained significant after adjusting for SES. Rhabdomyosarcoma incidence was lower among Hispanics (RR=0.85; p=0.02), but no effect was observed when controlling for SES. Incidence of GCT was higher among Hispanics (RR=1.30; p<0.001) and lower among Blacks (RR=0.52, p<0.001) and API (RR=0.79, p=0.003), but effects for Hispanics and API were modified by SES.

Conclusions

Ethnic disparities in the incidence of these tumors were documented using population-based data, particularly for neuroblastoma and hepatoblastoma. Effect modification or confounding by SES was observed in most subgroup analyses. Adequately controlling for SES is key when analyzing and interpreting racial and ethnic disparities in childhood embryonal tumors incidence.

P-093

Epidemiology

INFERIOR SURVIVAL AMONG ABORIGINAL CHILDREN WITH CANCER IN ONTARIO

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Objectives

Pediatric cancer distribution and outcomes have not been examined in Canadian Aboriginal children. Our objective was to describe the distribution, event-free survival and overall survival of Aboriginal children with malignancies that reside in Ontario compared with non-Aboriginal children.

Methods

This population-based study included 10,520 Ontario children (<18 years) with cancer diagnosed between 1985 and 2011. Cases were identified from the Pediatric Oncology Group of Ontario Networked Information System database. Aboriginal children were identified by self-reported ethnicity or postal code on Native reserve at diagnosis. Cases were presented with descriptive statistics and compared using the Fisher's exact test. Event-free and overall survival probabilities were calculated for Aboriginal and non-Aboriginal children, described with Kaplan-Meier curves and compared with log-rank tests.

Results

We identified 65 Aboriginal and 10,364 non-Aboriginal children with malignancy. Distribution of malignancy type was similar. There were no significant differences in baseline characteristics, presence of metastatic disease, or treatment approach (clinical trial, standard of care or individualized protocol) between the groups. Five-year event-free survival (± standard error) was 56.3±6.2% among Aboriginal children *vs.* 72.8±0.4% among non-Aboriginal children (P=0.0042), and 5-year overall survival was 64.0±6.0% *vs.* 79.3±0.4% (P=0.0017) respectively. Cause of death did not vary by Aboriginal ethnicity.

Conclusions

Survival was significantly inferior among Aboriginal children with cancer as compared to non-Aboriginal children with cancer Ontario. Future studies are required to define the etiology of this disparity, evaluate the issue nationally, and create interventions to improve outcomes for Aboriginal children.

P-094

Epidemiology

GENETIC SUSCEPTIBILITY TO LANGERHANS CELL HISTIOCYTOSIS: A PILOT GENOME-WIDE ASSOCIATION STUDY USING CASE-PARENT TRIADS

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Objectives

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by the accumulation of clonal CD207+ myeloid dendritic cells. LCH presents most commonly in infants and children. The incidence of LCH has been estimated to be two to ten cases per million in children 15 years of age or younger. In spite of the clinical complications associated with LCH, very little is known about genetic susceptibility to this condition. To further characterize germline genetic susceptibility to childhood LCH, we performed a preliminary genome-wide association study (GWAS) using case-parent triads.

Methods

A case-parent triad study design was utilized, which is robust to population stratification bias. The Baylor College of Medicine Institutional Review Board approved the study protocol, and informed consent was obtained from all participants. LCH cases and parents were recruited from Texas Children's Cancer Center. DNA samples on 69 case-parent triads were genotyped in the Laboratory for Translational Genomics at Baylor College of Medicine using the Illumina HumanOmni5-Quad BeadChip. Single nucleotide polymorphisms (SNPs) were excluded based on the following criteria: genotyping success rate $<10^{-6}$, and minor allele frequency http://www.biostat.harvard.edu/fbat/fbat.htm).

Results

After all exclusions, 1,702,122 SNPs were included in the association analysis. Eleven SNPs were identified with a p-value $^{-5}$. Three SNPs were identified with a p-value $^{-6}$. Specifically, intronic or intergenic SNPs on chromosome 12 ($p=3.5 \times 10^{-8}$); chromosome 10 ($p=4.7 \times 10^{-8}$); and chromosome 6 ($p=4.8 \times 10^{-7}$) were associated with LCH risk.

Conclusions

While our findings must be replicated in an independent population, they do suggest that inherited genetic variation may be relevant in susceptibility to LCH. We are currently expanding this study and have plans to validate our findings through expanded analyses and methodologies.

P-095

Epidemiology

A PRELIMINARY TRIO-BASED GENOME-WIDE ASSESSMENT OF MATERNAL GENETIC EFFECTS ON CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Recent evidence from genome-wide association studies (GWAS) suggests susceptibility to childhood acute lymphoblastic leukemia (ALL) is influenced by several genetic loci. While these studies have focused on the role of single nucleotide polymorphisms (SNPs) carried by affected individuals, other biological mechanisms may also be involved. As ALL may arise *in utero*, one such mechanism involves "maternal genetic effects." Specifically, variation in the maternal genome could affect the intrauterine environment essential to normal hematopoeisis. We therefore conducted a preliminary genome-wide assessment of maternal genetic effects and the risk of childhood ALL.

Methods

ALL cases and parents were recruited from the Texas Children's Cancer Center for the period 2009-2013. The Baylor College of Medicine Institutional Review Board approved the study protocol, and informed consent was obtained from all participants. DNA samples on 94 complete trios were genotyped using the Illumina HumanCore BeadChip. We applied log-linear models to investigate whether polymorphisms of maternal genes influence risk of ALL in cases.

Results

Three maternal SNPs were identified where the association was $p<5.0 \times 10^{-5}$. Specifically, maternal genotypes for *PPP1R12B* ($p=1.6 \times 10^{-9}$); *SYNE2* ($p=4.2 \times 10^{-5}$); and *TSC22D1* ($p=4.4 \times 10^{-5}$) were significantly associated with childhood ALL risk. These maternal genetic effects were independent of the respective genotypes of the child with ALL.

Conclusions

We completed a genome-wide evaluation of maternal genetic effects on leukemia risk. We were able to identify SNPs with significant effects in three genes that have been implicated in diverse physiology including previous GWAS of obesity-related and cardiovascular traits (*PPP1R12B* and *SYNE2*), transmission of alleles from fathers (*PPP1R12B*), and tumor suppression (*TSC22D1*). While our findings must be validated, they do suggest that maternal genetic effects may be relevant in ALL risk.

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P-096

Epidemiology

IMPROVEMENT OF ABANDONMENT AND REFUSAL OF THERAPY IN PEDIATRIC PATIENTS WITH CANCER IN GUATEMALA AT UNIDAD NACIONAL DE ONCOLOGÍA PEDIÁTRICA (UNOP)

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Objectives

Abandonment of cancer therapy is a major cause of therapeutic failure. Historically, Guatemala had a very high rate of abandonment, up to 42% in 1999. This study examines the rate of abandonment over time in Guatemalan children and identifies the factors associated with increased risk of abandonment.

Methods

A retrospective study of children with cancer, ages 0-18 seen at UNOP, of Guatemala from 2001-2008 was performed. Patient data collected from the Pediatric Oncology Networked Database was analyzed for 3 years after starting therapy. Abandonment was defined as a lapse of 4 weeks in planned treatment. Refusal was defined as failure to begin treatment. Cox proportional hazards analysis identified the effect of age, sex, year of diagnosis, distance, ethnicity, and principal diagnosis on abandonment of therapy. Outcome measures were abandonment and refusal.

Results

1789 charts were analyzed. 234 abandoned and 133 refused therapy. Over time, the rate of abandonment/refusal decreased from 21% in 2001 to 3.5% in 2008. Greater distance to the center ($p = 0.000$), younger age ($p = 0.017$) and earlier year of diagnosis ($p = 0.000$) were associated with increased risk of abandonment or refusal. Indigenous ethnicity ($p = 0.002$) was additionally associated with increased risk of abandonment. Sex and cancer diagnosis were not significant**.** Abandonment of therapy correlates with decreased survival in those patients with known outcomes; the cumulative survival at 5 years was 0.20±0.03 (survival±SE) for those that abandoned vs 0.59±0.01 for those that completed therapy.

Conclusions

Abandonment of therapy has decreased over time in Guatemala; and corresponds with the establishment of UNOP, a centralized pediatric cancer treatment center in 2000; and the creation of a psychosocial team in 2005 to target families at risk of abandonment. Research is needed to further investigate the effect of socioeconomic factors and targeted interventions on abandonment.

P-097

Epidemiology

SURVIVAL GAP FOR CHILDREN WITH CANCER IN A MIDDLE- INCOME COUNTRY: LESSONS FROM KING HUSSEIN CANCER CENTER IN JORDAN

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Objectives

With heterogeneity in the outcome of children with cancer around the world. A standardized method to compare outcome of children with cancer is needed. We used an open access database and compared survival of children at our center.

Methods

Our department used the Pediatric Oncology Network Database (POND) to register patients since Jun2006. Data collected included demographics, pathology, staging, risk stratification, major toxicities and outcome. We compared the distribution of cases and outcome registered from Jun2006 till Dec2013 to data obtained from the SEER database from Jan2006 till Dec2010.

Results

We compared 1721 patients registered in POND to 17505 patients registered in SEER. The mean age for the 2 groups were 7.4 and 8.2 years, respectively (P<.001). Diagnosis distribution was similar but with higher percentages of patients with bone tumors and retinoblastoma at our center. There was a significantly better survival in SEER patients when compared to our population (SEER 3-yr OS=85±0.33% vs. POND 3-yr OS=75±1.3%, P<.001). When analysis was restricted to specific diseases, survival of patients with ALL and lymphoma was similar to that recorded in the SEER (P,0.59 and 0.86; respectively). On the other hand, patients with AML, solid tumors, CNS tumors and retinoblastoma had worse outcome in our population. Among our patients, outcome of Jordanian was superior to that of Non-Jordanians, particularly in patients with solid tumors. When compared to previous reports from our center, we noticed previous publication bias in medulloblastoma and rhabdomyosarcoma but not in ALL and retinoblastoma.

Conclusions

We used a combination of prospective databases to calculate survival gap in our population. Further analysis is needed to study the reasons for this difference, particularly in patients with solid tumors and brain tumors. This could reflect different referral patterns and variations in management. The proposed method can be easily used in other centers to calculate survival gap accurately.

P-098

Epidemiology

ESTABLISHING THE INCIDENCE AND CHARACTERISTICS OF SYMPTOMATIC VENOUS THROMBOTIC EVENTS IN PEDIATRIC ONCOLOGY PATIENTS IN THE MARITIMES, CANADA: A POPULATION BASED STUDY

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Objectives

Venous thrombotic events (VTE) are recognized as an important complication in pediatric cancer patients. The reported incidence (0.7-73%) and characteristics of VTE in literature are highly variable due to varying study methodology and lack of population based data. The present study was done to establish the incidence and characteristics of symptomatic VTE in pediatric cancer patients in the 3 Maritime provinces of Nova Scotia, New Brunswick and Prince Edward Island who receive centralized oncology care at a single tertiary care centre.

Methods

All pediatric cancer patients in the Maritimes are managed at IWK Health Center in Halifax in a shared care model with regional provincial hospitals. After ethics approval, case records of all cancer patients (<20 years of age) diagnosed and managed at the IWK health center from January 2000 to March 2014 were retrieved.

Data from multiple databases was integrated including (i) pediatric oncology hospital database, (ii) Provincial Children in Young People (CIYP-C) database, (iii) Electronic medical records, (iv) Pharmacy database and (v) Hospital Health records. Using these databases, patients with symptomatic VTE (patients with ≥1 signs/symptoms directly related to VTE) who were treated with anticoagulants were identified. Data was analyzed using the SPSS version-22.

Results

854 cancer patients were diagnosed during the study period. Of these 2.7% (n=23) had symptomatic VTE. The mean age at VTE diagnosis was 12.1±6.4 months (65% >10 years). The male:female ratio was 1.5:1. Median time to VTE from cancer diagnosis was 46 days (46% within 1 month). Approximately 22% had a second VTE. Approximately 44% of the patients with VTE required >1 central venous catheters.

Conclusions

The present study is one of the first to establish a population based incidence of symptomatic VTE in pediatric oncology population. Additional analysis incorporating a larger geographic area and duration will be needed to further validate these observations.

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Epidemiology

ROUTES TO DIAGNOSIS FOR CHILDHOOD AND YOUNG ADULT CANCER WITHIN INPATIENT HOSPITAL CARE SERVICES IN YORKSHIRE, UK

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Objectives

The pathways to diagnosis for children and young adults (CYA) with cancer are often complex. Developing an understanding of these pathways is vital to the development of effective strategies for improving the time to diagnosis. This population-based study investigates pre-diagnosis admission routes to inpatient care for CYA's diagnosed with cancer in order to improve our understanding of how this unique cohort access healthcare.

Methods

All cases of cancer diagnosed aged 0-24 years between 2004 and 2009 in Yorkshire were identified from the Yorkshire Specialist Registry of Cancer in Children and Young People (N=1098). Case data were linked to inpatient hospital records containing coded clinical data and admission route for each inpatient event. Cancer specific alert codes were identified from inpatient events preceding or coinciding with the date of definitive diagnosis and reviewed against accepted UK CYA cancer awareness campaigns. Initial admission routes for pre-diagnosis inpatient events containing alert codes were identified, and assessed for children (0-14 years) and young adults (15-24 years).

Results

We identified 641 (58%) cases with cancer specific alert codes within their pre-diagnosis inpatient admissions. Of these, 418 cases (65%) were initially admitted via an emergency route. Emergency routes included 204 (32%) admissions via accident and emergency (A&E), 123 (19%) via primary care, 21 (3%) via outpatient care and 70 (11%) categorised as 'other emergency' routes. Overall, the proportion of initial emergency admission routes was similar for children (66%) and young adults (64%); the distribution of emergency subgroups was also similar between age groups.

Conclusions

Emergency admissions play an important role within the pathways to diagnosis for both children and young adults with cancer. The predominance of A&E admissions within the initial pre-diagnosis inpatient events potentially identifies the need for targeted interventions within this area of the healthcare structure.

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Epidemiology

CLINICAL FINDINGS OF ONCOLOGIC EMERGENCY AT DIAGNOSIS

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Objectives

Oncologic emergency is a life-threatening condition that requires immediate intervention. All children with cancer require an emergency response at the time of diagnosis; however, those requiring intensive care management are especially in need of rapid diagnosis and control.To aim of this study was to clarify how to care for oncologic emergency cases by examining the clinical features at the first visit as well as the prognosis.

Methods

We retrospectively reviewed the data for 200 patients with cancer treated at our institution during a period of seven years between 2007 and 2013.

Results

Seventeen children exhibited oncologic emergency at their first visit (17/200; 8.5%). The median age at diagnosis was 6.2 years among the oncologic emergency patients and 6.6 years among the non-emergency patients. The average length of stay in the PICU (Pediatric Intensive Care Unit) among the emergency patients was 9.2 days. The most frequent symptoms at the first visit to our hospital were dyspnea due to acute airway obstruction, followed by coughing and abdominal pain (41%, 29% and 29%, respectively). The most frequent oncologic emergency disease was lymphoma (41%). As to emergency treatments, intubation, surgery and drainage were performed (59%, 41% and 24%, respectively). Only one patient experienced death during the acute phase within 30 days from the first visit. There were no differences in overall survival between the oncologic emergency and non-emergency cases (3-year overall survival rate: 83.3% and 89.0%, respectively, P=0.46).

Conclusions

The prognosis of children with oncologic emergency is not necessarily poor, if the physician understands the clinical signs and provides appropriate management.

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Epidemiology

PERCEPTION AND ATTITUDES TOWARDS GENETIC TESTING FOR CANCER IN PARENTS OF CHILDREN WITH CNS TUMORS

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Objectives

Genetic predisposition is an increasingly accepted cause of childhood cancers. We aim to explore perception and attitudes of parents of children with CNS tumors towards genetics and cancer. This is especially important in countries with high consanguinity where cultural factors may have negative impact.

Methods

Paper validated 42-item questionnaire was administered to parents during their regular outpatient visit to the pediatric neuro-oncology clinic at King Hussein Cancer Center, Jordan. We analyzed parents' demographics, knowledge and perception about genetic predisposition, and attitudes toward genetic testing.

Results

Fifty-two questionnaires were distributed; with 100% response rate.Twenty-seven parents (33%) reported family history of cancer with 44% relatives' deaths from cancer.Consanguinity was found in 11.5% of families. Genetic predisposition is thought to cause cancer by 33 parents (63%), while half of parents agreed that consanguineous marriage increases that risk. Forty-eight parents (92%) believe that early detection and cancer screening improves cure rates and knowledge of a genetic predisposition may contribute to survival. More than half of parents think that a positive genetic test would affect negatively the future lives of their children. However, the majority (92%) believe that pediatric oncologists should inform them if genetic predisposition is suspected. Forty-eight parents (92%) would do a genetic test, if available, and 98% want to know a positive result. Forty-nine parents (94%) will inform other family members about a positive result to start screening and improve their survival. When a genetic test is positive, most parents (81%) will comply with cancer screening investigations, even if frequent.

Conclusions

Majority of parents want to do genetic testing for cancer and they strongly believe that cancer screening improves survival. This should encourage oncologists to challenge the social and cultural barriers to discuss this sensitive topic with families and offer genetic testing, especially in communities with high consanguinity.

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Epidemiology

CLINICAL CHARACTERISTICS OF PATIENTS WITH GERMLINE SUFU MUTATIONS

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Objectives

Germline mutations of the *SUFU* gene have recently been described in association to medulloblastoma. Only a few cases have been described in literature so far.

Methods

We performed a retrospective review of the clinical files and molecular data of all patients in whom a germline *SUFU* mutation had been diagnosed in Institut Gustave Roussy and Institut Curie genetics laboratories.

Results

21 patients from 17 families were diagnosed with a germline *SUFU* mutation: 6 frameshift, 6 splice, 2 nonsense, 2 large rearrangement, one missense. All patients but 2 had been diagnosed with a medulloblastoma at a median age of 18 months [range 1-35] (desmoplastic in 9, extensive nodularity in 6, classical in 4). The indication for testing the other two patients was the presence of familial history of medulloblastoma and criteria for a Gorlin syndrom with basocellular carcinomas (CBC) without germline *PTCH* mutation in the second. A macrocrania was described in 13 patients. An history of medulloblastoma in siblings was described in 4 families. Mutations were inherited in 12/13 patients whose parents underwent genetic testing and de novo in 2 cases. Overall, 36 healthy carriers have been identified in 12 families.

Second malignancies were described in 3 medulloblastoma patients including multiple CBC (1pt), ovarian tumor and meningioma (1pt) and thyroid carcinoma (1pt). In addition several mutation carriers in family members were diagnosed with cancer: breast cancer at 37, meningioma at 38, CBC at and sarcoma at 63 years of age.

Conclusions

SUFU germline mutations predispose to medulloblastomas mostly of desmoplastic/nodular or extensive nodularity subtypes during the first 3 years of life, often associated with macrocrania. Some patients also develop basocellular carcinomas. Due to incomplete penetrance, genetic counselling is difficult. International collaboration is necessary in order to better define the risk associated with these mutations and guidelines for surveillance.

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Germ Cell Tumours

RETROPERITONEAL TERATOMAS: LESSONS LEARNED FROM 16 CASES

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Objectives

Retroperitoneal teratoma (RPT) is an uncommon tumor in children. The purpose of this paper was to review the presentation, management and outcome of children with RPT between 2001 to 2014.

Methods

A retrospective multi centric (Melbourne Children Hospitals, National University Hospital Singapore and Nantes University hospital) review of 16 children with RPT encountered in over a 14 year period was carried out. Age at presentation, sex, tumor marker levels, operative findings, surgical complications, histology and outcomes were evaluated.

Results

13 patients were female. 2 had Down's Syndrome. 11 patients had surgery before 1 year of age. 2 of the patients had raised AFP for age. Median size of the tumor was 145mm (range 115 to 180mm). Surgical resection was performed for all patients. . Difficulty in resection due to distortion of vascular anatomy was reported in 11 with injury to vessels in 3 (IVC, splenic artery, polar renal artery) and organs removal in 2 (nephrectomies). Complete resection was achieve in 13 patients

The histology was mature teratoma for 11 patients and immature teratoma for 5. . Median duration of follow up was 19 months (range from 1 month to 12 years) with 1 recurrence of immature teratoma (lung, iliac bone). Post operative complications included 2 intussusceptions requiring operative reduction, one splenic artery thrombosis and one persistent hypertension.

Conclusions

RPT is an uncommon tumor in childhood, primarily presenting in infant . Majority of the tumors are benign. Preoperative evaluation by CT scan and/or MRI of anatomical distortions is mandatory to manage the complexity of surgical resection. Complete excision is the cornerstone of treatment.

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Germ Cell Tumours

IMPROVING SURVIVAL IN EXTRACRANIAL GERM CELL TUMOR IN A DEVELOPING COUNTRY: CHILDREN'S HOSPITAL LAHORE EXPERIENCE

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Objectives

Children's Hospital Lahore is a tertiary government centre providing the free cancer treatment to over 500 new cancer patients per year. The purpose of this study was to analyze the outcome of children with Extracranial GCT and to discuss the role of multidisciplinary team management and social support to improve the survival in a developing country.

Methods

Retrospective review of 80 patients enrolled between January 2011 – January 2014 was done. Data regarding their age,site,stage,histopathology,risk stratification,AFP levels,treatment, outcome and impact of MDT approach was analyzed. Patients were treated according to UKCCSG GC 2005 04 protocol.

Results

Total 80 patients with age ranging from< 1-12 years(60% <5 yrs) were included. M: F Ratio was 1:2.2. The HPE showed predominance of yolk sac tumor 30/80(38%) followed by mature teratoma 18/80(23%),dysgerminoma 7(9%) MMGCT 5(6%), JGCTO 4(5%), Immature 4(5%) unspecified 12(15%). 39/80(49%) presented with stage IV,30(38%) with stage III and 11(13%)at stage II. Gonads 32/80(40%) were the most common site followed by SCCT 23/80(29%) abdominal 20/80(25%) Head & Neck 3/80 and thorax 2/80(2%).AFP level >10,000 found in 36/80(45%) p-value-0.002. Total 53/80 (66%) have completed treatment, 4/80 (5%) are on treatment, 6/80 (8%) LAMA and 15/80 (19%) expired due to metastatic and progressive disease. 9/15(60%)expiries were in SCCT group 9/23(40%). Two patients(2.5%) relapsed after completed therapy.77 events were noted with 39/77(50%) in stage IV Patients and 28/77(37%) in stage III patients,p-value=0.012.Efficient MDT utilized in 50/80(63%) cases reducing the LAMA rate from 19% to 8%(comparing with 2011 SIOP DATA).

Conclusions

Survival is fair 53/80(66%) for the whole group and 51/53(96%) for the treated group.Mortality of 19% can be reduced by early management and infection control strategies.The prognosis can significantly be improved by public awareness to seek early treatment and establishing multidisciplinary team approach and effective social support especially for the SCCT group.

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ICCCPO (Parent/Survivors)

NATIONWIDE AWARENESS-RAISING ACTIVITIES FOR INTERNATIONAL CHILDHOOD CANCER DAY BY CHILDREN'S CANCER ASSOCIATION OF JAPAN (CCAJ) IN 2014

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Objectives

Children's Cancer Association of Japan (CCAJ) is a non-profit organization founded in 1968 through desperate efforts of two parents who have lost their children due to cancer. On or around the International Childhood Cancer Day (ICCD) this year, CCAJ and its nationwide 18 branches implemented an enlightening campaign together to let the ordinary public know that even children have chances to suffer from cancer through handing out our campaign cards, which include such statement as "early detection is very important to save children with cancer" with showing Early Warning Signs.

Methods

CCAJ defined the period between February 1 and March 14 as the dates for the campaign. As for the tools for the campaign, we prepared 40,000 campaign cards and 900 original blue T-shirts with a yellowish logo of "International Childhood Cancer Day 2014". Those T-shirts were distributed in exchange for donations. Also, we prepared 20,000 pieces of original pocket tissue with the description of CCAJ's contact lists.CCAJ announced the campaign for ICCD 2014 and its specific schedules to our members, government offices, hospitals, public health centers, business corporations and so on by means of our bulletin, website, and weblog. Our activities for the campaign were also released to the national and local media.

Results

As for the tools for the campaign on ICCD 2014, we handed out about 30,000 campaign cards and 20,000 pieces of original pocket tissue, and distributed 850 T-shirts.

Conclusions

We could strengthen our teamwork between CCAJ headquarters and its branches through our activities for the campaign on around ICCD. Also, we could share the importance of "awareness of childhood cancer" not only with our branch members but also with the third parties involved for the campaign, i.e. government offices, hospitals, public health centers, business corporations, and volunteers.

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ICCCPO (Parent/Survivors)

HISTORICAL FOCUS ON CHILDHOOD CANCER SURVIVORS, 1960-2014: LONGEVITY, AWARENESS AND NEW APPROACHES

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Objectives

To construct an overview of the historical development of childhood cancer survivorship from the 1960s and the first numbers of long term survivors to the present time. The study explores how survival issues changed as survival rates increased.

Methods

The author has consulted the archives of the National Cancer Institute, the National Library of Medicine. the National Institutes of Health Library and the archives of the Memorial Sloan Kettering Cancer Center. Personal accounts from childhood cancer survivors and their families as well as letters and articles authored by them are the primary source for the study. In the period since 1990 patient and family interviews were also a key source.

Results

From the 1960s to present a more focused, organized and proactive approach has been taken by medical and psycho social teams to provide 'cure of the whole child.' With the advance of supportive therapy and rehabilitation therapies diverse late effects in their are more often being identified in developed countries. In the United States, the focus of this study, more emphasis is being placed upon the role of the internist or family physician's role in providing follow up care to former pediatric cancer patients. Self awareness of long term effects are also a mission of the Children's Oncology Group, and the American Medical Association.

Conclusions

The identification of long term effects from childhood cancer and its treatment is a problem that only came about from the success of of therapy first in childhood leukemias in the 1960s and the evolution of effective multi modal therapies for most cancers in children by the 1990s. There is still a great need for the support of childhood cancer survivors as they age through adulthood. These efforts continue to be needed not only for medical assessment and disease prevention but psycho socially as well.

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ICCCPO (Parent/Survivors)

THE TOGETHER SERIES: THERAPEUTIC STORIES FOR CHILDREN AND FAMILIES

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Objectives

This project involved the development of a series of children's books designed to assist children to manage the physical and emotional impact of childhood cancer treatment, hospitalisation and the transition period following treatment.

Methods

A series of five story books were written by a parent of a young child undergoing leukaemia treatment to assist her child's adaptation to the cancer experience and in particular the end-of-treatment period. Topics include coping with hair loss, addressing fears of returning to school, attempting new activities, adapting to fewer hospital visits and understanding parental reactions to end of treatment. Both the individual stories and concept of the series were collaborated on by a family therapist, speech pathologist, play therapist and the author and an additional book was added for children to write their own story. A brief was sent to the illustrator outlining the therapeutic intention of each story. A formal evaluation of the books was undertaken with 26 participants: 6 children, 4 parents, 1 grandparent, 6 health professionals (5 psychologists, 1 social worker) and 9 teachers. The books were evaluated for their relevance, usefulness and creative appeal, using a specifically developed survey.

Results

Overall approval rating for the books from health professionals, parents and children was high, with the books assessed as most relevant to children aged 2-9. Specific comments were examined for editing purposes and two additional books directly addressing children's broader experiences of hospitalization were developed as a result. Philanthropic funding enabled publication of the books.

Conclusions

Cancer treatment and transitioning to end of treatment are well recognised as highly stressful times for children and families. Despite this, resources particularly for young children are limited. These books offer a creative and relevant resource for parents, enabling them to help their child adjust and potentially find their own stories to tell.

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ICCCPO (Parent/Survivors)

PERCEPTION OF CHILDHOOD CANCER: PARENTAL ASSESSMENT

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Objectives

The aim of the study to assess the parents' psychological adjustment, hospitalization problems, behavioral changes in children, financial problems and concern about child health and hygiene.

Methods

The sample of the study consisted of 50 parents whose children (age 2-10years) were undergoing treatment for acute leukemia.The questionnaires were made by investigator in local language (Hindi) for the assessment of parental adjustment about cancer.

Results

Most parents were unaware of cancer prior to diagnosis. Majority of children present with fever. 88% of parents suffer from depression and anxiety . 44% of parents found it difficult to get investigations done in the hospital.50% of patients faced financial problems and mental stress was seen in most. 64% have knowledge about government funding schemes but 52% have problem in documents preparation. 98% of parents were concerned about their child's hygiene. During treatment 58% noticed that their child's behavior had changed . In 33% the life of parents also changed due to child's illness. Siblings of patients also faced problem as 38% of parents are not able to give proper attention. 72% of family did not get any emotional and financial support from relatives.

Conclusions

In this study we found that parents experience high level of anxiety and depression at the time of diagnosis. The investigation and hospitalization affect their daily routine and also affects the siblings.

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ICCCPO (Parent/Survivors)

A DONOR FOR BELOVED BROTHER

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Objectives

to share, inspire and encourage other siblings willing to be a donor for their brother/sister with cancer in the family.

Methods

My name is Andri Astarisanna. I am the second child in the family. My brother suffered leukemia since he was 11 years old and I volunteered to be his donor before he finally passed away in 2008.

I was only 14 years old when they found out my blood was the one matched to his blood, therefore I was chosen to be the donor. My younger sister also included to be the other candidate for the donor, in the end i was the best option to give my stem cell to my brother.

The procedure was quite hard and new for me as of the first time i thought that they were going to take my bone marrow and then they explained me that they had achieved a new method, however I was brave and strong enough until the end of the procedure.

Results

Parents are usually looking for the other candidates outside the core family to be the donor, sometimes because if they choose another siblings to be the donor, it seems that they 'sacrifice' another child to do it. But for some other reasons it was easier, because then the procedure can be part of 'supporting' other sibling with cancer, reduce the risks and errors, also creates a tighter bond in the family.

Conclusions

Although then my brother still had to go, it was indeed a valuable and memorable experience.

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ICCCPO (Parent/Survivors)
HELP DESK FOR HEMATO-ONCOLOGICAL DEPARTMENT IN CROATIAN CHILDREN HOSPITAL

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Objectives

On average this disease occurs in 118 children in Croatia per year, which means that there is a child diagnosed with cancer every other day. Around 120 children are treated for cancer every year in the Children's Hospital in Zagreb. Inadequate access to information about the rights of the parents and the children regarding various fields. Dispersion and unavailability of information. Difficult psychological and emotional state of parents, who do not know who or how to ask for help and support
Need to organize a single, one-stop information point
Support to the parents and the children through assistance about their rights as well as active involvement in helping the parents exercise their rights.
Information about child treatment with cooperation and support from the Hospital's professional staff.

Methods

To set up a one-stop point providing full and up-to-date information regarding various issues.
Setting up parents' meetings with the medical staff and meetings with the persons from various government institutions and services essential for exercising many of their rights.
Organization of group support to the parents and the children, conducted by experts
Creative and educational workshops
Organizing and carrying out various activities and events to help the children and their families through the difficult times

Results

We are raised public awareness through many medias about malignant disease
We are facilitated the work of medical staff
We are raised the active life quality of children and families

We provide better integration of children and teenagers with reduced abilities in the public and social life.
210 HELP DESK USERS IN 2013 WITH MANY EXAMPLES OF PROBLEMS AND SOLUTIONS

Conclusions

This unit is very helpfull to integrate problems on one place for better solutions of solving them

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Late Effects

CHILDHOOD CANCER SURVIVORS OF BONE TUMORS AND SARCOMAS ARE AT AN INCREASED RISK OF HOSPITALIZATION

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Objectives

Identify if childhood cancer survivors of malignant bone tumors and sarcomas are at an increased risk of hospitalization.

Methods

Using data from population-based research resources in Utah, we identified all childhood and adolescent survivors of malignant bone tumors (N=97) and sarcomas (N=63) who were diagnosed from 1973-2005 and were ≥five years from diagnosis. We selected a birth year and sex matched comparison cohort (N=946). Hospitalizations from 1996-2010, excluding pregnancy and delivery, were determined from discharge records. Multivariable Cox, Poisson and Gamma regressions were used to evaluate risk of hospitalization, admission counts, and length of stay for survivors versus the comparison cohort. Estimates for bone tumors and sarcomas were aggregated since regression estimates were similar except where reported.

Results

Average follow-up since 1996 for survivors was 13.5 years (SD=8.7) and for the comparison 14.0 years (SD=9.1) (p=0.1). The hazard ratio (HR) of any hospitalization was higher for survivors than the comparison cohort (HR=1.58, 95% confidence interval (CI) 1.18-2.12). Survivors experienced a higher hospital admission rate (rate ratio (RR)=2.33, 95% CI 2.04-2.67, p<0.001) than the comparison cohort. Length of stay was longer for hospitalized survivors (RR=1.32, 95% CI 1.17-1.50, p<0.001) compared to the cohort. When sarcomas and bone tumors were examined separately, sarcoma survivors had a higher rate of hospital admissions (RR=2.01, 95% CI 1.67-2.43, p<0.001). Bone tumor survivors experienced an even higher hospitalization rate (RR=2.92, 95% CI 2.40-3.55, p<0.001) in reference to the comparison cohort.

Conclusions

The number of hospitalizations, rate of admissions, and lengths of stay are elevated among childhood cancer survivors of bone tumors and sarcomas. Childhood cancer survivors tend to receive less survivorship-focused health care the further they are from their diagnosis. Efforts to prevent and manage sarcoma and bone tumor survivors' health problems in outpatient settings could help reduce their hospitalization risk.

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Late Effects

BONE FRACTURE IN PEDIATRIC AND ADOLESCENT SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM PROJECT REACH AT DANA-FARBER CANCER INSTITUTE (DFCI)

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Objectives

Skeletal toxicities are recognized as serious complications of therapy for childhood cancer, but the occurrence of bone fracture in these survivors is infrequently described. This study assessed the prevalence of and risk factors for the development of fracture in a cohort of pediatric and adolescent survivors of childhood cancer.

Methods

Parents of 190/200 (95%) participants in Project REACH, a prospective cohort study of childhood cancer survivors, completed questionnaires reporting the occurrence of fracture**.** Medical records were reviewed for treatment and health outcome data. Cancer diagnoses included: acute lymphoblastic leukemia (32.1%), neuroblastoma (22.6%), Wilms tumor (11.6%), sarcoma (11.6%), lymphoma (9.5%), acute myelogenous leukemia/myelodysplastic syndrome (5.3%), hepatoblastoma (2.6%), other (4.7%). Median age at enrollment was 12.4 years (range = 6.0-18.0) and median time since diagnosis was 8.4 years (range = 2.1-17.8).

Results

Sixty-nine post-cancer treatment fractures were reported in 46 survivors (24%). 16/46 survivors (35%) experienced ≥1 fracture (10 survivors with 2 fractures, 5 with 3, and 1 with 4). Median time from completion of therapy to first fracture was 3.8 years (range 0.02-13.6 years). Therapy-directed corticosteroid exposure was associated with increased frequency of post-treatment fracture; 32% (27/84) of survivors who received corticosteroid experienced fracture compared with 18% (19/106) of those who did not receive corticosteroid (OR 2.2, 95%; CI 1.1-4.3, p=0.026). Survivors treated with dexamethasone had a higher frequency of fracture (37%) compared with survivors without corticosteroid exposure (p= 0.017). Fractures occurred in 28% of survivors exposed to other steroids not including dexamethasone, but this proportion was not significantly different from the no steroid group (p=0.15).

Conclusions

Almost a quarter of childhood cancer survivors experienced fracture after cancer therapy. Exposure to corticosteroid was associated with an increased frequency of post-treatment fracture. These data suggest that a treatment-associated fracture risk may extend beyond cancer therapy completion.

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Late Effects

ELECTROCARDIOGRAPHIC ABNORMALITIES IN AGING SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM THE ST. JUDE LIFETIME (SJLIFE) COHORT STUDY

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Purpose/Objective: Electrocardiographic (ECG) abnormalities, whether major or minor, are predictive of poor prognosis and provide a simple tool for cardiovascular risk assessment. We evaluated prevalence and determinants of ECG abnormalities among adult childhood cancer survivors (CCS).

Materials and Methods: This analysis included 2,706 participants of the SJLIFE cohort (51% male, 15.6% non-white, mean age 8.3±5.6 yrs. at diagnosis and 32.4±8.3 yrs. at evaluation). ECGs were recorded using standardized methods and centrally reviewed at an ECG core laboratory blinded to medical history. Abnormalities were classified into major and minor per the Minnesota ECG Classification. Frequencies were assessed and log-binomial regression models; adjusted for age, sex, race, BMI, and smoking; were used to estimate relative risk (RR) and 95% confidence intervals (CI) for patient and treatment characteristics.

Results: At least one ECG abnormality was identified in 63.7% of participants, 10.8% major, 52.9% minor. The most common major abnormalities were major isolated ST-T abnormalities (7.2%), evidence of myocardial infarction (3.6%), and left ventricular hypertrophy with strain pattern (2.8%). Highest frequencies were among Hodgkin lymphoma (20.2%), Wilms tumor (16.3%), and osteosarcoma (14.8%) survivors. Frequency of major and minor abnormalities by treatment was: chest radiation (RT) 21.7% and 53.7%; anthracyclines 7.6% and 52.6%; and chest RT+anthracylines 17.6% and 55.6%. In adjusted models, risk of major and minor abnormalities was associated with chest RT [RR=1.57 (CI, 1.33-1.85) and RR=1.07 (CI, 1.02-1.12)], male sex [RR=1.16 (CI,1.01-1.38) and RR=1.07 (CI,1.02-1.12)], and BMI < 18.5 mg/m^2 [RR=1.49 (CI,1.01-2.25) and RR=1.07 (CI,1.01-1.23)] but not anthracycline exposure ≥ 300 mg/m^2 [RR=1.12 (CI, 0.89-1.42) and RR=1.01 (CI, 0.94-1.09)]. Increasing age (5-year increments) was associated with major abnormalities (RR=1.05 CI, 1.01-1.11).

Conclusions: ECG abnormalities are common in CCS; nearly two-thirds had at least one abnormality, suggesting a high risk for cardiovascular disease. The risk is highest among those exposed to chest directed RT.

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Late Effects

THE IMPACT OF RADIATION, CARDIOVASCULAR RISK FACTORS AND PHYSICAL ACTIVITY ON ENDOTHELIAL PROGENITOR CELLS AMONG CHILDHOOD CANCER SURVIVORS

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Objectives

The relative-risk of atherosclerotic cardiovascular disease (ACVD) is elevated in childhood cancer survivors (CCS) secondary to cancer-therapies causing vascular endothelial impairment. Novel biomarkers of endothelial inflammation analyzed from the peripheral blood (PB) may aid in identifying CCS at risk for future ACVD. These biomarkers include the bona fide endothelial progenitor cells, termed endothelial colony-forming cells (ECFCs), that are essential for vascular homeostasis and repair, as well as, apoptotic mature circulating endothelial cells (CECs). The purpose of this study was to analyze ECFCs and CECs from the PB of CCS using a novel multi-parametric flow-cytometry protocol.

Methods

In this cross-sectional study we compared Cardiovascular Risk Factors (CRFs), quality of life measures, diet, physical-activity (PA), brachial-artery flow-mediated dilatation (FMD), a measure of endothelial function, and ECFCs and CECs between CCS and age and body-mass index matched healthy controls (HC). In addition, we investigated the effect of cancer therapies on FMD, ECFCs, and CECs and the associations between these measures and CRFs, PA and diet.

Results

We enrolled 24 CCS, 17 with a prior diagnosis of leukemia. The CCS had significantly lower physical functioning and PA, worse diet, higher fatigue and lower high-density cholesterol (HDL-C) compared to HC (all $p<0.05$). There was no difference in FMD, ECFCs and CECs between CCS and HC. Within the CCS cohort, those with any radiotherapy (RT) had significantly lower ECFCs and CECs (both $p=0.02$). In addition, significant positive correlations included, HDL-C with FMD and PA with ECFCs while significant negative correlations included systolic blood-pressure with ECFCs (all $p < 0.05$).

Conclusions

This is the first study of its kind involving CCS showing that ECFCs are affected by cancer-therapies, such as RT, further worsened by CRFs such as hypertension and life-styles with inadequate PA. Altering these modifiable risk-factors can potentially improve vascular health to prevent future ACVD.

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Late Effects

ELECTRORETINOGRAPHY AND VISUAL EVOKED POTENTIALS IN CHILDHOOD BRAIN TUMOR SURVIVORS

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Objectives

To evaluate clinical value of electroretinography (ERG) and visual evoked potentials (VEP's) in childhood brain tumor survivors.

Methods

A total of 104 primary brain tumor patients diagnosed below 17 years of age between 1983 -1997 were treated in Tampere University Hospital. Of the 80 survivors 75 potentially eligible patients were invited to participate in this population-based cross-sectional study. Fifty-two (69%) participated and were examined at a mean age of 14.2 years (range 3.8-28.7 years) after a mean follow-up time of 7.5 years (1.5-15.1 years). A flash ERG and a checkerboard reversal pattern VEP or a flash VEP were done.

Results

Abnormal ERG in one and bilaterally delayed abnormal VEP's were obtained in 22/51 (43%) cases. VEP's were abnormal in all patients with chiasmatic, hypophyseal or pineal tumor location and in most patients with hypothalamic tumor location, but the tumor location in the visual pathway was not associated with abnormal responses (p=0.567). Nine out of 25 (36%) patients with infratentorial tumor location had abnormal VEP's. Age at diagnosis (p=0.358), follow-up time (p=0.400), chemotherapy (p=0.765), radiotherapy (p=0.565), combined therapies (p=0.743), hydrocephalus (p=0.568), shunt revisions (p=1.000) and antiepileptic medication (p=1.000) were not associated with abnormal VEP's.

Conclusions

Abnormal ERG's are rarely observed, but abnormal VEP's are common and indicate damage in the visual pathway. The fact that the VEP's are bilaterally delayed suggests a general toxic/adverse effect on the visual pathway, which is possibly multifactorial. ERG and VEP tests may have both clinical and scientific value while evaluating long-term effects of childhood brain tumors and tumor treatment.

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Late Effects

EXPERIMENTAL FERTILITY PRESERVATION (FP) INTERVENTIONS IN PRE-PUBERTAL (PP) BOYS WITH CANCER: A REPORT ON PREFERENCES OF TEENAGE CANCER SURVIVORS, PARENTS, AND PROVIDERS

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Objectives

Risk of infertility from cancer therapy is a source of great distress for young cancer survivors. FP can be a challenge in PP boys who are unable to produce bankable sperm through ejaculation. We sought to determine factors influencing patient, parental and provider preferences for testicular biopsy (TBx) even though the utility of PP tissue for FP remains experimental.

Methods

Oncology providers, parents, and teenage cancer survivors were recruited from 3 pediatric centers in Canada. During participant interviews and surveys, a hypothetical decision was made between TBx and no TBx. Willingness to accept complications, costs, risk of infertility, chance of technology developing and desire to help others were used to measure strength of preference for TBx. Multiple regression was used to associate predictors with TBx desirability scores (under risk of infertility condition).

Results

The proportion of respondents who preferred TBx (vs no TBx) were: 110/153 (72%) parents, 22/30 (73%) providers, and 52/77 (67%) cancer survivors. The top ranked factor influencing decisions for all groups was risk of infertility. Survivors ranked rate of complications and cost lower and desire to 'help others' higher compared to parents ($p<0.005$). All 3 groups had similar strengths of preference for TBx compared to no TBx when risks of infertility and chance of technology developing were varied. Child age, type of cancer, ethnicity, or hospital were not significant factors associated with preference for TBx, but parents who reported a higher income were more likely to prefer TBx ($p=0.05$).

Conclusions

Parents, survivors, and providers strongly favor TBx and ranked risk of infertility as most important in decision-making. Parental income was the only predictor of preferences under the risk of infertility condition. Addressing the costs associated with FP should remain an important focus of advocates for FP.

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Late Effects

OVARIAN TISSUE CRYOPRESERVATION IN PEDIATRIC ONCOLOGY: A GAMBLE ON THE FUTURE

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Objectives

Because of a significant improvement in the survival of children and adolescents with cancer, fertility preservation has to be a major concern for paediatric oncologists.
The aim of our study was to report all our ovarian tissue cryopreservation's (OTC) cases in order to specify the interest and indications of this method and to study the clinical and hormonal outcome in girls.

Methods

From September 2000 to September 2013, 36 girls had an OTC in our center. Eight patients had no malignant disease and 28, a malignant disease. After informed consent, the surgical ovarian collection consisted in the biopsy of a third of each ovary by laparoscopy which was frozen by a slow cooling protocol. A histological analysis and a follicular account were performed.

Results

Among our 36 patients, OTC's indications were 13 auto-SCT, 19 allo-SCT and 4 sterilizing chemotherapy. Ovarian tissue harvest was performed by intraumbilical laparoscopy using a 3 to 7-mm laparoscop. Two 3 to 10-mm trocars were used. No major postoperative complications occurred excepted for one patient with sickle cell disease and protein S deficiency who had a severe haemorrhage of one ovary. The following chemotherapy regimens were not delayed and started at a median range of 10 days [1-81] after OTC. The anatomopathologic analysis showed 10 primordial follicles/mm² [0-83] and no malignant cells in any ovarian tissues. The median follow-up after harvest was 29 months [0-111], 21 girls were alive in complete remission, 1 was still on treatment and 10 died. Hormonal results were evaluable for 26 patients with a median age at 17 yrs [5-26] and 14 were in premature ovarian failure.

Conclusions

Feasibility of OTC with sample of a third of each ovary seems to be an appropriate method before transplantation with no consequences on therapeutic program for children to preserve potentially fertility.

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Late Effects

DISEASES OF RENAL FUNCTION AND BONE METABOLISM IN LONG-TERM FOLLOW-UP FOLLOWING TREATMENT OF EARLY-ONSET CANCER. A REGISTRY-BASED STUDY.

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Objectives

Constant progress in cancer therapy has led to a growing number of early-onset cancer survivors who are prone to increased morbidity owing to the late-effects of their anticancer therapy. The aim of this study was to investigate pediatric and young adult cancer survivors' morbidity on renal diseases and on diseases of bone metabolism in a registry setting in a population-based level.

Methods

The patient cohort was identified from the Finnish Cancer Registry, and consisted of 13,860 5-year-survivors of cancer diagnosed below the age of 35. Their siblings without early-onset cancer were identified from the central population register and were used as the control cohort. Information on their morbidity on renal diseases and on diseases of bone metabolism was collected from the national hospital discharge registry and was used to assess hazard ratios for various outcomes. The patient cohort was separated into two age groups, pediatric (age at cancer diagnosis 0-19 years) and young adults (age at cancer diagnosis 20-34 years).

Results

Significantly elevated hazard ratios compared to the controls were observed in the following outcomes: scoliosis HR 1,6 (95% CI 1,3-2,0), osteoporosis HR 5,2 (95% CI 2,4-11,4), osteonecrosis HR 12,7 (95% CI 5,4-29,7), nephritis HR 1,9 (95% CI 1,5-2,2) and kidney failure HR 3,6 (95% CI 2,4-5,3), $p<0,0001$ for all. All of the mentioned hazard ratios were significantly elevated in both diagnostic age groups. The hazard ratio for obesity was elevated in the pediatric age group for females HR 3,4 (95% CI 1,6-7,2) and for all survivors of CNS tumors HR 2,8 (95% CI 1,4-5,7).

Conclusions

Survivors of pediatric and young-adult cancers are at increased risk for several long term adverse outcomes, and this must be taken into account in their follow-up. Our study provides new population-based information on the early-onset cancer survivors' morbidity on renal diseases and on diseases of bone metabolism.

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Late Effects

RENAL LATE EFFECTS AFTER TREATMENT OF UNILATERAL NON-SYNDROMIC WILMS TUMOR

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Objectives

Due to the improvement in prognosis and increase in survival rates the long term renal consequences in Wilms tumor patients are of greater concern. We aimed to investigate the long term effects of treatment on survivors of non-syndromic unilateral Wilms tumor.

Methods

A total of 45 unilaterally nephrectomized survivors of Wilms tumor treated and followed at our center were enrolled in the study. After the second year following the cessation of treatment; glomerular filtration rate (GFR), urinary protein excretion, urinary ß2 microglobulin levels and blood pressure were assessed as well as general health status and quality of life. Results were analyzed for correlation with clinical variables, chemotherapy and radiotherapy as possible risk factors.

Results

At a median follow-up time of 8.7 years (mean:10.9, range: 2.3-35.4 years), none of the patients included in the study developed end-stage renal disease (ESRD). During the follow-up, 6/45 (13.3%) patients had any of the renal problems; hypertension, proteinuria or tubulopathy. None of the patients had increased urinary ß2 microglobulin levels. Compensatory hypertrophy was observed under ultrasound in 31 patients (72%). Median maximum bipolar length was significantly higher in patients diagnosed after the age of 36 months. 10/45 (23%) and 3/45 (7%) of the patients were hypertensive at the time of diagnosis and study, respectively. Median GFR values were significantly lower at the time of diagnosis. Although at the time of the study all patients had normal GFR values; with longer follow-up intervals, especially after 10 years, a significant declining trend in GFR was observed (p=0.004).

Conclusions

Although the risk of developing ESRD is remarkably low in non-syndromic unilateral Wilms tumor, a group of less serious but progressive renal dysfunction is of concern. Detailed analysis of renal functions should be performed during the long term regular follow-up.

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Late Effects

LONG TERM AUDIOLOGIC OUTCOMES IN CHILDREN TREATED WITH PLATINUM CHEMOTHERAPY

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Objectives

Childhood cancer survivors treated with platinum chemotherapy appear to be at risk for progressive hearing loss after treatment. The purpose of this study was to evaluate the prevalence and severity of delayed-onset and progressive hearing loss, to evaluate the time course of hearing changes after treatment, and identify possible risk factors.

Methods

A retrospective cohort study of children and adolescents treated with platinum chemotherapy at Oregon Health and Science University was conducted. Inclusion criteria included treatment with cisplatin and/or carboplatin, an end-of-therapy audiologic evaluation within 6 months after the final platinum treatment, and at least one long term follow-up hearing evaluation (LTFU) 12 months or more after completion of platinum therapy. Progressive hearing loss was defined as a ≥20 dB decrease in pure tone threshold(s) at LTFU relative to the end-of-treatment evaluation. Severity of hearing loss was graded according to the SIOP Boston hearing loss grades.

Results

128 patients with various cancer diagnoses met inclusion criteria. 92 were treated with cisplatin, 18 with carboplatin, and 17 with both agents. 52 also received cranial radiation prior to cisplatin. 85 (66%) of patients had ototoxic hearing loss at completion of chemotherapy. Mean length of time from the end-of-treatment hearing evaluation to the most recent post-treatment evaluation was 3.6 years (range 0.6-15.8). Of patients with ototoxicity at the end of therapy, 23/85 (27%) exhibited progressive hearing loss at LTFU. Three medulloblastoma patients had normal hearing at the end of treatment, but had delayed-onset hearing loss at LTFU. Variables including diagnosis, age at treatment, length of LTFU, cranial radiation and platinum dose were examined to explore potential risk factors.

Conclusions

Results document the need for long-term audiologic monitoring and management in childhood cancer survivors treated with platinum agents. Strategies to reduce or prevent hearing loss are needed.

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Late Effects

FATIGUE IN CHILDHOOD CANCER SURVIVORS: A REPORT FROM PROJECT REACH

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Objectives

To better understand the prevalence and etiology of fatigue in adolescent and young adult survivors of childhood cancer and how fatigue-associated factors may differ from older childhood cancer survivors.

Methods

Participants were 270 childhood cancer survivors (Mean age 23 yrs; Mean age at dx 8 yrs; 52% female), enrolled in Project REACH, a longitudinal research study. Fatigue was measured using the PedsQL Multidimensional Fatigue Scale, validated in age groups 25 years. Participants 1 standard deviation below the mean of standardized populations were classified as significantly fatigued. Measures also included the PedsQL, SF-12, BDI-Y, and BSI-18.

Results

Thirty-seven participants (14%) reported fatigue, which is not significantly different from population norms. Stratification by age group (25 years) demonstrated similar results, with age not a significant predictor of fatigue, however a trend of increased fatigue with age was noted (p=0.076). Fatigue cases were associated with poor QoL (PedsQL and SF-12; p< 0.001) and poor mental health functioning (BDI-Y and BSI-18; p25 population (p=0.002), but not in the

Conclusions

The prevalence of fatigue was lower than expected in this survivor population. Fatigue was highly correlated with psychosocial well-being across all age-groups, underscoring the importance of fatigue assessment to promote optimal adjustment and QoL. While fatigue was closely related to the number of chronic conditions in older adults, this was not seen in adolescents and young adults closer to treatment. These findings may reflect advancements in cancer care aimed at reducing late-effects or delayed onset of late-effects in younger survivors. Ongoing cohort evaluation will help better elucidate the evolution of fatigue in childhood cancer survivors.

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Late Effects

EXERCISE TOLERANCE AND ENERGY EXPENDITURE AMONG ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A REPORT FROM THE ST. JUDE LIFETIME COHORT STUDY.

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Objectives

Adult survivors of childhood ALL are less active than peers. Lean muscle mass deficits and problems with energy expenditure and fitness may explain low activity levels. The aim of this analysis was to evaluate energy expenditure and fitness among ALL survivors and compare them to controls with no cancer history.

Methods

We evaluated total daily (TDEE) and activity (AEE) energy expenditure in 247 ALL survivors and 247 race-, sex-, and age-matched controls, using the doubly labeled water method. Resting energy expenditure (REE) was estimated with indirect calimetry and exercise capacity (VO_2peak) with cardiopulmonary exercise testing. Energy expenditure was compared between groups in general linear models adjusted for total body mass (TBM). Associations between fitness and energy expenditure were also evaluated in linear models adjusted for TBM.

Results

Survivors were 47.3% male, 90.5% white, a median age of 29 (18-44) years, a median of 5 (0-18) years of age at diagnosis, and had survived a median of 23 (11-30) years. Survivors had similar TBM (mean ± SD: 80.4±21.8 vs. 81.2±22.3 kilograms (kg), p=0.72), but were shorter (167.8±10.2 vs. 171.1±9.2 centimeters (cm)), and had lower lean mass (54.6±13.3 vs. 57.0±13.3 kg, p=0.05) and VO_2peak (23.7±0.4 vs. 26.6 ±0.4 milliliters/kilogram/minute (ml/kg/min), $p < 0.001$) than controls. After adjusting for fat mass, there were no differences between groups for TDEE (3013.2±35.1 vs. 2973.9±35.0 (kilocalories) kcal), AEE (1295.2±34.4 vs. 1217.4±34.3 kcal), or REE (1416.6±21.8 vs. 1459.2±21.7 kcal). Among survivors a 3.5 ml/kg/min higher VO_2peak was associated with 94.3±23.0 kcal higher AEE ($p< 0.001$) and a 175.8±21.3 kcal higher TDEE ($P < 0.001$). This association was not evident among controls.

Conclusions

Adult survivors of childhood ALL do not appear to have deficits in energy expenditure when TBM is taken into account. Lower than expected exercise tolerance may explain low activity among survivors whose energy expenditure is associated with VO_2peak.

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Late Effects

OBESITY INDEPENDENTLY INFLUENCES GONADAL FUNCTION IN VERY LONG-TERM ADULT MALE SURVIVORS OF CHILDHOOD CANCER

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Objectives

Although obesity is associated with gonadal dysfunction in the general population, gonadotoxic treatment might diminish the impact of obesity in childhood cancer survivors (CCS). We aimed to evaluate whether altered body composition is associated with gonadal dysfunction in male CCS, independent of gonadotoxic cancer treatment.

Methods

351 male CCS were included. Median age at diagnosis was 5.9 years (0-17.8); median age at follow-up 25.6 years (18.0-45.8). We studied total/free testosterone, sex hormone-binding globulin, inhibin B and FSH. Potential determinants were BMI, waist circumference, waist-hip ratio and body composition measures (dual energy X-ray absorptiometry).

Results

Free testosterone was significantly decreased in survivors with high BMI (BMI ≥30 kg/m^2) (adjusted mean 9.1 nmol/L versus 10.2 nmol/L, P=0.015), high fat percentage (10.0 versus 11.2, P=0.004), and high waist circumference (>102 cm) (9.0 versus 11.0, P=0.020). Survivors with high fat percentage (≥25%) had significantly lower inhibin B/FSH ratios (inhibin B / FSH ratio: ß -34%, P=0.041).

Conclusions

Obesity is associated with gonadal dysfunction in male CCS, independent of the irreversible effect of previous cancer treatment. Longitudinal studies and randomized controlled trials will be required to evaluate whether weight normalization through diet modification and physical activity or bariatric surgery could improve gonadal function, especially in obese survivors with potential other mechanisms then lifestyle causing their obesity.

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Late Effects

LONG-TERM BRAIN STATUS AND COGNITIVE FUNCTIONING IN CHILDREN TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA WITH HIGH-DOSE CHEMOTHERAPY ALONE OR COMBINED WITH REDUCED CNS RADIOTHERAPY

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Objectives

The aim of study was to assess the long term consequences of CNS prophylaxis in children treated due to ALL according to ALL IC-BFM 2002 (high-dose chemotherapy alone vs high-dose chemotherapy combined with prophylactic CNS radiotherapy reduced to 12 Gy).

Methods

Seventy-eight children aged 6.3-21.4 years with ALL treated between 2002-2010 were studied, including 34-treated with chemotherapy, 23-treated with chemo- and radiotherapy, and 21-before treatment (control group). To assess volumetric measurements of subcortical structures responsible for cognitive functioning, volumetric MRI sequences were used. Neuropsychological assessment based on battery neuropsychological tests.

Results

In both groups treated due to ALL, with or without CNS radiotherapy, significantly smaller volumes of hippocampus (p=0.027), amygdala (p=0.007), putamen (p=0.002) and globus pallidus (p=0.001) in comparison to control group were found. In addition, patients treated with CNS irradiation had significantly lower total brain volume as compared to the control group (p=0.025).

All patients treated for ALL had lower IQ level in both verbal (p=0.005) and performance scale (p=0.018) measured by Wechsler Intelligence Scale, worse visual-spatial memory (p=0.025) via Benton's Visual Retention Test, auditory-verbal memory (p=0.001) via Verbal Fluency Test and the level of executive functioning (p=0.001) via Stroop Test and Wisconsin Card Sorting Test, when compared to the control group.

Moreover, patients who received CNS irradiation had lower learning curve (p=0.002) via Rey Test and worse processing speed (p=0.026) compared to patients treated with chemotherapy alone and to control group.

Conclusions

In all children treated for ALL according to the ALL IC-BFM 2002 reduction of subcortical structures volumes is observed. In children treated with or without CNS radiotherapy, cognitive deficits in domain of memory and executive functions are found. Children who were irradiated present decrease in learning process probably caused by lower processing speed in this group.

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Late Effects

RADIOTHERAPY RELATED PREMATURE ARTERIAL AGING IN YOUNG ADULT AND ADOLESCENT SURVIVORS OF HIGH RISK NEUROBLASTOMA

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Objectives

The aim of the study was to evaluate arterial morphology and function in the Finnish national cohort of very long term survivors (>10 years) of high risk neuroblastoma (NBL) treated with high-dose chemotherapy and autologous hematopoietic stem cell transplantation with or without total body irradiation (TBI).

Methods

Common carotid, femoral, brachial and radial artery morphology was assessed with very-high resolution ultrasound (25-55 MHz), and carotid artery stiffness and brachial artery endothelial function were evaluated with conventional vascular ultrasound in 19 adult or pubertal (age 22.7±4.9 years, range 16-30) NBL survivors transplanted during 1984-1999 at the mean age of 2.5±1.0 years, and compared with 20 age- and sex-matched healthy controls. Cardiovascular risk assessment included history, body-mass index, fasting plasma lipids and glucose, and 24h ambulatory blood pressure (BP).

Results

The NBL survivors had consistently smaller arterial lumens, increased carotid intima-media thickness (IMT), plaque formation (N=3) and carotid stiffness compared with the controls. Survivors displayed higher plasma triglyceride and cholesterol levels, increased heart rate, and increased systolic and diastolic BP's. Multiple regression analysis identified TBI (N=10) and a low body surface area as independent predictors for decreased arterial lumen size and increased IMT. Plaques occurred only among survivors who had received TBI.

Conclusions

Adolescent and young adult high risk NBL survivors treated with TBI display signs of premature arterial aging.

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Late Effects

SUPPORTING THE ACADEMIC NEEDS OF PEDIATRIC CANCER SURVIVORS: A MODEL OF CARE

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Objectives

The study objective was to evaluate the effectiveness of a model of psychoeducation, consultation, and advocacy provided by a School Liaison Program (SLP) for families and schools of children whose cancer-related diagnosis or treatment involved the central nervous system compared to a control group of parents of children at risk for neurocognitive deficits based on a diagnosis of Neurofibromatosis type 1 (NF1) who did not receive school-based services.

Methods

After IRB approval, a survey was completed by parents of school-aged children demonstrating academic difficulties associated with their medical diagnosis. Surveys were sent to 125 families of pediatric cancer survivors who received psychoeducation and consultation through the SLP and to the control group of 125 families of children with NF1. The responses of intervention (SLP) and control (NF1) groups were compared using a Wilcoxon rank-sum test.

Results

Ninety-three surveys were returned from the SLP group (74%) and 81 from the NF1 group (65%). Results demonstrated between-group differences in parents' belief that children are meeting academic potential, with parents who received SLP services reporting greater satisfaction with their child's progress, better understanding of learning needs, and an increased ability to access school supports (p=0.02. 0.003, and 0.096, respectively). In addition, parents of children with longer SLP involvement (> 3 years) had better parental understanding (P=0.02) and ability to advocate (P=0.04) than parents of children who had less than 1 year of SLP services. Finally, when the SLP clinician came to patients' schools, there was better parental understanding, better ability to advocate, less difficulty accessing services and greater belief in the child's ability to meet academic potential (p=0.04,0.03,0.04,and 0.004, respectively).

Conclusions

: The consultation, psychoeducation, and parental advocacy training provided by the School Liaison Program improves parent-reported knowledge of special education supports, satisfaction with children's school services, and increased belief that children are meeting their academic potential.

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Late Effects

RISK AND PATTERNS OF UTILIZATION OF COMMUNITY CARE AND MENTAL HEALTH SERVICES AMONG CHILDHOOD, ADOLESCENT AND YOUNG ADULT CANCER SURVIVORS IN BRITISH COLUMBIA, CANADA

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Objectives

The CAYACS (Childhood, Adolescent and Young Adult Cancer Survivorship) program examines multidimensional survivorship issues though linkage of clinical data to population-based administrative databases that contain outcome information. This study describes utilization of home and community care (HCC) and mental health (MH) services among a population-based cohort of 5-year survivors of cancer diagnosed before age 25, in British Columbia, Canada.

Methods

Demographic and clinical records of 5-year survivors diagnosed under age 25 years between 1970 and 1999, identified from the provincial cancer registry, were linked to provincial HCC and MH service records from 1990 to 2004. A comparison group was randomly selected from the provincial health insurance plan registry, frequency-matched by birth year and gender. Frequencies and proportions of services for survivors and comparators were calculated and compared.

Results

500 of the 3,425 survivors (14.6%) had a HCC client record on file, compared to 2.5% of their comparators, a 5.8-fold difference. Survivors showed higher registration rate for each type of HCC service (direct care and long term care (LTC)). Among those who had a client record on file, HCC service utilization by type varies between survivors and the population comparators. 483 of the 500 HCC registered survivors (96.6%) had received direct care services, compared to 743 of the 753 (87.1%) HCC registered comparators. 11.6% of the HCC registered survivors had received LTC care advice; compared to 16.4% of HCC registered comparators. Utilization of MH services showed a different pattern than for HCC. The use of MH services among cancer survivors is only slightly higher than their peers (12.4% vs. %9.2).

Conclusions

CAYAC survivors showed much higher HCC utilization overall than their non-cancer peers, but were only slightly more likely to use MH services. Adult survivors of childhood and AYA cancer require continual surveillance for long-term morbidities.

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Late Effects

MILITARY SERVICE IN MALE SURVIVORS OF CHILDHOOD BRAIN AND SOLID TUMORS

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Objectives

The aim of this study was to examine the acceptance of childhood solid and brain tumor (BT) survivors to the still mandatory military service in Finland, how the conscripts perform in the physical and cognitive tests during the service, and what is the level of military education in childhood cancer survivors compared to healthy controls.

Methods

Male survivors of childhood BT and solid tumors, born from 1960 to 1992, and alive at the age of 18 years (call-up age) (N=1143) were identified from Finnish Cancer Registry. From the Population Registry, five age, sex and place of residence matched controls were identified (N=5714). Information on call-up decisions and military service of the study subjects was collected from the databases of Finnish Defence Forces.

Results

Enlistment frequency was 55% in Hodgkin lymphoma, 35% in BT, 55% in neuroblastoma, 13% in malignant bone tumors, 56% in soft tissue sarcomas, and 68% in kidney tumors. Treatment with irradiation ($p<0.001$) and older age at cancer diagnosis ($p=0.04$) affected the military fitness category. Interruption of service occurred to same extent in survivors and controls. The level of military education did not differ between groups. On average, enlisted solid tumor survivors managed physical tests and training similarly as controls. Only performance in standing long jump was worse ($p=0.005$). Enlisted BT survivors had slightly poorer physical performance than controls ($p=0.05$), both in Cooper running test ($p=0.011$) and in general muscle strenght ($p=0.023$). Solid tumor survivors managed well in cognitive tests, but BT survivors had a decline in all tested cognitive skills. Irradiation treatment did not explain the findings.

Conclusions

Frequency of enlistment was still quite low for cancer survivors. Proportion of those completing service and the level of military education, however, resembled those of controls. Our data give valid information for discussions with cancer survivors preparing for military call-ups.

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Late Effects

TRANSITIONING CHILDHOOD CANCER SURVIVORS TO ADULT CARE: A SURVEY OF PEDIATRIC ONCOLOGISTS

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Objectives

Pediatric oncologists are challenged with transitioning adult childhood cancer survivors to adult-focused care. This study describes transition practices, perceived barriers to transfer, and identifies potential areas for intervention.

Methods

An electronic survey of U.S. members of the Children's Oncology Group; 492/1449 responded (34%) and 347/492 (71%) met eligibility (pediatric oncologist caring for outpatients age > 11 years).

Results

Of the 347 respondents, 50% are male, median years practicing 10 (range 5-22), and 37% practice at a free-standing children's hospital. Almost all care for patients up to age 21 years (96%), 42% report care of patients over age 25 years, and only 16% over age 30 years. While 89% of oncologists report having other staff provide transition education to their patients, 66% report also providing this education to their patients themselves. Compared to the 147 (42%) caring for adult patients >25 years, those who do not were more likely to endorse specific criteria for transfer including survivors' age (p=0.006), pregnancy (p=0.014), marriage (p=0.010), college graduation (p=0.006), and substance use (p=0.036). Most oncologists identified barriers to transfer including patients'/parents' attachment to provider (91%), lack of knowledgeable adult providers (86%), cognitive delay (81%), and unstable social situation (80%). Oncologists who care for patients age >25 years are more likely to perceive parents' attachment to provider (p=0.037) and unstable social situation as barriers to transfer (p=0.044). Four themes emerged from 75 responses to an open ended question inviting further input on transition/transfer practices: importance of standardized transition practices, need for flexible transfer criteria, lack of adult providers with survivorship expertise, and lack of resources.

Conclusions

Most pediatric oncologists report transferring adult childhood cancer survivors to adult care and providing transition education to their patients. Transition practices that include education for adult providers, and address survivors' psychosocial challenges might further facilitate successful transfer.

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Late Effects

SECONDARY CANCERS AFTER CANCER DIAGNOSIS IN CHILDHOOD: A HOSPITAL-BASED RETROSPECTIVE COHORT STUDY IN JAPAN

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Objectives

The objectives of current study are to assess the incidence and risk factors for secondary cancers (SC) in children with malignancies through a nationwide survey in Japan.

Methods

A retrospective cohort study comprising 10,069 children with cancer who were treated between 1980 through 2009 were conducted in 15 Japanese hospitals. The cumulative incidence rate of SC was calculated using competing risk as death and compared by Gray method. The standardized incidence rate ratio (SIR) was defined as the ratio of the number of observed divided by the number of expected cancers using the regional cancer registry data in Japan. The risk factors were analyzed using Cox regression analysis.

Results

One-hundred twenty-nine SC patients (1.3%) were identified in the cohort with a median follow-up of 8.4 years (2 months to 30 years) with total 77,151 person-years observation. The most common SC were acute myeloid leukemia (n=29) followed by myelodysplastic syndrome (n=23), brain tumors (n=17), sarcoma (n=15), adult-type carcinoma (n=15), thyroid cancer (n=12), lymphoid malignancy (n=7) and others (n=11). The cumulative incidence rate was 1.1% (95%CI, 0.9-1.4) at 10 years and 2.6% (95%CI, 2.1-3.3) at 20

years after the diagnosis, respectively. The sensitivity analysis limited to 10 years or longer duration survivors (n=3,155) confirmed these low incidence rates. The SIR of SC was 12.6 (95% CI, 10.5-14.9). In Cox analysis, the hazard ratios for SC were 3.98 in retinoblastoma (95%CI, 1.98-10.0), 3.02 in bone and soft tissue sarcomas (95%CI, 1.57-5.84), 2.27 in allogeneic stem cell transplantation (95%CI, 1.47-3.50), respectively.

Conclusions

The cumulative incidence rate of SC in Japan was not high but SIR was relatively high. Allogeneic stem cell transplantation, and retinoblastoma or sarcoma as a primary cancer were significant risk factors for SC.

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Liver Tumours

DE NOVO MUTATION OF RB1 IN MONOZYGOTIC TWINS WITH HEPATOBLASTOMA

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Objectives

Hepatoblastoma (HB) is the most common malignant liver tumor in childhood and characterized by *ß-catenin* mutations in about 80% of patients. However, the genetic basis of the remaining cases still remains elusive. We aimed at identifying genes that caused early-onset HB development in a pair of monozygotic twins lacking *ß-catenin* mutation

Methods

Genomic DNA of liver tumor tissue and peripheral blood was analyzed by exome sequencing and subsequent Sanger verification. Blood from the parents and the unaffected brother was analyzed as a control. Transcript variants were disclosed by reverse transcription PCR and gel electrophoresis.

Results

Using whole-exome sequencing, we found a heterozygous single nucleotide exchange at the splice-site of intron 21-22 of the *retinoblastoma 1* (*RB1*) gene in a pair of monozygotic twins who developed HB at the age of 8 months. This mutation was detected both in the patients' tumor and blood samples, but was absent in the parents and the unaffected brother, indicating a *de novo* occurrence either in the germ cell of one of the parents or the fertilized egg. On the RNA level, the splice-site mutation gave rise to transcripts skipping exon 21 and/or 21/22, which were expressed in parallel to the wild-type transcript. The patients are alive and disease free eight months after liver transplantation and now closely monitored for retinal pathologies.

Conclusions

This is the first study reporting a point mutation affecting *RB1* integrity in HB. These data advocate the screening of *ß-catenin*-unmutated HB patients for *RB1* mutations.

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Liver Tumours

INTRAOPERATIVE DETECTION OF MICRO-SIZED PULMONARY METASTASES OF HEPATOBLASTOMA USING INDOCYANINE GREEN FLUORESCENT IMAGING

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Objectives

We previously demonstrated that thorough surgical resection of the pulmonary metastatic lesions improves the prognosis of patients with hepatoblastoma. We have introduced intraoperatively indocyanine green (ICG) fluorescent imaging to visualize non-palpable small lesions in 2011. We herein present the usefulness of this modality to complete a thorough resection.

Methods

Five patients with hepatoblastoma associated with multiple lung metastases underwent metastasectomy guided by this method. Their age ranged from 1 to 6 years old. Intraoperative ICG fluorescence imaging was done as follows: ICG (0.5mg/kg) was administered intravenously 24 hours before the operation. Through a thoracotomy, a fluorescent detector combined with an infrared ray radiator (Photodynamic Eye^{R}, Hamamatsu Photonics, Japan) was used to visualize metastatic lesions. All resected lesions were examined histopathologically, and some lesions were examined by a fluorescent microscope specifically made for ICG fluorescence observation. The size of lesions was measured by a microscope.

Results

37 lesions in total were detected as fluorescent-positive and resected. Among them, 11 were CT-negative and 5 were non-palpable. All lesions were diagnosed as hepatoblastoma histopathologically. The smallest diameter of the lesion was 0.062mm. On the other hand, 7 fluorescent-negative and palpable lesions were also resected. All of these lesions were diagnosed as benign histology. Fluorescent microscopy revealed that the fluorescence was observed in the cytoplasm of the tumor cells, and in a case, small blood thrombus was also detected as an origin of fluorescence.

Conclusions

Our results suggested ICG fluorescence imaging was valuable for identifying CT-negative or non-palpable micro-sized pulmonary lesions. But we should pay attention to possibility of false positive originating from thrombus.

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Liver Tumours

HISTOPATHOLOGICAL STUDY OF PRE- AND POST-CHEMOTHERAPEUTIC HEPATOBLASTOMA FOCUSING ON THE SIGNIFICANCE OF IMMATURE-LOOKING CELLS

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Objectives

Comparative histopathological study on hepatoblastoma of pre- and post-chemotherapy has not been carried out sufficiently. Degrees of post-chemotherapeutic histological alternation differ in each case. A subset of hepatoblastomas contain so called 'immature-looking cell' (ILC), described by Zimmermann, which consist of small round cells with marked nuclear expression of beta-catenin and low proliferative activity. However, significance of ILC has not been yet clarified. We verified the histopathological correlation of pre- and post-chemotherapy, and the property of ILC in hepatoblastoma.

Methods

Fourteen hepatoblastomas with pre-chemotherapeutic biopsied specimens and post-chemotherapeutic resected specimens, were collected from archives of our institute. Histological subtype and presence of ILC for pre-chemotherapeutic specimens, and histological pattern of residual tumor and the ratio of necrosis/fibrosis/osteoid for post-chemotherapeutic specimen, were reviewed. Immunohistochemical study were performed for beta-catenin, LEF1, hepatocyte specific marker, AFP, DLK1, glypican-3, and Ki67.

Results

Histological diagnosis of biopsied specimens included one fetal subtype, eleven combined fetal and embryonal type?and two mixed epithelial and mesenchymal type (MEM). Among 14 cases, 5 biopsied specimen, including two MEM, contained foci of ILC (ILC+). Among 5 ILC+ cases, four contained osteoid in the post-chemotherapy specimen, and the remaining one showed extensive fibrosis. In addition, foci of squamous epithelia were observed after chemotherapy in 2 ILC+ cases. Osteoid was also observed in 6 of 9 post-chemotherapeutic ILC- cases. Ratio of necrosis/fibrosis/osteoid area in the tumor after chemotherapy was more than 90% in three (all ILC+ cases), 50%-90% in six (2 ILC + cases), 10%-50% in four, and less than 10% in one.

Conclusions

The results suggested that ILC might be related to the histological alternation including mesenchymal differentiation and/or necrosis/fibrosis, deviating from hepatic cells.

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Liver Tumours

IMPROVING SURVIVALS OF HEPATOBLASTOMA IN DVELOPING COUNTRIES -A CASE SERIES FROM INDIA

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Objectives

to describe overall survival rates of children managed with hepatoblastoma at tertiary care Children's Hospital in India

Methods

eighteen children who were diagnosed with hepatoblastoma , in the age group of 2 months to 10 years from October 2007 to 2013 March were analysed. It is 3 years prospective and 2 nad half years retrospective descriptive study.

Results

Majority of them are between 2 months to 2 years of age(13/18). 10/18 are females. Most common presenting symptom(15/18) was abdominal distention. Two cases were picked up during vaccination visit. None of them had syndromic association. All underwent ultrasound as initial investigation followed by CT abdomen & chest, along with bone scan. Renal functions , liver function , clotting were assessed along with alfa fetoprotein(AFP)levels. AFP was elevated in 16/18 cases, in the range of 44,000 to 5 lakhs. 2 had normal AFP levels. Out of 18, 5 had inoperable tumor, 13had gone through the surgery. Before surgery they received 4 to 6 cycles chemotherapy PLADO(Cisplatin and Doxorubicin) followed by tumor excision through lobectomy. Post op chemotherapy 2-3 cycles given as per AFP levels. All children who had gone through surgical resection are off treatment in the range of 4.2 yrs to 1 year, overall survival is 72%. Out of 5 children with inoperable tumor one child is alive 1.7 years off chemotherapy. Two died secondary to relapsed tumor after initial response. 2 died with progressive tumor.

Conclusions

Hepatoblastoma is chemosensitive tumor , results are good even in developing countries when surgery is combined with chemotherapy and good supportive care.

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Liver Tumours

RHABDOID TUMORS OF THE LIVER : REPORT OF 5 PEDIATRIC CASES TREATED AT A SINGLE INSTITUTE.

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Objectives

Rhabdoid tumors (RTs) of the liver are rare, aggressive and non-secreting malignancies mainly occurring during the first year of life. The definition of RT is histological and relies on characteristic morphology and on the inactivation of the hSNF1/INI1 tumor suppressor gene which encodes a subunit of the SWI/SNF chromatin remodeling complex. The aim of this study was to analyze clinical data, treatments and outcomes in our patients.

Methods

We report retrospectively the cases of 5 patients treated in our institution for RT of the liver between January 2007 and December 2013. Examined variables included age at diagnosis, tumor stage, variable treatment and long-term survival.

Results

Median age at diagnosis was 6 months (range: 4-23). Four patients had diagnosis by percutaneous biopsy and one by laparoscopic biopsy. All patients presented a loss of INI1 expression. Normal or minimally increased serum AFP levels were observed in all patients. No patient presented metastasis at diagnosis. Median follow up was 9 months (range: 9-80). All patients received chemotherapy, with variable regimens, completed by surgical treatment. Two patients (40%) died of disease. They both were mistaken for non secreting hepatoblastomas at diagnosis and had recurrence shortly after completion of treatment. Three patients (60%) are long-term survivors. All of them received multimodal therapy including chemotherapy according to protocol EpSSGNRSTS with doxorubicin and complete surgical removal of the tumor performed within 3 months after diagnosis. One patient had adjuvant radiotherapy.

Conclusions

According to our results, search of INI1 mutation in non secreting hepatoblastomas is mandatory to exclude RT. Chemotherapy with doxorubicin and an aggressive and early surgical treatment seems justified to improve long term survival.

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Lymphomas

PD1+ CELLS IN PEDIATRIC CLASSICAL HODGKIN LYMPHOMA IS ASSOCIATED WITH BETTER OUTCOME

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Objectives

Classical Hodgkin lymphoma (cHL) is characterized by few neoplastic cells in a background of inflammatory cells. Many studies have described the T cell composition of tumour microenvironment in adult cases and we have demonstrated differences between pediatric and adult cHL in this respect. Two studies recently described that high numbers of PD1+ cells were associated with worse survival in adult cHL. PD1 is a receptor expressed by CD8+ and CD4+ T cells upon activation, as well as by T follicular helper cells, exhausted CD8+ T cells and effector memory CD8+ T cells. The objective of this study was to evaluate PD1+ cells in 100 paediatric cHL cases (3 to 18y, median: 14y).

Methods

PD1+ cells were identified by immunohistochemistry and the numbers of these cells were evaluated using computer assisted microscopical analysis. The results were compared with the other T-cell populations as determined in our previous study of these cases.

Results

A median of 5 PD1+ cells/mm^2 was observed (1 to 363 cells/mm^2), while 40% of cases did not show any PD1+ cell. A direct correlation was observed between the numbers of PD1+ and CD4+ cells (P= 0.018), as well as PD1+ and CD8+ cells (P= 0.02). Higher numbers of PD1+ cells were observed in cases with cytotoxic microenvironment profile (P= 0.016), as disclosed by the ratio TIA1+ cells/FOXP3+ cells > 1.5. The numbers of PD1+ cells were not associated with age group or EBV-status. Cases with higher numbers of PD1+ cells (> 5 cells/mm^2) were associated with better 5-years overall survival (P= 0.019).

Conclusions

Our results suggest that the majority of PD1+ cells in the tumour microenvironment of paediatric cHL may contribute to the immune response against the neoplastic cells. A more detailed characterization of these cells is in progress.

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Lymphomas

PATHOGENESIS OF PAEDIATRIC LYMPHOMA: POLYCOMB PROTEIN ANALYSIS

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Objectives

Polycomb genes are a set of epigenetic effectors in multimeric repressive complexes. EZH2 is the catalytic subunit of Polycomb repressive complex 2 (PRC2), which methylates histone H3 lysine 27, thereby silencing several tumor-suppressor genes. EZH2 expression is required in the bone marrow for progression of pro-B cells into pre-B cells. Therefore, genetic inactivation of EZH2 leads to an accumulation of cells at the pro–B-cell stage. However, if EZH2 is inactivated after this phase, additional maturation steps are not hindered, suggesting that EZH2 functions early in B-cell differentiation. EZH2 has been reported to harbour a gain-of-function mutation affecting exon 15 that replace the tyrosine 641 (Y641) residue in 22% of diffuse large B-cell lymphomas (DLBCLs) and 7% of follicular lymphomas (Fls) in adult patients. Aim of our study was to evaluate EZH2 expression and Y641 mutation to estimate its role in paediatric patients with Lymphoma.

Methods

We analysed by Real Time PCR and Western Blotting the expression levels of EZH2 in 20 lymph node biopsies of paediatric patients with Hodgkin/non-Hodgkin lymphoma. We have also studied the EZH2/Y641 mutation by Sanger sequencing.

Results

Our analysis revealed one DLBCL paediatric sample with heterozygous Y641N mutation. Furthermore, a significant increase (75%) in EZH2 mRNA was observed in the patients with advanced stages of Hodgkin lymphoma. Protein expression of EZH2 was detected in 45% of the samples, in particular a higher level of expression in the sample with Y641 mutation.

Conclusions

Our preliminary data showed that EZH2 in paediatric lymphomas, to date not yet been analysed, it seems to have a role in the pathogenesis of these cancer. Further investigations to gain better insight into the dependence of cancer growth on EZH2 is warranted, particularly to unravel the complexity of the protein’s capacity to induce both pro-oncogenic and tumor-suppressive effects.

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Lymphomas

SERUM TARC LEVELS IN A COHORT OF PEDIATRIC PATIENTS WITH HODGKIN LYMPHOMA (HL): A PROMISING BIOMARKER?

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Objectives

TARC (thymus and activation-regulated chemokine) is expressed by Hodgkin Reed-Sternberg cells detectable in serum. TARC seems to have a correlation with adult HL prognosis but there are no data published in pediatrics.

Methods

TARC serum level was prospectively tested in 23 consecutive patients, considering pathological level >500 pg/ml, after report on healthy controls: 20 naïve (Group1); 2 at relapse after autologous stem-cell-transplantation (autoSCT) and one primary-refractory (Group2). In group1 TARC samples were collected at diagnosis, after the 2nd cycle, and at treatment end; in group2 every 2 cycles, after auto-alloSCT, and during follow-up. Patients' characteristics were: median age 13 years (range 5-18), stage III-IV 10, B-symptoms 11, bulky disease 13, extranodal involvement 6.

Results

Basal TARC level (median 51223pg/ml) was high in 21/23patients (range 344-184833pg/ml) and significant higher in bulky disease (p=0.03), higher but not significant in Bsymptoms/stage III-IV patients. In Group1 only two patients had a normal value at diagnosis (1 with stage IIB nodular/lymphocyte predominant variety, the other with stage IIA classical variety), 18 had a significant decline (p =0.0001) after the 2nd cycle, normalization persisted during follow-up; 1 patient (stage IVB) had a significant decrease without reaching normalization while in CCR. Two primary refractories had TARC increasing (>1000 pg/ml) at relapse as compared to remission values. In Group2 two were monitored for TARC during reinduction: one patient had PD with concomitant increasing TARC, the other had TARC normalization while in PR before subsequent allo-SCT. After transplantation, TARC increased before radiological detection of relapse. The primary refractory patient had TARC decrease correlated with PR status.

Conclusions

This preliminary study shows a correlation between TARC both with some clinical risk factors and radiological response. Our first pediatric series needs to be validated in a larger cohort to confirm the clinical application of TARC monitoring.

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Lymphomas

IBRUTINIB SIGNIFICANTLY ALTERS CELL PROLIFERATION AND APOPTOSIS IN BL AND PMBL: IBRUTINIB MAY BE A POTENTIAL ADJUVANT THERAPY IN THE TREATMENT OF BL AND/OR PMBL

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Objectives

BL and PMBL are two common subtypes of B-cell non-Hodgkin Lymphoma in children and adolescents (Miles/Cairo, BJH 2012). Children with relapsed or progressive BL develop chemotherapy-resistant disease and can rarely be cured with salvage therapy (Cairo et al, JCO 2012). Previously, we reported a significant decrease in EFS among pediatric PMBL patients compared with stage III non-PMBL pediatric DLBCL patients following FAB/LMB-96 therapy (Gerrard/Cairo et al, Blood 2013). Bruton's tyrosine kinase (BTK) is a regulator of normal B-cell development and is a component of BCR signaling. Chronic active BCR signaling through BTK activation can be inhibited by the selective and covalent BTK inhibitor, ibrutinib, which recently gained FDA approval in adults with relapsed CLL and MCL. We hypothesize that ibrutinib may be a therapeutic agent in the treatment of BL and PMBL.

Methods

Rituximab-sensitive (Raji, Ramos) and -resistant (Raji 2R) BL cells and PMBL-derived Karpas-1106P cells were exposed to ibrutinib (0-50uM) for 24 hours and evaluated for cell proliferation. Raji, Ramos, and Karpas-1106P were also evaluated for apoptosis and phospho-BTK expression. Ibrutinib was generously provided by Janssen Pharmaceuticals, Inc.

Results

Ibrutinib significantly decreased proliferation in Raji (25uM, 0.622±0.020, p=0.0005, IC50=25.9uM), Ramos (15uM, 0.418±0.040, p=0.015, IC50=11.59uM), Raji 2R (50uM, 0.409±0.165, p=0.001, IC50=31.48uM), and Karpas-1106P (25uM, 0.348±0.035, p=0.006, IC50=16.44uM) cells vs. control. Significant increases in caspase 3/7 activities were observed in ibrutinib-treated Raji (25uM, 1.477±0.133, p=0.013), Ramos (15uM, 2.453±0.053, p=0.008), and Karpas-1106P (25uM, 7.409±1.345, p=0.008) vs. control. Significant decreases in phospho-BTK expression were observed in ibrutinib-treated Raji (5uM, 0.067±0.009, p=0.002), Ramos (5uM, 0.127±0.006, p=0.002), and Karpas-1106P (5uM, 0.166±0.003, p=0.001) vs. control.

Conclusions

Ibrutinib significantly inhibits cell proliferation in Raji, Ramos, Raji 2R, and Karpas-1106P, and increases apoptosis with a concomitant decrease in phospho-BTK expression in Raji, Ramos, and Karpas-1106P. Ibrutinib may be a potential therapeutic

agent in BL and PMBL.

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Lymphomas

CHARACTERIZING STANDARDIZED UPTAKE VALUES ON DIAGNOSTIC PET / CT SCANS ACCORDING TO PEDIATRIC LYMPHOMA SUBTYPES

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Objectives

^{18}Fluorodeoxyglucose Positron Emission Tomography / Computerized Tomography (FDG PET/CT) is being used increasingly in pediatric lymphoma for diagnostic staging, assessment of treatment response, and identification of relapsed disease. PET / CT measures tissue metabolic activity in terms of the Maximum Standardized Uptake Value (SUV max). Whether SUV max at diagnosis is related to pathologic subtype of lymphoma is unknown. The purpose of this study was to characterize SUV max in pre-treatment FDG PET/CT scans in pediatric lymphoma according to pathologic subtype.

Methods

This was a retrospective chart review. Subjects included all patients diagnosed with lymphoma at a tertiary children's hospital from 2005 – 2012 who had a PET/CT scan at the time of diagnosis. Data collected for each subject included the initial SUV max and pathologic subtype of lymphoma. Descriptive statistics were used to summarize the data.

Results

A total of 69 subjects were included, with pathologic diagnoses of Hodgkin Lymphoma (HL), Anaplastic Large Cell Lymphoma (ALCL), Burkitt Lymphoma (BL), Diffuse Large B Cell Lymphoma (DLBCL), B-Lymphoblastic Lymphoma (BLL), and T-Lymphoblastic Lymphoma (TLL). The results are as follows:

	Lymphoma pathologic subtype					
	HL	ALCL	BL	DLBCL	BLL	TLL
Number of subjects	40	3	7	12	2	5
SUV max range	2.2 - 26.8	14.4 - 48.4	13 - 36.8	2.2 - 26.8	2.1 - 5.6	8.2 - 16.4
SUV max mean	8.8	29.3	21.1	16.5	3.9	11.6
SUV max median	11	25.1	16.6	16.1	3.4	11
95% confidence interval	14.4 - 18.5	9.2 - 49.4	14.7 - 27.5	14.4 - 18.5	2.5 - 5.3	9.5 - 12.5

Conclusions

This data suggests that different subtypes of pediatric lymphoma are characterized by different SUV max on pre-treatment FDG PET/CT scans. However, there appears to be significant overlap in ranges of initial SUV max across subtypes. Larger prospective studies are needed to validate this data, and to investigate whether SUV max and change in SUV max with treatment are related to outcomes in pediatric lymphoma.

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Lymphomas

OUTCOME OF SPANISH PATIENTS OUTSIDE EURONET-PHL-C1

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Objectives

In November-2008 Spanish hospitals started accrual to the Euronet-PHL-C1 trial.Due to local difficulties in completing legal requirements some patients from different hospitals were treated outside the trial according to the standard arm and did not benefit from the national pathology review and the central imaging review in Halle for staging and early response assessment.

Objective: Compare outcome of Spanish patients treated outside the trial according to standard arm of Euronet-PHL-C1 trial and those in the trial.

Methods

Patients from Spanish hospitals treated inside Euronet-PHL-C1 trial and those to standard arm of the trial from November 2008 to October 2012.Descriptive statistics.Event free survival Kaplan-Meier estimates.Log-rank test

Results

From November 2008 to October 2012 103 Spanish patients from 19 hospital entered the Euronet-PHL-C1 trial (C1-Spain),accounting for 5% of the 2018 C1 patients.From September-2008 to October-2013 36 Spanish patients from 10 hospitals were treated according to standard arm (noC1-Spain).Treatment group distribution:C1-Spain, TG1-40(39%), TG2-24(23%), TG3-39(38%); noC1-Spain, TG1-15(42%), TG2-15(42%), TG3-6(16%);other C1: TG1-657(34%), TG2-431(22%), TG3-827(43%).EFS at 36 months for C1-Spain is similar to that of other C1-countries (93 vs 88% p=0,45). EFS at 36 months for noC1-Spain is lower than C1-Spain (93 vs 78%,p=0,074).

Conclusions

Outcome of Spanish patients registered into Euronet-PHL-C1 trial is similar to those of other C1-countries. Although numbers are small,understaging may explain the worse outcome trend in Spanish patients treated outside the trial. Participating in prospective international randomized trials with reference pathology and central image review should be encouraged in all Spanish hospitals. National and regional authorities and parents' associations must be made aware of these results in order to facilitate and encourage participation in clinical trials.

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Lymphomas

ASSESSMENT OF TREATMENT OUTCOMES AMONG CHILDHOOD ENDEMIC BURKITT LYMPHOMA AT JARAMOGI OGINGA ODINGA TEACHING AND REFERRAL HOSPITAL, KENYA

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Objectives

To evaluate clinical characteristics and treatment outcomes of children diagnosed with endemic Burkitt lymphoma (eBL) at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH), a regional referral center for pediatric oncology in western Kenya, and to identify factors that are associated with long-term survival.

Methods

A retrospective analysis was conducted for children diagnosed with eBL at JOORTH from 2003 - 2011. Patients were treated with a dose-modified cytotoxic regimen including cyclophosphamide, vincristine, adriamycin, prednisone and intrathecal methotrexate. Kaplan-Meier method and multivariate Cox proportional hazards model were used to evaluate survival probabilities and identify prognostic factors. Age, gender, body surface area (BSA), Plasmodium falciparum malaria infection, hemoglobin levels, tumor staging and deviations from recommended cytotoxic dosing were all evaluated.

Results

Four hundred eight-eight children were included in the analysis; 265 (61%) were male. Mean age at diagnosis was 7.5 years. Murphy stage distribution was stage I, 155 (36%); II, 224 (52%); III, 45 (10%); and IV, 9 (2%). Cyclophosphamide, vincristine and methotrexate dosing deviated by >15% of the recommended dose based on BSA in 13%, 12% and 15% of patients, respectively. Overall in-hospital survival was 67% with an average of 52 days on the ward. Tumor stage and cyclophosphamide dosing emerged as independent factors influencing prognosis. Tumor stage of II or higher, and overdosing with cyclophosphamide were both associated with a significantly increased risk of death, with hazard ratios of 1.9 (95% CI 1.2-3.2, p=0.007) and 3.4 (95% CI 1.4-7.9, p=0.004), respectively.

Conclusions

Our findings suggest: i) advanced stage of presentation remains a barrier to improving long-term survival among children with eBL, ii) lower doses of cytotoxic agents may be better tolerated in settings with limited supportive care, and iii) insufficient pharmacy and nursing support may contribute to treatment failure, particularly with the administration of complex chemotherapeutic regimens.

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Lymphomas

CLINICAL OUTCOME OF CHILDREN WITH ANAPLASTIC LARGE CELL LYMPHOMA WHO UNDERWENT IN POLAND ALLOGENEIC OR AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN YEARS 2000-2013

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Objectives

Risk of relapse and progression of disease in children with anaplastic large cell lymphoma(ALCL) remains very high(28%). Here we report the clinical characteristics and outcome of patients(pts) with relapsed ALCL,who underwent either autologous or allogeneic haematopoietic stem cell transplantation(HSCT).

Methods

27pts with ALCL were registered in Polish Paediatric Leukemia/Lymphoma Study Group(PLLSG) in years 2000-2013. 25of them(28,7 %) developed relapses during or after the 1st line treatment (7F/18M). Clinical stages: II/4, III/11, IV/10 ;risk groups: standard/4 ,high/21. All relapsed pts were treated according to the ALCL-Relapse 2004 protocol. After 2ndor 3rd line of treatment 17pts achieved CR,8pts died of disease progression(DOD). 13pts with relapsed ALCL underwent 15 transplantation: 4/autologous(autoHSCT), 3/matched sibling donor(MSD), 8/matched unrelated donor(MUD),2pts had to be retransplanted due to relapse after auto-HSCT (1/MUD,1/MSD), the transplantation center were:9/Wroclaw, 6/others: Poznan, Lublin, Bydgoszcz). Median age at HSCT:12.08 years(range3.4-18.8). The source of stem cells were: bone marrow(BM)(n=2), peripheral blood stem cells(PBSC)(n=13). Primary conditioning regimen for transplant procedures: auto-HSCT: BEAM (BCNU+VP-16+Melphalan+ARA-C), allogeneicHSCT: MUD/MSD:TBI,Thiotepa+VP-16+/-ATG. ATG was used in all MUD transplant recipients as a GvHD/graft rejection prophylaxis.

Results

All of 13pts engrafted and achieved CR after HSCT,2pts after auto-HSCT relapsed and underwent subsequent allogeneic HSCT. Outcome after 15 HSCT in 13pts: 5pts died due to TRM:1pt/ cardiac and renal dysfunction 26days after HSCT, 3pts/GvHD late posttransplant (6,6.5 and 24 months after HSCT),1pt/pulmonary aspergillosis 14months after HSCT. 8pts remain alive in CR after HSCT: 7/without any transplant-related complications, 1/chronic GvHD(liver, skin) and pulmonary aspergillosis. 2/4pts after

auto-HSCT remain alive in 2nd CR, 2pts relapsed and achieved persistent CR after allogeneicHSCT but died due to TRM.

Conclusions

As the risk of relapse for pediatric ALCL is very high (28%) the use of allogeneicHSCT seems to be a potentially curative option. Reduction of toxicity leading to TRM is essential to improve the overall results of allogeneic HSCT.

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Lymphomas

ANESTHETIC MANAGEMENT OF CHILDREN WITH ANTERIOR MEDIASTINAL LYMPHOMAS (AML)

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Objectives

Children with aML may experience serious complications during general anesthesia, due to compression of trachea/bronchi, hearth and main vessels. In our Institution, specific guidelines for anesthesia have been used since 2004 and recognize three groups of patients:

Methods

Groups A (no respiratory symptoms, no compression of trachea/hearth/main vessels): 27 patients

Group B (mild respiratory symptoms, no vascular compression, tracheal compression <50%): 15 patients

Group C (severe respiratory symptoms and/or vena cava syndrome and/or tracheal compression >50%): 15 patients

Results

Group A. Six, cooperative, underwent supra-clavicular/cervical lymph-node biopsy (CLNb) with local anesthesia (LA); 14, non cooperative, underwent CLNb using mild sedation (midazolam, ketamine, alfentanyl); 2 underwent CLNb and 5 Chamberlein procedure under general anesthesia (GA) with tracheal intubation, spontaneous ventilation, and without using muscle relaxant drugs. Median MMR (mediastinal mass to chest diameter ratio) was 0.36.

Group B. Two underwent CLNb with LA; 5 underwent Chamberlein procedure and 1 CLNb under GA as above; 7 had CLNb or trucut of the mass under LA and anxiolytic medications (midazolam): in 2/7, since diagnosis was not obtained, a Chamberlein procedure and CLNb were necessary under GA. Median MMR was 0.42.

Group C. Four underwent CLNb, 1 trucut biopsy of the mass, 5 Chamberlein procedure under LA and anxiolytic medications; 4 had CLNb under LA; 1 patient was treated with steroids before the biopsy. In 3 cases, mild episodes of cardiorespiratory breakdown occurred, requiring a change of the patients' position during the procedure. Median MMR was 0.47.

Conclusions

The anesthesiologic risk in patients with aML always needs to be carefully calculated and discussed in a multidisciplinary setting, including children' parents. In our recent experience, since the use of these guidelines, which combine a thorough preoperative assessment, less invasive anesthesiologic methods, whenever feasible, and a possible rapid surgical procedure, we could obtain the correct diagnosis, without severe complications.

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Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

EVALUATION OF AN ESTABLISHED TREATMENT RELATED MORTALITY RISK SCORE FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN IN A SINGLE CENTER OVER A TWENTY YEARS PERIOD

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Objectives

Matthes et al. [1] described a risk score for 1year treatment related mortality (1-TRM) after hematopoietic stem cell transplantation in children. Age ≥10 years, advanced disease, and donors other than matched sibling donors (MSD) were characterized as risk factors. We evaluated this risk score in patients transplanted over a 20 year period at our center which is a reference center for myelodysplastic/myeloproliferative syndromes (MDS/MPS) including juvenile myelomonocytic leukemia (JMML).

Methods

Data from 265 consecutive patients transplanted between 1994 and 2011 were analyzed retrospectively.

Results

Median age at transplantation was 8.6 (0.3-21.0) years. Diagnosis included MPS/MDS (n=98), other malignancies (n=88), and non-malignant disorders (n=79). Most patients received a myeloablative preparative regimen (76.6%), had a matched unrelated donor (62%) and received a bone marrow graft (66%). The 5-year overall survival was 69% (63-75). 1-TRM occurred in 41 (15.5%) patients. 1-TRM was 6.4%, 17.5%, 13.4% and 37.5% for patients with a risk score of 0, 1, 2 and 3, respectively, thus not demonstrating a steady increase of 1-TRM with increasing risk score. However, 1-TRM increased according to the risk score and was comparable to the results of Matthes in the earlier time period (1994-2003). This observation may reflect the decline in 1-TRM in patients transplanted from an unrelated donor due to better HLA-Typing. Due to our center's specialization, several diagnoses, like JMML and advanced MDS were overrepresented. Adapting the risk score by considering these disorders as advanced disease the score system worked well.

Conclusions

The 1-TRM score of Matthes has to be adjusted when patient subgroups are heavily overrepresented in cohorts studied as compared to the reference cohort.

1. Matthes-Martin, S., et al., *Risk-adjusted outcome measurement in pediatric allogeneic stem cell transplantation.* Biol Blood Marrow Transplant, 2008. 14(3): p. 335-43.

P-146

Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

THE +3010G-G AND +3142C-C HOMOZYGOUS HAPLOTYPES AT THE HLA-G 3' UNTRANSLATED REGION ARE ASSOCIATED WITH DECREASED OVERALL AND EVENT-FREE SURVIVAL IN CHILDHOOD ACUTE MYELOID LEUKEMIA

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Objectives

HLA-G, a major histocompatibility complex class 1b molecule, exhibits immunomodulatory functions with a role in cancer and allotransplantation, but much controversy has arisen regarding its role in leukemia. We aim to evaluate the possible association of the *HLA-G* 3'untranslated region (UTR) alleles with Acute Myeloid Leukemia (AML), to measure soluble HLA-G (sHLA-G) levels in bone marrow of children with AML, and assessed HLA-G features of childhood AML according to overall and event-free survival.

Methods

A hundred and nine consecutive unselected children with AML referred to the Instituto de Medicina Integral Professor Fernando Figueira in Recife, Northeastern Brazil, from 2005 to 2012, were studied. At diagnosis, the leukemia was characterized by blast morphology, phenotyping and genetic abnormalities. Polymorphic sites at the 3'UTR of the *HLA-G* gene were investigated in 97 AML and 91 healthy unrelated children by gene amplification and sequencing. Allelic and genotypic frequencies were estimated using Genepop and Arlekin softwares. sHLA-G was measured in leukemia and normal free-cell bone marrow by ELISA. Statistical analyses were done using R-software.

Results

AML patients were classified into non-APL (n=76), APL (n=25) and secondary AML (n=8). In non-APL, children exhibiting the +3010C-C/+3142G-G diplotype showed a worsened overall survival in relation to those exhibiting the +3010G-G/+3142C-C diplotype (*P*=0.058; hazard=2.06; 41% x 24% deaths) and in relation to patients exhibiting the heterozygous +3010C-G/+3142C-G diplotype (*P*=0.051; hazard=1.94; 41% x 35% deaths). The majority of AML patients exhibited low bone marrow sHLA-G levels (mean=120.44 ± 160.21 units/mL and median=44.16 units/mL). The variance of sHLA-G levels in children exhibiting +3010G-G/+3142C-C homozygous haplotype was different compared with children carrying +3010C-C/+3142G-G or +3010C-G/+3142C-G haplotypes (*P*=0.0098).

Conclusions

Down regulation of bone marrow' sHLA-G might be involved in childhood AML pathogenesis, and disease outcome.

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Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

CYTOGENETIC PROFILE OF ACUTE MYÉLOBLASTIC LEUKAEMIA IN TEENAGERS AND YOUNG ADULTS: A SINGLE CENTER EXPERIENCE

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Objectives

At present, cytogenetic aberrations detected at the time of acute myeloblastic leukaemia (AML) diagnosis constitute the most common basis for predicting clinical outcome.There have been minimal data on the cytogenetic profile of AML in young adults in low-income countries.

Aim:

To analyze the cytogenetic characteristics of young patients with the novo AML.

Methods

From 25/1/04 to 1/12/10, eligible patients aged between 15 and 30 years old with de novo AML were included to the AML-MA2003 protocol. Were excluded patients with Acute Promyelocytic Leukemia (APL), secondary AML and AML with myélodysplasia. Cytogenetic analysis was done at diagnosis. We separate our cytogenetic findings into three broad prognostic categories: favourable, intermediate and adverse*.Treatment included two inductions and two consolidations.

Results

989 patients with AML were followed in our department. 236 patients were aged between 15 and 30. 24 patients were excluded, 14 had APL. 212 patients with de novo AML were included. AML subtype 2 was the most frequent in 74 (35%) patients. Karyotype was done in 189 (89%) patients and Cytogenetic analysis failed in 8 cases (4%). 23 (11%) patients didn't have a cytogenetic study.

181 patients with cytogenetic analysis results were eligible. Cytogenetic findings were divided into three groups:

- Favorable: 51 (28%), 44(24%) had t(8;22) and 7 (4%) had Inv 16.
- Intermediate: 103 (57%), 60 (33%) had a normal caryotype.
- Adverse: 27 (15%).

176 patients were treated. The OS rate among favourable, intermediate and adverse group was respectively at 36% 28% and 22%.

Conclusions

Our cytogenetic profile reveals some particularities: the High range of t(8,21) at 24% probably due to the young age of our patients and a majority of intermediate group (67%).The challenge of our future studies is to determine the prognosis significance of normal caryotype with molecular technical such as FLT3 and NPM1.

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Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

SOMATIC THROMBOPOIETIN (TPHO) GENE MUTATIONS IN CHILDHOOD MYELOID LEUKEMIAS

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Objectives

We report, for the first time, a non-syndromic infant with a myeloproliferative condition that harbors a germline hereditary thrombopoietin (*THPO*) gene mutation. Our patient was from a Dutch family with a G>C mutation at the splice donor site of intron-3 of the *THPO* gene, which is known to induce familial thrombocytosis (FT) at increasing age, involving the regulation of megakaryopoiesis. FT is generally characterized by sustained proliferation of megakaryocytes resulting in elevated platelet counts.

The five known mutations in the *THPO* gene are located in the 5'untranslated region (5'UTR) of the *THPO* gene. These mutations lead to increased translation of *THPO* by inhibiting or removing the upstream open reading frames (uORFs).

The monocytic hyperproliferation at infant age of our patient seemed to occur in conjunction to her germline*THPO* mutation, which could suggest that THPO is involved in hyperproliferation of the monocytic progenitor and -cell lineage.

It was recently suggested that gain-of-function mutations in the *THPO* gene might predispose to adult acute myeloid leukemia, myelofibrosis and multiple myeloma. In contrast, the occurrence of somatic *THPO* mutations in sporadic pediatric AML patients was never described.

Methods

We performed a mutation screening of a representative and well-characterized cohort of pediatric AML (*n*=264), ML-DS (*n*=16) and JMML (*n*=47) samples by amplifying the 5'UTR region of *THPO*.

Results

The screening revealed 1/327 case with a gain-of-function mutation, in the exon-3 intron-3 splice site (c. 13+3 G>A) in a 7-year-old AML patient (inv16).

Conclusions

We conclude that somatic mutations in the *THPO* gene seem to be rare in sporadic childhood myeloid malignancies. Nevertheless, a germline *THPO* mutation may be considered in an infant with a TMD-like disease, without dysmorphic features and cytogenetic aberrations, as this diagnosis may have important implications for clinical course, treatment and genetic counseling.

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Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

FLT3 INTERNAL TANDEM DUPLICATION AND NPM1 MUTATIONS IN PAEDIATRIC AML: A SINGLE CENTRE EXPERIENCE

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Objectives

FLT3 internal tandem duplications (ITD) and high alleleic ratio are associated with high relapse risk in AML, although additional NPM1 mutations may reduce the risk. Relatively little paediatric data about treatment and outcome is available. To date, no therapy is of proven benefit. FLT3 inhibitor, sorafenib and haematopoetic stem cell transplantation (HSCT) are treatment options. We present our experience of FLT3 and NPM1 mutations in paediatric AML.

Methods

Retrospective data analysis was carried out to identify children with FLT3/ITD with/without NPM1 mutation. Clinical profile, response to chemotherapy and outcome was noted. Treatment was according to UK guidelines.

Results

FLT3-ITD and NPM1 mutations were evaluated in 48 paediatric patients (age ≤ 18 years) with AML since year 2008. Eight patients, median age 9 years (range 7-17 years), were identified with FLT3/ITD giving a frequency of 16.6% in this cohort. Four patients entered remission after one course of ADE. One of these had isolated skin relapse immediately before planned HSCT. Second remission was achieved with clofaribine, DaunoXome, sorafenib followed by transplant. Another relapsed 3 months after completing chemotherapy and died of refractory diseases despite FLA-X and sorafenib. Three patients had refractory disease after first course of ADE. Sorafenib and FLA-IDA was used in second course. One patient with additional NPM1 mutation had pharyngeal granulocytic sarcoma without marrow involvement and responded well to chemotherapy. Six patients were transplanted successfully (5 unrelated including one double cord and one matched sibling), 5 in CR1 and one in CR2. All remain in remission, median 441 days (range 80-2081 days).

Conclusions

Inspite of small numbers, this experience is consistent with previous reports that children with FLT3 ITD have an aggressive course of AML often with poor response to first course of chemotherapy. Longer follow up is required to see whether HSCT improves disease control and overall survival.

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Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

BASELINE HIGH RESOLUTION CT SCAN (HRCT) THORAX FOR DETECTING RESPIRATORY INFECTION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) AT PRESENTATION

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Objectives

Intensive chemotherapy in AML increases infectious complications; especially pulmonary (bacterial and fungal) leading to dismal prognosis. The aim of this study was to assess the incidence of baseline pulmonary infection by HRCT chest in AML patients before starting induction.

Methods

This is a prospective, observational, single centre study of consecutive pediatric (< or = to 21 years) AML (excluding APML) patients who were treated at Tata memorial centre from 1st June 2013 to 31st January 2014. All eligible patients underwent baseline HRCT thorax before initiating induction; which were centrally reviewed by the radiologist.

Results

Out of 40 patients enrolled, the mean age was 12 years (1-21); 82.5% were males; 80% had fever; 30% had respiratory symptoms; 7.5% had abnormal chest examination; 75% had good and intermediate ; and 25% had poor risk cytogenetics. Their mean symptom duration was 2 months. Twenty two patients (55%) had an abnormal HRCT thorax. Among these, 5 (22.7%) had possible bacterial; 12(54.5%) had fungal infection and 10(45.4%) had miscellaneous findings like tuberculosis, pneumocystis carinii and non specific nodules. On univariate analysis, the presence of fever (p=0.007), respiratory symptoms (p=0.018), and poor risk cytogenetics (p=0.01) were significantly correlated with abnormal HRCT scan. However, on multivariate analysis, only respiratory symptoms and poor risk cytogenetics were statistically significant (p = 0.023 each).

Conclusions

HRCT Chest is an excellent imaging modality in AML to detect baseline pulmonary infection and should be included in diagnostic work up in centres with significant rate of infection. This would help to choose antifungal prophylaxis versus treatment thereby improving morbidity and mortality during intensive AML induction.

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Myeloid Leukemias, Myelodysplastic Syndromes, Myeloproliferative Syndromes

UNDERLYING UNDIAGNOSED INHERITED MARROW FAILURE SYNDROMES AMONG CHILDREN WITH CANCER

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Objectives

To determine the prevalence of children with cancer who have an underlying inherited bone marrow failure syndrome (IBFMS)

Methods

A retrospective review of medical records of newly diagnosed pediatric cancer patients at The Hospital for Sick Children from June 2009 to May 2010 was conducted. Clinical, laboratory and radiologic parameters were extracted from the patient charts focusing particularly on findings suggestive of possible underlying IBMFS.

Table I. Findings suggestive of underlying IBMFS in newly diagnosed cancer patients

Family history of cancer at age < 50 years
Associated physical anomalies (on physical or radiological examination)
History of previous cytopenia
Elevated MCV
Elevated hemoglobin F
Severe toxicities from chemotherapy or radiation treatment.

Results

Records of 276 patients were reviewed. Five candidate patients (1.8%) were identified. Three presented with acute leukemia. Two presented with kidney malformations and elevated MCV and elevated hemoglobin F was seen in one patient. One patient developed grade 4 toxicities in response to chemotherapy. The fourth patient presented with a brain tumor, later developed severe toxicities to chemotherapy (prolonged pancytopenia) and his father was diagnosed with nasopharyngeal carcinoma in his 30s. The fifth patient presented with Wilms tumor, congenital anomalies and elevated hemoglobin F.

Conclusions

Our data suggest that a small fraction of patients with cancer have clinical features that indicate an investigation to rule out underlying IBMFSs. Careful evaluation of indicators of IBMFSs is helpful to personalize treatment, minimize toxicity and provide appropriate family counseling and prognosis. Prospective studies are necessary to accurately determine the prevalence of IBMFSs among newly diagnosed cancer patients

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Neuroblastoma

LNCRNA EXPRESSION SIGNATURES OF NEUROBLASTOMA REVEALS THE POTENTIAL ROLE OF LNCRNA IN CONTRIBUTING TO NEUROBLASTOMA PATHOGENESIS

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Objectives

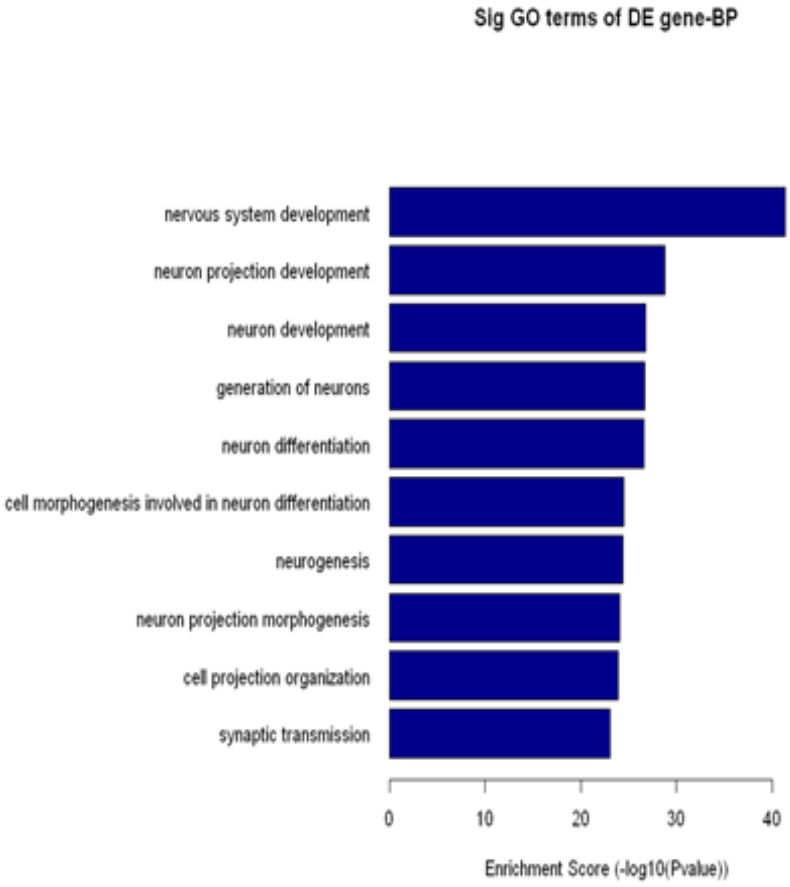
Long non-coding RNAs (lncRNAs) are broadly defined as transcribed RNA molecules greater than 200nt in length and lacking an open reading frame of significant length (less than 100 animo acids). The purpose of our study is to investigate the differentially expressed lncRNAs in neuroblastoma.

Methods

The tumor tissues and para-tumor tissues were collected and stored in the past two years (2011.12-2013.12). In this study, lncRNA microarray (Human LncRNA Microarry V3.0) was used to investigate the differentially expressed lncRNAs in 12 samples (6 tumor tissues, 6 para-tumor tissues).

Results

There were 4802 lncRNAs and 5130 mRNAs differentially expressed between the tumor tissues and para-tumor tissues(tumor VS para-tumor, 3098 lncRNAs and 2526 mRNAs up-regulated, while 1704 lncRNAs and 2604 mRNAs down-regulated). In Gene ontology (GO) analysis, there were 1609 differentially expressed genes, involved in 728 biological processes, up-regulated (341 genes' fold enrichment?2, $P<0.05$) while 1698 genes that involved in 943 biological processes down-regulated (456 genes' fold enrichment?2, $P<0.05$) in tumor tissues. By comprehensively analyzing, 140 enhancer-like lncRNAs and 325 nearby coding genes had been demonstrated to express differentially meanwhile (fold change?2, $P<0.05$). Especially, the RP11-204E9.1 lncRNA up-regulated (fold change=7.112, $P<0.01$) with the nearby coding gene SOX4 up-regulated synchronously (fold change=28.1, $P<0.01$) in tumor tissues. Those findings were comfirmed by the subsequent PCR results in 30 neuroblastoma samples and 10 para-tumor tissues.


Sig GO terms of DE gene-BP
nervous system development
neuron projection development
neuron development
generation of neurons
neuron differentiation
cell morphogenesis involved in neuron differentiation
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0
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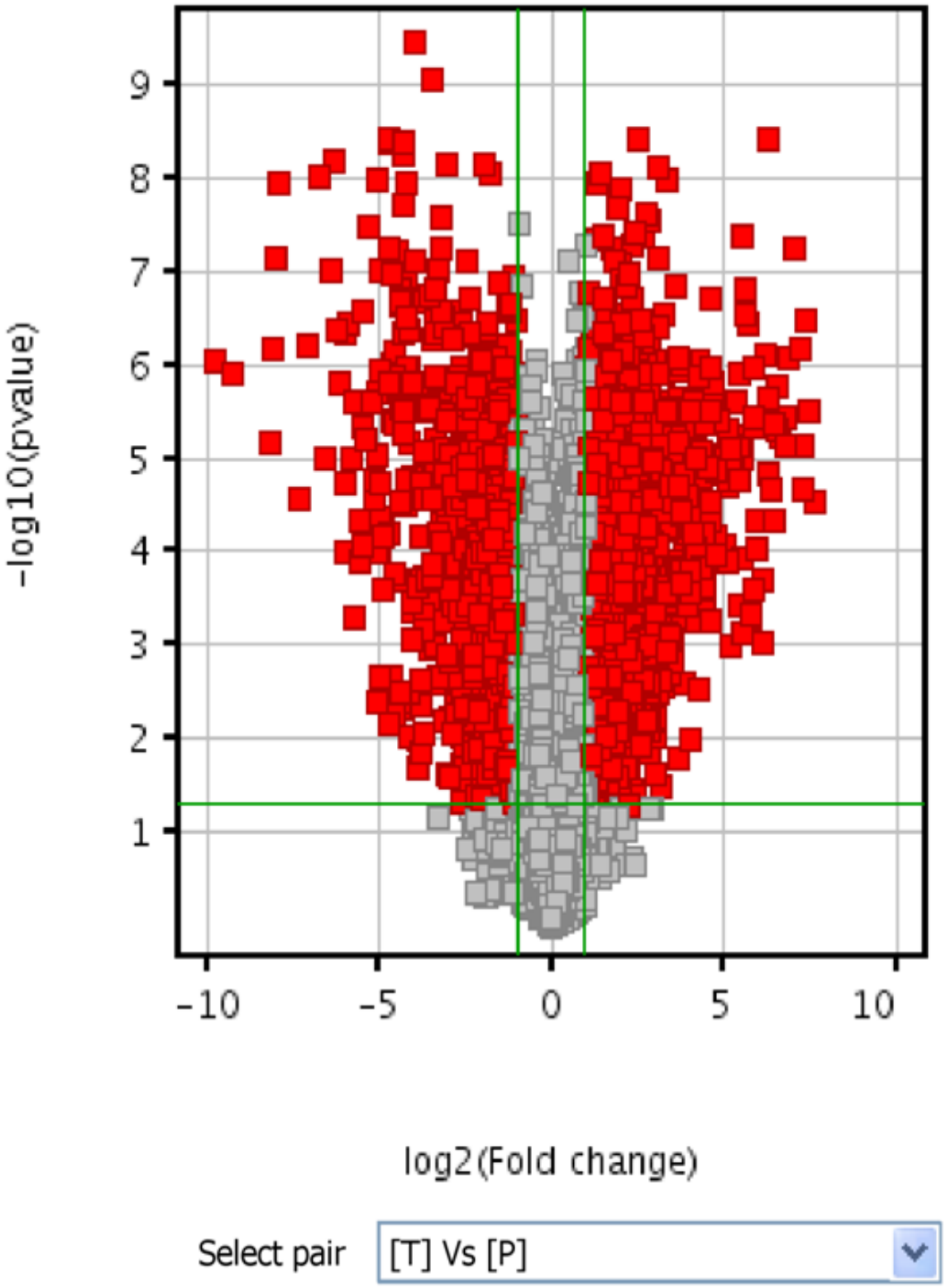
Enrichment Score (-log10(Pvalue))



Conclusions

Our experiments provide a list of differentially expressed lncRNAs and mRNAs in neuroblastoma that could be useful for further study. The novel lncRNA RP11-204E9.1 maybe play an important role in neuroblastoma pathogenesis by regulating its nearby coding gene SOX4.

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Neuroblastoma

COPY NUMBER VARIATIONS (CNVS) CAN DEFINE THE PROGNOSIS IN NEUROBLASTOMA PATIENTS

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Objectives

1p, 11q deletions, *MYCN* amplification (MNA) are known to be adverse prognostic markers in neuroblastoma, while significance of many other CNVs is unclear.

Methods

We analyzed 108 neuroblastomas by MLPA for loci 1p,2p,3p,11q,17q and 100 tumors for 4p,7q,9p,12q,14q. Prognostic significance was estimated by overall (OS) and event-free survival (EFS) with median of follow-up time 28 months (range 1-166 months).

Results

In 29 patients (26.9%) 1p deletion was revealed and had prognostic impact (EFS 0.33±0.10 vs. 0.67±0.06, p=0.002, OS 0.46±0.10 vs. 0.73±0.06, p=0.003). 17q gain was detected in 54 patients (50.0%) and led to decreased survival rates (EFS 0.42±0.08 vs. 0.71±0.07, p<0.001, OS 0.48±0.09 vs. 0.80±0.06, p=0.002). Both 1p deletion and 17q gain retained prognostic significance in *MYCN* non-amplified patients.

2p24 gain including *MYCN* was observed in 15 patients (13.9%) and showed prognostic significance in patients under 1 year (EFS 0.53±0.25 vs. 0.96±0.04, p=0.047).

4p gain detected in 8 patients (8.0%) decreased EFS in patients under 1 year (0.00 vs. 0.88±0.06, p=0.055). Gain of both 7p and 7q (6 patients, 6.0%) led to reduced EFS in the whole group (0.33±0.19 vs. 0.56±0.06, p=0.053) and in *MYCN* non-amplified patients (0.40±0.22 vs. 0.64±0.06, p=0.044).

In 8 patients (8.0%) 9p deletion was found. Presence of this aberration resulted in dramatic decreasing of survival rates: both EFS and OS were 0.00 vs. 0.60±0.06 and 0.68±0.06 correspondingly, p=0.035, p=0.014).

In multivariate analysis of OS performed by stage, age, MNA, 1p, 9p deletions and 17q gain as covariates patients with stage IV (p=0.042), MNA (p=0.049) and 9p deletion (p=0.041) had significantly poor survival.

Conclusions

In our cohort of patients MNA, 1p, 9p deletions and 17q gain demonstrated negative prognostic significance. MNA and 9p deletion were defined as independent molecular adverse factors. Presence of 2p24 and 4p gains led to decreased EFS in the group of patients below 1 year.

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Neuroblastoma

ROLE OF LMO1 IN NEUROBLASTOMA INITIATION AND MAINTENANCE: ANALYSIS IN THE ZEBRAFISH MODEL OF CHILDHOOD NEUROBLASTOMA

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Objectives

Neuroblastoma, an embryonic tumor of the peripheral sympathetic nervous system (PSNS), accounts for 10% of all childhood cancer deaths. We recently developed a robust zebrafish model of neuroblastoma and demonstrated that activated ALK synergizes with MYCN by inhibiting a developmentally-timed apoptotic response that is otherwise induced by MYCN. We have now used this model to provide evidence in support of the results of a genome-wide association study (GWAS) conducted by Dr. John Maris's group. Their study revealed that inherited common single nucleotide polymorphisms (SNPs) within the LIM domain-only 1 (LMO1) gene locus are highly associated with the development of advanced neuroblastoma. In children with a higher risk of developing neuroblastoma, LMO1 is overexpressed without alteration of the coding sequences.

Methods

Accordingly, we developed two independent transgenic lines in which the human *LMO1* gene is overexpressed in the PSNS under control of the zebrafish dopamine-beta-hydroxylase (dβh) promoter. Both lines were bred to heterozygous transgenic fish overexpressing MYCN-EGFP in the PSNS under the control of the dβh promoter.

Results

Our recent results show that overexpression of LMO1 in the zebrafish model markedly accelerates the onset and increases the penetrance of MYCN-induced neuroblastoma, providing in vivo evidence for the role of LMO1 overexpression in the initiation of neuroblastoma. LMO1 accelerates tumorigenesis primarily by increasing the proliferative rate of MYCN expressing sympathetic neuronal progenitors. In addition, we found that coexpression of LMO1 with activated ALK induced neuroblastoma, which is the first time that neuroblastoma has been induced in the zebrafish system without MYCN overexpression.

Conclusions

Thus, the zebrafish model system appears to be ideal for "functional genomics analysis" to provide in vivo evidence and investigate mechanisms and pathways underlying new associations emerging from GWAS, tumor genome resequencing and other genome-wide technologies that are currently under intense investigation in human cancers.

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Neuroblastoma

PROGNOSTIC VALUE OF FLOW CYTOMETRIC BONE MARROW INVESTIGATION IN NEUROBLASTOMA PATIENTS

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Objectives

Bone marrow (BM) micrometastases detection in children with neuroblastoma (NB) is crucial for correct patients staging and risk group stratification. Flow cytometry (FC) is widely available, fast and easy-to perform approach for finding NB cells among normal BM hematopoietic cells. Aim of the study was to investigate prognostic significance of flow cytometric tumor cells' detection in BM of children with NB at the time of diagnosis.

Methods

51 patients (24 boys and 27 girls) aged from 6 days to 15 years (median age 1 year 3 months) with NB were included in the study. BM samples at the time of diagnosis were obtained from 1-5 aspiration sites per patient (median 3 samples per patient). 4-5-color FC was applied for CD45(-)CD56(+)CD81(+)GD2(+)CD9(+)-cells evaluation.

Results

NB cells were detected in BM by FC more frequently comparing to conventional cytomorphology (49.0% and 29.4% patients respectively, ?=0.043). Patients with NB cells detected in BM by FC had significantly worse event-free survival, overall survival and progression-free survival (28.0±9.0%, 35.8±10.7% and 34.3±10.4% respectively) in comparison to children with negative result of immunophenotyping (83.5±7.6%, 87.7±6.7% ? 86.8±7.1% respectively, $p<0.001$ in all cases). BM involvement detection by FC maintained its prognostic significance in following patients groups distinguished by other stratification criteria: patients without *MYCN* amplification, patients without BM lesion as assessed by cytomorphology, patients younger than 1 year, patients older than 1 year, patients with stages I-III and IVS, patients with stage IV, patients with localized tumor (stages I-III). In multivariate analysis immunophenotyping proved to be an independent prognostic factor when analyzed jointly with other risk factors such as age, disease stage and *MYCN* amplification.

Conclusions

Thus flow cytometric BM involvement detection could be used in combination with other parameters for the treatment strategy choice in patients with NB.

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Neuroblastoma

PROTEIN SIGNATURES IN THE SERUM OF PATIENTS WITH NEUROBLASTOMA

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Objectives

Neuroblastoma is a very heterogeneous tumor with outcomes ranging from excellent survival to high risk of failure. With the goal of developing better prognostic indicators, the Children's Oncology Group (COG) has collected serum samples from a large number of subjects at the time of diagnosis. These samples can be used to characterize protein signatures in the blood indicative of tumor type, response to therapy, and relapse post treatment.

Methods

We measured the relative concentration of 103 low abundance proteins with a customized human cytokine antibody array (Raybiotech, Inc.) in 50 subjects with osteosarcoma, 50 subjects with Wilms tumor, and 87 subjects with neuroblastoma (30 with stage 2 favorable histology, 30 with stage 4 MYCN amplified, and 27 with stage 4 MYCN-non-amplified). Sera were collected at diagnosis locally and through the COG. These samples were compared to 150 age- and gender-matched samples from healthy subjects using a mixed effects model. Several standard statistical learning approaches were used to classify the serum of children with neuroblastoma versus those of healthy controls.

Results

In comparison to healthy control samples, 34 proteins were differentially abundant in samples of subjects with MYCN amplification and high risk neuroblastoma, and 13 proteins were differentially abundant in samples of subjects with low risk neuroblastoma. Samples of subjects with MYCN amplification and high risk neuroblastoma contained 22 proteins differentially abundant when compared to sera from subjects with Wilms tumor or osteosarcoma, with 4 proteins differentially abundant for both and 9 unique to each. The classification results were consistent across the five classification algorithms used, with an average specificity of 90% and an average sensitivity of 74%.

Conclusions

This study demonstrates that multiple low abundance proteins form an accurate signature that can distinguish healthy and diseased subjects as well as different cancer types.

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Neuroblastoma

BONE MORPHOGENETIC PROTEIN RECEPTOR II SUPPRESS NEUROBLASTOMA PROLIFERATION IN VITRO AND IN VIVO

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Objectives

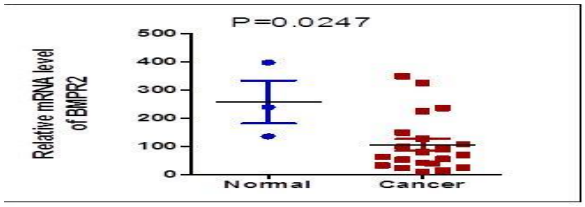
BMPR2, Bone morphogenetic protein receptor II, encodes a member of the bone morphogenetic protein receptor family of transmembrane serine/threonine kinases. The aim of this study was to determine whether the different expression of BMPR2 will affect neuroblastoma cell proliferation.

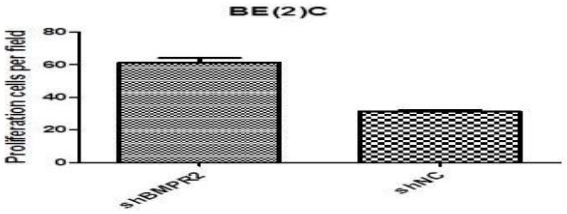
Methods

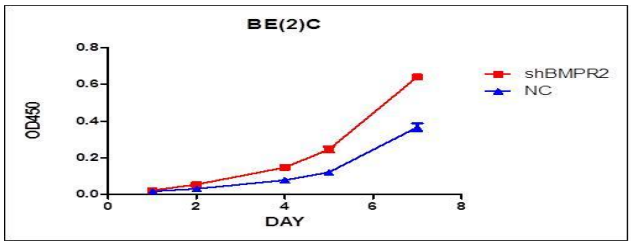
Specimens of neuroblastoma were obtained from hospital. The BMPR2 shRNA vector was transfected to NB cell lines SK-N-BE(2) and KP-N-NS, the BMPR2 overexpression vector was transfected to NB cell lines IMR-32, SK-N-SH and SH-SY5Y. The efficiency of gene silence or overexpression was confirmed by Quantitative real-time PCR and western-blot. Cell proliferation ability was measured by Cell-Counting Kit and colony formation assay. Cells were injected subcutaneously into the nude mice. The tumor size was quantified in two dimensions using calipers. Immunohistochemical staining was used for BMPR2 expression. The statistical analysis and graphical presentation were performed using GraphPad Prism 5.0.

Results

Quantitative real-time PCR and immunohistochemical staining showed the expression levels of BMPR2 in neuroblastoma were higher than that of non-tumor adrenal tissues($P<0.05$). The CCK-8 assays and colony formation assays showed that disruption of BMPR2 gene expression had a positive effect on the proliferation of neuroblastoma cells. On the contrary, overexpression of BMPR2 had a negative effect. In vivo, we found that BMPR2 could inhibit neuroblastoma cells growth in mouse models.







Conclusions

The data presented here indicate a significant role of BMPR2, which could suppress proliferation of neuroblastoma both in vitro and in vivo.

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Neuroblastoma

NLRR2 IS INVOLVED IN CELL SURVIVAL AND DIFFERENTIATION THROUGH JNK PATHWAY IN NEUROBLASTOMA

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Objectives

Neuronal Leucine-rich repeat protein 2 (NLRR2) is a transmembrane protein of human NLRR gene family. Of NLRR family, NLRR1 is associated with unfavorable prognosis, while NLRR3 is correlated to favorable outcome of neuroblastoma (NB). However, the clinical significance and function of NLRR2 in NB are still uncovered. In the present study, we were interested to investigate the functions and the transcriptional regulation of *NLRR2* in NB.

Methods

We evaluated the NLRR2 and c-Jun expression in SK-N-BE, TGW and SMS-SAN cells by RT-PCR, quantitative real time PCR and western-blot. Retinoic acid (RA) was used to induce neuronal differentiation in NB cells. *NLRR2* promoter activity and c-Jun recruitment were analyzed by dual luciferase and ChIP assays respectively. SK-N-BE cells were used for tumor xenograft study.

Results

We have found that enforced expression of NLRR2 increased NB cell growth. The knockdown of NLRR2 significantly reduced NB cell growth *in vitro* and *in vivo*. In *NLRR2* knockdown cells, RA-mediated differentiation was significantly enhanced. After the RA treatment, NLRR2 expression was increased which was correlated with the upregulation of c-Jun, a member of activator protein-1 (AP-1) family. Interestingly, the treatment of JNK inhibitor reduced the expression of c-Jun and NLRR2. Promoter analysis revealed that RA treatment enhanced *NLRR2* transcription which was suppressed by JNK inhibitor. The AP-1 binding site was identified in the *NLRR2* promoter region and c-Jun recruitment was confirmed by ChIP assay. Moreover, the knockdown of c-Jun reduced *NLRR2* expression, suggesting that *NLRR2* is an inducible gene regulated by JNK pathway with the functions to enhance NB cell survival and inhibit cell differentiation.

Conclusions

Accumulated evidences suggest that NLRR2 acts as a negative feedback regulator for RA-mediated differentiation. NLRR2 might play a role in NB drug resistance and could give us a possible therapeutic approach to treat aggressive NB.

P-159

Neuroblastoma

COMPARING 123I-MIBG SCINTIGRAPHY WITH MRI-STIR IN PATIENTS WITH STAGE 4 NEUROBLASTOMA TO INVESTIGATE BONE AND BONE MARROW METASTASES

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Objectives

To compare radionuclide 123-Iodide-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy with magnetic resonance imaging (MRI) with short tau inversion recovery (STIR) to investigate bone and bone marrow metastases in neuroblastoma.

Methods

Diagnostic ^{123}I-MIBG-scans and MRI-STIR images from 10 patients with stage 4 neuroblastoma were evaluated to assess metastatic spread in 14 skeletal segments. First presence or absence of lesions were scored. Then morphological characteristics of the lesions were compared: with 'focal', being sharply demarcated, limited to one location in the skeletal segment or 'diffuse', indistinct margins, dispersed throughout the skeletal segment.

Results

A total of eighty-nine skeletal segments were evaluated with both modalities. In 36 segments, lesions were visible both MIBG^{pos}/MRI-STIR^{pos}. In 33 segments, discrepancies were seen: 26 lesions were ^{123}I-MIBG^{neg}/MRI-STIR^{pos} and 7 ^{123}I-MIBG^{pos}/MRI-STIR^{neg}.

The morphological investigation revealed that ^{123}I-MIBG-scintigraphy showed focal lesions in 12 segments, diffuse in 30 and a combination of both in 1 segment. MRI-STIR showed focal lesions in 30 segments, diffuse in 10, and a combination of both in 22. Concordant morphological findings were seen in 30 segments: 10 focal, 19 diffuse and in 1 segment both types of lesions. In 36 segments morphological discordant findings were found. MRI-STIR^{pos}/^{123}I-MIBG^{neg} lesions were: 22 focal and 4 both. Discordant ^{123}I-MIBG^{pos}/MRI-STIR^{neg} were diffuse lesions in 7 segments.

In eight affected segments (in 3 patients), cortical destruction was seen on MRI-STIR. These lesions were all of the diffuse type on ^{123}I-MIBG-scans; on MRI-STIR 5 were of the diffuse type and 3 were focal.

Conclusions

MRI-STIR showed more affected skeletal segments than ^{123}I-MIBG-scintigraphy. Because all included patients were stage 4, these findings did not affect staging. Discrepancies were most ^{123}I-MIBG$^{\mathbf{neg}}$**,** but also MRI-STIR$^{\mathbf{neg}}$. Morphological investigation indicated that MRI-STIR showed more focal and ^{123}I-MIBG-scintigraphy more diffuse lesions.

P-160

Neuroblastoma

FEASIBILITY OF I131-MIBG AND TOPOTECAN THERAPY FOLLOWED BY CONSOLIDATION WITH BUSULFAN, MELPHALAN AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR REFRACTORY METASTATIC NEUROBLASTOMA

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Objectives

To evaluate the safety of MIITOP (MIBG therapy with topotecan) followed by busulfan and melphalan (BuMel) with ASCT in patients with refractory metastatic neuroblastoma.

Methods

In this retrospective analysis, toxicity data from patients with refractory neuroblastoma enrolled in the MIITOP protocol followed by BuMel were assessed. During MIITOP, patients received an activity of 12 Mci/kg of ^{131}I-mIBG combined with topotecan. In vivo dosimetry was used to calculate a second activity of ^{131}I-mIBG to be given on day 21 to deliver a total whole-body dose of 4 Gy, with a second course of topotecan. ASCT was performed on day 32. After MIITOP, patients without progressive disease could receive BuMel consisting of IV busulfan on days -7 to -3 (0.8-1.2mg/kg according to body weight strata), melphalan (140 mg /m2) on day -2 with ASCT on Day 0. Toxicity was assessed after MIITOP and after Bu-Mel.

Results

Seven patients completed MIITOP followed by BuMel/ASCT (median interval 11 weeks after MIITOP). Immediate tolerance of MIITOP was good with grade 3 non-hematologic toxicity limited to two patients (fever of unknown origin (FUO)). Two patients developed late complications: 1 grade 4 adrenal insufficiency and 1 grade 2 hypothyroidy. After BuMel, two patients developed bacterial sepsis and five FUO. Grade 3 and 4 mucositis occurred in five patients. One patient developed grade 4 sinusoidal obstructive syndrome that recovered on day 32. Median duration of neutropenia and thrombocytopenia was 12 and 36 days respectively. One patient had a persistent thrombocytopenia 140 days post ASCT. At the end of treatment, there were one complete remission, five stable diseases and one progressive disease.

Conclusions

BuMel can be safely administered 11 weeks after MIITOP therapy (MIBG up to 24 mCi/kg with topotecan) in refractory metastatic neuroblastoma. The impact on survival of this treatment combination should now be evaluated in a phase II trial.

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Neuroblastoma

UTILITY OF 18F-FDG PET-CT IN PAEDIATRIC NEUROBLASTOMA AND COMPARISON WITH 131I-MIBG SCINTIGRAPHY: SINGLE INSTITUTIONAL EXPERIENCE

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Objectives

To evaluate the utility of ^{18}F-FDG PET-CT in patients with paediatric neuroblastoma and compare the results with that of ^{131}I-MIBG scintigraphy.

Methods

Data of 44 patients (male: 35, female: 9) with histopathology proven neuroblastoma who underwent ^{18}F-FDG PET-CT (staging-23, restaging-21) was retrospectively evaluated. ^{131}I-MIBG scintigraphy was available for 30/44 patients (mean interval 15 days). ^{131}I-MIBG scintigraphy and ^{18}F-FDG PET-CT images were independently evaluated by two nuclear medicine physicians and in separate sessions 1 week apart to minimize recall bias. Histopathology (n=53 lesions) and/or clinical/imaging follow-up (n=92 lesions) were taken as reference standard.

Results

Patient wise sensitivity, specificity, PPV, NPV and accuracy of ^{18}F-FDG PET-CT were 100%, 57.14%, 92.50%, 100% and 93.18% respectively. A total of 145 lesions (primary-40, lymph node-32, bone-51, bone marrow-15, and others-7) were detected on ^{18}F-FDG PET-CT in 44 patients. In 30 patients undergoing both the modalities, sensitivity, specificity, PPV, NPV and accuracy of ^{18}F-FDG PET-CT were 100%, 66.67%, 92.31%, 100% and 93.33% respectively and that of ^{131}I-MIBG were 95.83%, 66.67%, 92%, 80% and 90% respectively. In these 30 patients, ^{18}F-FDG PET-CT detected 108 lesions (primary-26, lymph node-22, bone/bone marrow-56 and others-4) and ^{131}I-MIBG detected 75 lesions (primary-25, lymph node-5, and bone/bone marrow-45). On patient wise comparison there was no significant difference between ^{18}F-FDG PET-CT and ^{131}I-MIBG, but ^{18}F-FDG PET-CT detected more lesions than ^{131}I-MIBG. While no difference was noted for primary lesion, PET-CT was significantly better than ^{131}I-MIBG scintigraphy for the detection of lymph nodal and bone/bone marrow lesions.

Conclusions

^{18}F-FDG PET-CT is a highly accurate modality in patients with neuroblastoma and detects more lesions as compared to ^{131}I-MIBG scintigraphy in such patients.

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Neuroblastoma

123I-MIBG SCINTIGRAPHY AND 18F-FDG-PET(-CT) IMAGING FOR DIAGNOSING NEUROBLASTOMA: A COCHRANE DIAGNOSTIC TEST ACCURACY REVIEW

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Objectives

Many studies reporting on the diagnostic accuracy of Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG)-scintigraphy in neuroblastoma patients, are very heterogeneous in number of included patients and performance of the imaging methods. Still, prognosis, treatment and response of patients are based on extension-scoring of ^{123}I-MIBG-scans. Therefore, we assessed the diagnostic accuracy of ^{123}I-MIBG and that of a possible add-on test: Fluorine-18-fluorodeoxy-glucose (^{18}F-FDG) positron emission tomography (-computed tomography) (PET(-CT)).

Methods

We searched databases of MEDLINE/PubMed (1945-September 2012) and EMBASE/Ovid (1980-September 2012), reference lists of relevant articles and reviews, conference proceedings and contacted experts.

Inclusion criteria: cross-sectional studies comparing results of ^{123}I-MIBG-scintigraphy, ^{18}F-FDG-PET(-CT), or both with the reference standards or with each other; diagnostic design; children 0-18 years old; neuroblastoma of any stage at first diagnosis or at recurrence.

Two review authors independently selected studies, extracted data and assessed methodological quality.

Two-by-two tables were used to calculate sensitivity and/or specificity for each study and, if possible, forest plots were generated.

Results

Of 4693 references, we included 11 studies with 621 eligible patients. The pooled mean sensitivity of ^{123}I-MIBG-scintigraphy was 92.4% (95% confidence interval 84.6-96.4%; 95% prediction interval 63.0-98.9% (in 608 patients)). The specificity was 85% in 115 lesions in 22 patients, described in one study. The sensitivity of ^{18}F-FDG-PET(-CT) alone and compared to ^{123}I-MIBG-scintigraphy was reported in one study as 100%. The specificity could not be calculated. None of the studies provided outcome data on the diagnostic accuracy of ^{18}F-FDG-PET(-CT) in patients with negative ^{123}I-MIBG-scintigraphy. All studies had methodological limitations.

Conclusions

The pooled sensitivity of ^{123}I-MIBG-scintigraphy was 92.4%, analysis of the specificity was difficult, because only one study provided data on false positive and true negative results. Although currently not enough evidence is available, a possible add-on test is ^{18}F-FDG-PET(-CT) for ^{123}I-MIBG negative tumours.

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Neuroblastoma

THE ROLE OF CHEST COMPUTED TOMOGRAPHY (CT) AS A SURVEILLANCE TOOL IN CHILDREN WITH NEUROBLASTOMA

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Objectives

The amount and frequency of imaging in children with neuroblastoma varies among institutions. This study examines the value of chest CT in a cohort of pediatric patients with high-risk neuroblastoma.

Methods

Medical records and imaging of 88 patients with high-risk neuroblastoma, diagnosed at St. Jude Children's Research Hospital between January, 2002 and December, 2009, were reviewed. Surveillance imaging was conducted through 2013. Ten patients with thoracic disease at diagnosis were excluded. Event free survival (EFS) and overall survival (OS) were estimated using the method of Kaplan and Meier. Size specific dose estimates for CT scans of the chest, abdomen, and pelvis were used to estimate absolute organ doses to 23 organs. Organ dosimetry was used to calculate cohort effective dose.

Results

Seventy-eight patients underwent 2,489 CTs, including 872 chest, 857 abdomen, and 760 pelvis scans. The 5 year OS and EFS were 48.8%±7% and 49.4%±7% respectively. Forty-two (54%) patients progressed/recurred and 37 (47%) died of disease. Eleven patients (14%) developed thoracic disease progression/recurrence identified by chest CT (1 with pulmonary nodules, 1 paraspinal mass, and 9 nodal). MIBG (metaiodobenzylguanidine) scans confirmed thoracic disease in 6 of these patients. Five of the 11 had normal MIBG scans of the chest; 2 had symptomatic disease, 2 were asymptomatic with normal chest MIBG scans but avid bone disease and 1 had bone/chest pain with a normal MIBG, but abnormal positron emission tomography scan. The estimated radiation dose savings from gender neutral CT surveillance without chest imaging was calculated as 33%, a relative risk reduction of 43%.

Conclusions

Neuroblastoma progression/recurrence in the chest is rare and often presents with symptoms or is identified using non-CT imaging modalities. For patients diagnosed with high-risk neuroblastoma, who lack thoracic disease initially, omission of chest CTs from on-therapy/surveillance imaging can save approximately 33% of the radiation burden without compromising disease detection.

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Neuroblastoma

FEASIBILITY OF THERAPEUTIC I131 METAIODOBENZYLGUANIDINE (MIBG) PREVIOUS TO BLOOD STEM CELL COLLECTION AS "PURGING IN VIVO" FOR HIGH-RISK NEUROBLASTOMAS (HRNB)

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Objectives

To estimate the feasibility of MIBG as 'purging in vivo' for HRNB.

Methods

Starting in 199**5 (ASCO Proceedings, 1996/XXXII Annual Meeting, Philadelphia/PA/USA, v.15, p.353/T1037), 44** children with HRNB underwent high-dose chemotherapy with autologous hematopoietic stem cell support (AHSCS), being the cell collection proceeded by exposure to I^{131} MIBG (8–12 mci/kg). Data related to 30/44 of these procedures (all children whose follow up as outpatients was done exclusively at ITACI), focusing mainly on their feasibility and toxicity, are here presented. Conditioning regimen included CBDCA/ETO/MEL in 26/30 (86.7%) and BU/MEL in 4/30 (13.3%) children.

Results

Peripheral blood stem cells (PBSC) sufficient for allowing hematological recovery (≥ 2.0 CD34+ cells X 10^6/kg) were obtained in 28/30 (93.3%) children (requiring**:** median of 5 apheresis), **whose transplantation was done** only with PBSC support. 2 additional children received either PBSC + marrow support (MS) (1) or exclusive MS (1). No stable ANC > 500/mm^3 **was obtained** before the 19th day after cell reinfusion; only 11/30 (36.7%) and 14/30 (46.7%) children respectively achieved stable platelet counts ≥ 20,000/mm^3 before the 27th day and independence of red cell transfusions before the 44th day after AHSCS. Most relevant immediate toxicities were**:** death secondary to sepsis in 2/30 (6.7%) children and 1 episode (3.3%) of severe, non-fatal VOD. Late toxicities included 2/28 (7%) secondary neoplasia (1 thyroid carcinoma and 1 fatal abdominal NHL). Within 15 survivors, 2 (13.3%) require thyroid hormone supplementation **(**oral iodine **was given** at the time of MIBG exposure**)**. Considering the patients whose procedures were done after January/2010, when cell collections with previous I^{131}MIBG (10 mci/kg) became a routine step within ITACI, 9/11 children are surviving, being the EFS (death/progression/2nd neoplasia) of 68.6% ± 18.6%.

Conclusions

Therapeutic use of I^{131}MIBG before cell collection for AHSCS is feasible and deserves analysis regarding its potential usefulness for treating HRNB.

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Neuroblastoma

CHARACTERTICS OF IMAGE DEFINED RISK FACTORS (IDRFS) IN PATIENTS ENROLLED THE LOW RISK PROTOCOL (JNB-L-10) FROM THE JAPANESE NEUROBLASTOMA STUDY GROUP (JNBSG)

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Objectives

The Japanese Neuroblastoma Study Group (JNBSG) has been conducted the protocol (JNB-L-10) for low risk patients to minimize treatment complications using Image Defined Risk Factors (IDRFs) as the main factor for treatment decision. In this preliminary report, we analyzed IDRF results in JN-L-03 protocol in order to clarify characteristics of IDRF in low risk neuroblastoma (NB) patients.

Methods

IDRFs were evaluated at diagnosis, as well as at the time after 3, 6, 9 courses of chemotherapy in JN-L-03 protocol (2010-2013 registry). Three low dose chemotherapy protocols were included in this study, such as LI-A (VCR / CPA), LI-B (VCR / CPA / THP-ADR), LI-C (VCR / CPA / CBDCA). If no IDRFs were present, the patient underwent surgery. If any IDRFs were present, the patient underwent further chemotherapy. IDRF results from 60 localized NB patients enrolled in JN-L-03 were collected. We analyzed the relationship between IDRF results and tumor location as well as INSS.

Results

IDRF results were available in 58 of 60 patients. Twenty-nine of 58 patients were identified

IDRFs present at the onset of disease. Two of 4 tumors originated from neck, 9 of 12 tumors from mediastinum, 7 of 29 tumors from adrenal gland, 8 of 9 tumors from retroperitoneal, 1 of 1 tumor from kidney, 2 of 3 tumors from pelvis had IDRFs at diagnosis. None of 24 INSS stage 1 tumors, 13 of 15 stages 2A tumors, 4 of 5 stage 2B tumors, all of 10 stage 3 tumors had IDRFs at diagnosis.

Conclusions

IDRFs were present in 50% of low risk NB patients at diagnosis. Tumors originated from mediastinum or retroperitoneum and INSS stage 2A, 2B, 3 tumors more likely have IDRFs compared to the tumors originated from adrenal grand and stage 1 tumors.

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Neuroblastoma

A SYSTEMATIC REVIEW OF THE LITERATURE REVEALS NO UNIFORM DEFINITIONS ON DIAGNOSTIC IMAGING FOR BONE AND BONE MARROW METASTASES IN NEUROBLASTOMA PATIENTS

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Objectives

Since the presence of bone and/or bone marrow (BM) metastases correlates with bad prognosis, it is important to have clear and uniform definitions. The objectives of this review were: 1. To identify all definitions of bone and BM metastases used in imaging studies; and 2. To determine diagnostic accuracies for bone and/or BM metastases of all imaging tests.

Methods

We searched MEDLINE/PubMed (1945-April 2013) and EMBASE/Ovid (1980-April 2013) and bibliographies of relevant articles. Studies were included if they reported on diagnostic imaging of patients with suspected metastatic neuroblastoma and defined bone and/or BM metastases. Two review authors selected studies, extracted data and assessed methodological quality. Disagreements were resolved by discussion. Sensitivity and/or specificity were calculated using data in two-by-two-tables.

Results

Thirty of 400 identified studies were eligible for inclusion. The main exclusion reason was not providing a definition for bone and/or BM metastases (n=52).

Of the 30 included studies 9 defined bone, 13 defined BM and 8 defined both metastases (objective 1). Definitions of bone and BM metastases varied widely between included studies. Bone metastases were frequently defined as focal lesions or hotspots on scintigraphy and as osteolytic lesions with periosteal reaction on radiography; BM metastases as diffuse lesions on MRI and on scintigraphy (with or without focal lesions). BM metastases on MRI were additionally defined as: low-intensity on T1- and high-intensity on T2-weighted-images.

Fourteen studies reported data on diagnostic accuracy (objective 2). Sensitivity and specificity values varied enormously between studies for both bone and BM metastases.

Conclusions

Despite the fact that many studies report on outcome data of patients with bone and/or BM metastases, the majority do not provide definitions. Furthermore, in the studies that do provide definitions, both the definitions and the diagnostic accuracy varied so widely that no conclusions can be drawn.

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Neuroblastoma

PATTERNS OF RELAPSE IN HIGH-RISK NEUROBLASTOMA PATIENTS

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Objectives

We performed a retrospective review of pediatric patients treated for high-risk neuroblastoma to identify whether patients relapsed at original sites of disease or previously disease-free sites, with particular emphasis on the impact of radiotherapy to metastatic sites.

Methods

All patients from 1994-2008 who relapsed after treatment for stage IV neuroblastoma were included in our cohort. Sites of disease, as defined by anatomic location of MIBG avidity, were compared at diagnosis and at first relapse. Fisher's exact test was performed to determine relationship between radiation therapy technique and relapse at previously involved sites.

Results

45 patients with relapse of high-risk neuroblastoma were included. 62% of patients were male, and the median age at diagnosis was 3.6 years old. 44% of patients were treated with total body irradiation (TBI), and 56% were treated without TBI, instead using local radiation to the primary site with or without focal radiation to metastases. Median time from diagnosis to relapse was 1.9 years, with 67% relapsing in at least one previously MIBG avid site and 16% of patients relapsing in a previously irradiated site. 11% of patients had involvement of the primary site at relapse. When grouped by radiation technique, 50% of patients treated with TBI (n=20) relapsed in previously involved sites compared with 80% of patients treated without TBI (n=25) (p=0.05).

Conclusions

Overall, the majority of neuroblastoma patients relapsed in at least one site of previous MIBG-avid disease, with a small number relapsing in previously irradiated locations. Patients who did not receive TBI were significantly more likely to relapse in a previously involved disease site.

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Neuroblastoma

HEALTH-RELATED QUALITY OF LIFE IN A POPULATION-BASED SAMPLE OF SURVIVORS OF ADVANCED NEUROBLASTOMA IN CANADA

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Objectives

To examine the health related quality of life (HRQL) of survivors of advanced neuroblastoma (AN) who underwent intensive chemotherapy followed by myeloablative therapy with autologous stem cell transplant (SCT).

Methods

A national population-based survey was conducted in survivors of AN treated between 1991 and 2010. Parents of survivors completed a proxy Health Utilities Index (HUI) questionnaire, scored on a scale of 0.00 to 1.00. Comparative data for other clinical groups were obtained from previous studies and for the general population from Statistics Canada. Differences $\geq$0.03 in overall HRQL scores and $\geq$0.05 in single attribute scores are considered clinically important

Results

Data were collected from 13/17 pediatric centres, including all 6 SCT centres, with 99 of 105 questionnaires returned being complete for scoring. The overall mean HRQL utility score was 0.84 (SD=0.18); significantly less than that of children (5-12 years of age) in the general population (0.96; $p<0.001$). There was no significant difference ($p=0.660$) in mean overall HRQL between survivors of AN treated with SCT (mean age at dx 3.6yrs) and those treated without transplant (n=20; mean age at dx 1.2yrs). However a clinically important (0.06) difference was observed in the attribute of hearing, with greater morbidity reported in the SCT group. Survivors of ALL (0.90; $p=0.009$), and Wilms tumour (0.93; $p=0.002$) had significantly better HRQL than survivors of AN, with substantially lower morbidity in the attribute of hearing ($p<0.0001$). Survivors of AN experienced better HRQL than survivors of brain tumours (0.81); a difference considered to be clinically important.

Conclusions

In survivors of AN, HRQL is no worse with than without transplant. The differential effect on hearing reflects additional exposure to platinum-based chemotherapy in the SCT group. AN survivors enjoy better HRQL than survivors of brain tumours but have poorer HRQL than survivors of ALL and Wilms tumour.

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Neuroblastoma

VALIDITY AND RELIABILITY OF IMAGE-DEFINED RISK FACTORS IN LOCALIZED NEUROBLASTOMA: A REPORT FROM 2 TERRITORIAL CENTERS IN JAPAN

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Objectives

The Japanese Neuroblastoma Study Group (JNBSG) has been employing a protocol using image-defined risk factors (IDRFs) for localized neuroblastoma to minimize surgical complications since 2010. However, the report from the INRG Project (Radiology, 2011) supplemented the description of renal vessels, in which even isolated contact is considered IDRFs-positive. The aim of this study was to evaluate the validity and reliability of IDRFs by comparing the previous and new guidelines.

Methods

Medical records of patients with localized neuroblastoma, who were treated at 2 centers in West Japan from 2002 to 2013, were retrospectively reviewed and classified as having IDRFs or not at diagnosis by radiologists. Before 2009, the indication of surgery was based on the surgeon's judgment.

Results

A total of 47 patients were enrolled, and their median age was 13 months (0 - 78). Primary tumor locations were the abdomen (adrenal gland and retroperitoneum) in 38, pelvis in 2, and mediastinum in 7. For all sites, IDRFs was present in 22/47 (46.8%) using the previous guideline (PG), and 38/47 (80.9%) using the new guideline (NG). For abdominal neuroblastomas, IDRFs was present in 15/38 (39.5%) usign PG, and 31/38 (81.6%) using NG. Moreover, the IDRFs-positive rate increased from 26.7% (4/15) to 80.0% (12/15) in 15 cases diagnosed at mass screening. Of IDRFs-positive cases, complete primary resection was achieved in 2/15 (13.3%) usign PG and 17/31 (54.8%) using NG. There was only one major surgical complication (renal atrophy) occurring in an IDRFs-positive case using either guideline.

Conclusions

Although it was expected that the IDRFs-positive rate would increase and resection rate would decrease according to NG, IDRFs could be not used to predict precisely the surgical risk in our limited series. NG might overestimate surgical risks and lead to unnecessary chemotherapy and a prolonged hospital stay.

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Neuroblastoma

RECENT TRENDS AND DISPARITIES IN HIGH-RISK NEUROBLASTOMA SURVIVAL IN THE UNITED STATES: A POPULATION-BASED PERSPECTIVE

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Objectives

Recent changes in treatment for children with high-risk neuroblastoma have led to significant increases in survival. Patients who receive the full complement of therapy (chemotherapy, radiation, surgery, autologous bone marrow transplant, and immunotherapy) now experience a two-year event-free survival of 66% (NEJM 2010). Using publicly available registry data, we examined whether outcome improvements for patients >12 months of age have been consistent across racial, ethnic, and socioeconomic groups. Given the complexity of new treatment modalities, we hypothesized that access limitations could lead to disparities in survival gains.

Methods

We analyzed the 3-year relative survival of neuroblastoma patients diagnosed at >12 months of age between 1992 and 2007 in the 13 cancer registries of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program according to individual characteristics such as race and ethnicity and county-based measures such as education, income, and immigration status.

Results

Survival rates improved for all analyzed populations between 1992 and 2007, with an annual percent change (APC) in relative survival of 2.01% per year (p=0.032), but these gains were experienced disproportionately by some populations. Greater survival improvements were seen in counties with few immigrants than in those with many immigrants (APC 2.03% vs 0.92%, p=0.032), in low-poverty counties than in high-poverty counties (APC 2.42% vs 1.53%, p=0.032), and in highly-educated counties than in less-educated counties (APC 2.74% vs 1.54%, p=0.002). Disparities were also found according to race, ethnicity, metropolitan residency, and language isolation, but these findings did not reach statistical significance.

Conclusions

Recent improvements in survival for children with neuroblastoma diagnosed at >12 months of age have preferentially benefited some racial, ethnic, and socioeconomic groups. This may be due to disproportionate access to advanced treatment modalities by some patient populations. As care for children with cancer becomes more complex, addressing disparities in access will require further research and resources.

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Neuroblastoma

CHYLE LEAK FOLLOWING SURGICAL MANAGEMENT OF NEUROBLASTOMA: AN UNDERRATED COMPLICATION

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Objectives

Surgery is a mainstay in the management of neuroblastoma in children. While the incidence of complications like infection and organ dysfunction are documented, literature on chyle leak is lacking. We have attempted to fill this void by evaluating the incidence, risk factors and implications of chyle leak following surgical management of neuroblastoma.

Methods

We retrospectively analysed the prospectively collected data on 150 patients who underwent surgery for neuroblastoma over a period of ten years. The possible risk factors including stage, lymph nodes dissected, side and site of disease was analysed. To determine the oncological implications we evaluated the hospital stay and the delay in further treatment.

Results

Chyle Leak was documented in 30 (20%) of the patients. It was more commonly seen in lesions arising from the adrenal gland (24% VS 13%), higher stage disease, previous chemotherapy and left sided disease (25% VS 13%). However none of these reached statistical significance. The only risk factor that showed a statistically significant increase in chyle leak was number of lymph nodes dissected with a 11% leak rate for patients with less than 5 lymph nodes sampled and 24% if more than 5 lymph nodes were sampled. (p=0.028). All patients were managed conservatively. The duration of hospital stay was prolonged by 5 days compared to those without chyle leak however adjuvant chemotherapy was not compromised.

Conclusions

Chylous ascites is a common and under reported complication following surgical management of intra-abdominal neuroblastoma which settles with conservative management. It does not compromise the further oncological treatment and hence should not be a deterrent to aggressive surgery. Vigilance in detection however is advisable.

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New Drugs/Experimental Therapeutics

IMMUNOTHERAPY OF ACUTE LEUKEMIAS WITH CHIMERIC ANTIGEN RECEPTORS (CARS)-ENGINEERED CYTOKINE INDUCED KILLER (CIK) CELLS BY SLEEPING BEAUTY SYSTEM

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Objectives

T cell engineering with CARs has been recently proved to be effective in redirecting effector activity towards leukemic blasts. Since the profile of efficacy, safety and feasibility of cell manufacturing and gene therapy by viral vectors still remain major concerns, we explored here the use of Sleeping Beauty (SB) Transposon-mediated gene transfer in CIK cells for targeting Acute Leukemias.

Methods

With an optimized clinical-grade stimulation protocol, we genetically modified CIK cells to express two distinct CARs specific for myelogenous leukemia (AML) CD123+ or acute lymphoblastic leukemia (ALL) CD19+ blasts.

Results

The nucleofection minimally affected the phenotype of CIK cells, and the optimized protocol was effective in inducing T-cell expansion, with a fold increase sufficient to be translated into clinical protocols. Modified CIK cells displayed stable expression of CD123.CAR or CD19.CAR with a frequency of 51.4%±2.9 (n=13) and 48.8%±6.8 (n=7), respectively, and exerted efficient lysis of leukemic primary blasts. Interestingly, CAR triggering by the antigen expressed by leukemic cells promoted specific cytokine secretion and proliferation that was restricted to the modified fraction of CIK cells. The loss of the expression of transposase during the differentiation was assessed to assure the genome stability of the cellular product by absolute quantification through RT-PCR. Finally, preliminary insertion-site analysis by LAM-PCR confirmed that the integrations in the genome of SB system do not correlate with the genes-enriched regions.

Conclusions

SB system together with an optimized method of differentiation efficiently expand CD123.CAR+ and CD19.CAR+ CIK cells, redirect their activity towards AML and ALL cells, and retain a safe pattern of integrations in the genome. An easy clinical-grade adoptive cell therapy platform based on an innovative non viral method of gene transfer will be fundamental to improve the range of applications of immunotherapy to control relapse in leukemic patients.

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New Drugs/Experimental Therapeutics

A PHASE I DOSE-ESCALATION STUDY OF PEGCRISANTASPASE ADMINISTERED BY INTRAVENOUS INFUSION IN ADULT PATIENTS WITH RELAPSED OR REFRACTORY HEMATOLOGICAL MALIGNANCIES

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Objectives

Asparaginase is an important component of chemotherapy to treat acute lymphoblastic leukemia and lymphoma. Hypersensitivity occurs in 10%-30% of patients receiving *Escherichia coli*-derived asparaginases, often necessitating a switch to asparaginase *Erwinia chrysanthemi*. Due to a short half-life, asparaginase *Erwinia chrysanthemi* is administered 3 times a week. To improve pharmacokinetics and reduce immunogenicity, recombinant PEGylation technology was used to create a new *Erwinia chrysanthemi*-asparaginase, pegcrisantaspase. The objective of this open-label, multicenter, dose-escalation study was to determine the maximum tolerated dose, safety, and pharmacokinetics of pegcrisantaspase in patients with relapsed or refractory hematological malignancies.

Methods

Patients aged 18-50 years received pegcrisantaspase intravenously once every 2-4 weeks; initial dose was 500 IU/m^2. Dosing continued until disease progression if judged appropriate by the investigator. Dose escalation was based on the number of patients experiencing dose-limiting toxicity (DLT) within 14 days of first infusion. Patients with active CNS disease or previous hypersensitivity (grade ≥2) to asparaginase *Erwinia chrysanthemi* were excluded.

Results

Ten patients (mean age: 40.6 years) have enrolled to date. All patients had failed multiple therapy regimens. Six and 3 patients dosed at 500 IU/m^2 and 750 IU/m^2, respectively, maintained asparaginase activity >0.1 IU/mL at 14 days. Three patients maintained target activity after week 5 following the second dose of 500 IU/m^2. One DLT was observed with 750 IU/m^2 (neutropenia lasting >7 days). Most common adverse events (>30%) were diarrhea, anemia, hypoalbuminemia, decreased antithrombin III, and nausea. Three deaths occurred following 500 IU/m^2 (1 cerebral hemorrhage; 2 disease progression), and 1 after 750 IU/m^2 (disease progression); none were considered study drug-related.

Conclusions

Pegcrisantaspase 500 IU/m^2 and 750 IU/m^2 provide effective serum asparaginase activity for 14 days following intravenous infusion. Safety data are consistent with the known safety profile of asparaginase treatment and with comorbidities and disease

progression in this patient population.
Study funded by Jazz Pharmaceuticals plc or its subsidiaries.

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New Drugs/Experimental Therapeutics

SFCE METRO-01 FOUR-DRUG METRONOMIC REGIMEN PHASE II TRIAL FOR PEDIATRIC EXTRACRANIAL SOLID TUMOURS

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Objectives

To investigate the anti-tumour activity of a 4-drug metronomic therapy (MT) in relapsing/progressing pediatric extracranial solid tumours (EST). Primary objective was no progression after 2 cycles of therapy.

Methods

Patients of ≥4 to 25 years of age with progressing EST and adequate organ function. Treatment consisted of an 8-week cycle of oral celecoxib BID, weekly vinblastine 3 mg/m2, oral cyclophosphamide 30 mg/m2/d qd for 3 weeks alternating with oral methotrexate 10 mg/m2 twice a week for 3 weeks, with a 2-week rest. Maximum treatment was 2 years. Kepner- Chang two steps model was used with 10 patients in first stage. If primary objective was reached in 2 or more patients, 8 additional patients were included according to 4 groups: Neuroblastoma (NBL), Soft-tissue sarcoma (STS), Bone sarcoma (BS), Miscellaneous (Misc). IRB approval was obtained.

Results

38 patients were evaluable: 6 STS with 1 SD and 1 MR (angiosarcoma) after 2 cycles: 1 patient with metastatic hemangioendothelioma stabilized and is currently at 16 months of therapy; 8 Misc with no significant stabilization observed; 10 BS (8 osteosarcoma and 2 Ewing) all progressed. In the NBL group the second stage opened with currently 3 out of 14 patients (21%) being stable after 2 cycles. Of the patients with SD, 1 stopped MT after 4 cycles being stable (physician’s choice) and 2 patients remained stable for 1 year. Ten patients progressed before cycle 3, 1 not yet evaluated. Median number of cycles was 1.5 (range 0.5-6). Treatment was interrupted temporarily in 8 patients for grade 3/4 toxicity (2 hepatic and/or 6 haematological).

Conclusions

This MT has no activity in BS and Misc and limited though interesting activity in NBL and STS with some patients being stable for > 1 year. (This study was supported by “Enfants et Santé” Foundation and PHRC-grant).

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New Drugs/Experimental Therapeutics

SFCE METRO 01 FOUR-DRUG METRONOMIC REGIMEN HAS ANTI-TUMOUR ACTIVITY IN PEDIATRIC LOW-GRADE GLIOMA

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Objectives

To investigate the anti-tumour activity of a 4-drug metronomic regimen in relapsing/progressing pediatric brain tumours (BT) as defined as progression-free survival (PFS) after 2 cycles (4 months) of therapy.

Methods

Patients of ≥4 to 25 years of age with progressing BT and adequate organ function. Treatment consisted of an 8-week cycle of oral celecoxib BID daily (D1-D56), 100/200/400 mg according to BW, weekly IV vinblastine 3 mg/m^2, oral cyclophosphamide 30 mg/m^2/d qd for 3 weeks alternating with oral methotrexate 10 mg/m^2 twice a week for 3 weeks, with a 2-week rest period. Maximum treatment was 2 years. Kepner and Chang two-steps model was used with 10 patients in the first stage. If primary objective was reached in 2 or more patients, 8 additional patients were recruited. This regimen was considered efficacious if PFS after 2 cycles was over 34% (alpha 10%, beta 10%). Approval was obtained from IRB and french medical agency.

Results

16 patients were included: 2 medulloblastoma (MB), 4 high grade glioma (HGG) (2 of which DPIG), 9 low grade glioma (LGG, one BSG), 1 meningioma. One patient with HGG (anaplastic oligodendroglioma) stabilized for 2 years. None of the other HGG or MB were stabilized. Of the 9 patients with LGG, median age was 9 years, median duration of illness at inclusion was 6 years and 7 patients received vinblastine previously. 1 PR was observed, 6 SD, 2 PD (1 BSG) after 2 cycles. Median number of cycles was 4.0 (range 1.0-12). Four patients received at least 1 year of therapy and 7 are alive. Treatment was interrupted temporarily in 4 patients for grade 3/4 toxicity (hepatic and/or hematological).

Conclusions

This metronomic regimen is active in patients with LGG, even if patients had received vinblastine previously. (This study was supported by “Enfants et Santé” Foundation and National PHRC-grant).

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New Drugs/Experimental Therapeutics

ANALYSIS OF ANGIOGENIC MARKERS DURING SFCE METRO-01 FOUR-DRUG METRONOMIC REGIMEN PHASE II TRIAL FOR PEDIATRIC MALIGNANCIES IN PROGRESSION

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Objectives

Circulating endothelial cells and progenitors have been suggested as biomarkers indicative of angiogenic activity, with potential clinical value in monitoring of metronomic chemotherapy. This study investigated changes in angiogenic biomarkers during a 4-drug metronomic regimen in relapsing/progressing pediatric solid tumours (ST).

Methods

Patients of ≥4 to 25 years of age with adequate organ function with progressing ST. Treatment consisted of an 8-week cycle of oral celecoxib BID daily (D1-D56), weekly iv vinblastine 3 mg/m2, oral cyclophosphamide 30 mg/m2/d qd for 3 weeks alternating with oral methotrexate 10 mg/m2 twice a week for 3 weeks, with a 2week rest. Venous blood samples were obtained at inclusion, days 22, end of the first and second cycle and at progression. CD34+CD45-7AAD- Endothelial Progenitor Cells (EPC) were enumerated using flow cytometry. Circulating Endothelial Cells (CEC) counts, and Vascular Endothelial Growth Factor (VEGF) levels were determined using CD146-based immune-magnetic separation and ELISA respectively. IRB approval was obtained and patients/parents gave informed consent.

Results

21 patients were included: 8 with brain tumours and 13 extracranial tumours. EPC and VEGF levels did not significantly vary during the metronomic regimen. At baseline, CEC values were widely distributed with 5 patients having high CEC levels. Metronomic regimen is associated to a trend toward CEC decrease. Interestingly, CEC counts significantly increased at progression compared to value at the preceding time (81 cells/mL +/- 110 vs 9,53 cells/mL +/- 15,61).

Conclusions

Among biomarkers of angiogenesis, changes in CEC may reflect the impact of SFCE METRO-01 four-drug metronomic regimen on neovascularization. Sequential measurement of CEC levels may provide tools for monitoring the response to treatment and/or progression.

(This study was supported by “Enfants-et-Santé” Foundation and PHRC-grant).

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New Drugs/Experimental Therapeutics

PROGNOSTICATION OF PEDIATRIC ONCOLOGY PATIENTS ENROLLED IN PHASE I CLINICAL TRIALS DESIGNED FOR ADULTS

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Objectives

Most pharmaceutical industry sponsored trials exclude patients less than 18 years in phase 1 clinical trials. Even in the era of targeted therapy pediatric patients have to wait for most phases of trials to be completed in adults to enroll in clinical trials in the advanced metastatic and relapsed setting. We report the preliminary analyses of the outcomes of pediatric patients enrolled in phase 1 studies designed for adults at a major cancer center.

Methods

We reviewed the medical records of 40 pts < 18 years treated in ≥ 1 phase I trial at MD Anderson(2005-2012). We used univariate and multivariate analyses to determine which baseline clinicopathologic characteristics, including RMH and MDACC scores, were associated with increased or decreased overall and progression-free survival.

Results

The median overall survival duration from the time of enrollment in a phase I trial was 8.5 months (95% CI, 5.5-13.2 months). In the multivariate analysis, age ≥15 was the only independent factor that predicted increased overall survival (P = 0.0065), and >3 prior therapies (P = 0.053) predicted decreased overall survival. The median progression-free survival duration was 2.8 months (95% CI, 2.3-4.1 months. In the multivariate analysis, independent factors that predicted increased progression-free survival were age ≥15 years (P < 0.001) and prior radiation therapy (P = 0.049); performance status >1 (P < 0.001) and >3 prior therapies (P = 0.002) predicted decreased progression-free survival.

Conclusions

It is feasible to conduct phase I studies in pediatric patients based on adult protocols. There was no mortality related to phase 1 therapy. A composite score using a larger number of patients needs to be developed using the RMH and MDACC scores in future trials. In the era of targeted therapy more trials should allow pediatric patients earlier in the drug development especially if deemed safe in adults in early phase trials.

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New Drugs/Experimental Therapeutics

SOLID TUMORS OF CHILDHOOD DISPLAY SPECIFIC SERUM MICRORNA PROFILES

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Objectives

Currently, the diagnosis and risk-stratification of childhood solid tumors is heavily reliant upon histopathological findings. The availability of serum biomarkers would improve the accuracy and timeliness of diagnosis and reduce the need for invasive procedures for patients with these tumors. We hypothesized that the differential expression and/or release of microRNAs by solid tumors of childhood may be detected as altered serum microRNA profiles.

Methods

We undertook global quantitative reverse-transcription polymerase chain reaction (qRT-PCR) microRNA profiling (n=741) on RNA extracted from 54 serum samples, representing 34 taken from patients at the time of diagnosis of common childhood cancers (including neuroblastoma, Wilms tumor, sarcoma, hepatoblastoma, lymphoma, central nervous system glioma) plus 20 reference samples.

Robust quality control steps for RNA extraction and qRT-PCR efficiency using non-human spike-in RNA/DNA and hemolysis assessment were next performed and 53/54 samples (98.1%) were suitable for full profiling. Multiple methods to normalize the global data were assessed, which showed that the 'global mean' approach was optimal.

We generated a panel of six top-ranking most stable microRNAs suitable for normalization for microRNA qRT-PCR in pediatric serum samples.

Results

Tumor-specific serum microRNA profiles were identified for each tumor type. Selected microRNAs underwent confirmatory testing using a subset of 17 tumor and four control samples from the profiling set, plus four independent samples from patients with neuroblastoma.

Striking findings for *MYCN*-amplified high-risk neuroblastoma (MYCN-NB) were noted, with a panel of microRNAs (miR-124-3p/miR-9-3p/miR-218-5p/miR-490-5p/miR-1538) highly over-expressed compared with the other tumor and control groups, including non-*MYCN*-amplified low-risk neuroblastoma (NB).

Other 'differential diagnosis' panels were also identified for distinguishing an abdominal mass (Wilms tumor *vs.* MYCN-NB/NB), liver mass (hepatoblastoma *vs.* MYCN-NB/NB), subtypes of sarcoma and lymphoma.

Conclusions

This study demonstrates the feasibility of robust diagnostic serum microRNA profiling in solid tumors of childhood, and has identified candidate microRNA profiles for testing in larger, prospective studies.

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New Drugs/Experimental Therapeutics

CHIMERIC HCMV/HSV-1 IS SUPERIOR TO ICP34.5-DELETED HSV-1 AT INFECTING PEDIATRIC-DERIVED GLIOBLASTOMA XENOGRAFT CELLS INCLUDING CD133+ GLIOMA STEM CELLS IN PHYSIOLOGIC HYPOXIA

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Objectives

Oncolytic engineered herpes simplex virotherapy has emerged as a promising treatment for glioblastoma, however the efficacy of a $\gamma_1$34.5-deleted (ICP34.5-) HSV-1 (C101), similar to viruses previously used in high-grade glioma clinical trials, was reduced in physiologic hypoxia, a hallmark of glioblastoma. Physiologic hypoxia supports and maintains the glioma stem cell (GSC) phenotype and has a vital role in tumor development, invasiveness, and resistance to chemotherapy and radiation. We investigated the ability of a chimeric HCMV/HSV-1 virus (C154), which contains the HCMV *IRS1* gene to improve late viral protein synthesis, to infect and kill tumor cells including CD133+ GSCs in hypoxia from a pediatric patient-derived glioblastoma xenograft. A non-green fluorescence protein (GFP)-expressing version of C154 (C134 HSV) is being prepared for clinical trials.

Methods

D456 tumors, maintained in the flanks of nude mice, were disaggregated, placed under hypoxia (1% oxygen) and maintained as neurospheres in stem cell-defined medium. Relative infectivities of tumor cells and CD133+ GSCs by GFP-expressing C101 and C154 at 10 plaque-forming units (PFU)/cell were quantified 30 hours post-infection by FACS analysis. Virus recovery measured by limiting plaque dilution and cytotoxicity measured by the AlamarBlue assay were determined 48 and 72 hours post-infection, respectively.

Results

By 30 hours post-infection, C154 infected 48.9 ± 1.2% of cells compared to only 26.4 ± 0.9% of cells for C101 ($p<0.0001$). C154 infected significantly more CD133+ cells (1.5x, $p<0.0001$) than C101. A significantly lower dose of C154 was required to kill 50% of the cells (LD_{50}) than C101 (3.9 ± 0.4 PFU/cell versus 10.7 ± 0.8, $p=0.0002$). Over 200-fold more C154 virus was recovered than C101 ($p=0.0004$).

Conclusions

The Chimeric HCMV/HSV-1 virus is superior to $\gamma_1$34.5-deleted HSV-1 at infecting a pediatric-derived glioblastoma xenograft under physiologic hypoxic conditions, and may be effective at targeting pediatric high-grade gliomas including chemotherapy and radiation resistant GSCs.

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New Drugs/Experimental Therapeutics

NATURAL KILLER CELL BASED THERAPIES FOR METASTATIC OSTEOSARCOMA

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Objectives

Metastatic osteosarcoma has a dismal prognosis despite conventional treatment. New therapeutic approaches are urgently needed to improve survival. Natural Killer (NK) cells are lymphocytes with cytotoxic activity toward malignant cells. Crosstalk between NK cell receptors and tumour cell ligands is necessary for anti-cancer activity. In the present study we explored ex-vivo and in vivo feasibility of NK cell–mediated therapies against primary metastatic osteosarcoma.

Methods

HLA class I, Fas, NKG2D and DNAM-1 ligands expression in 19 metastatic primary osteosarcoma and NK receptors on activated and expanded NK (NKAE) cells were analyzed by multiparametric flow cytometry. NKAE cells were obtained by co culture of peripheral blood mononuclear cells (PBMCs) from donors and patients with the K562mbIL15-41BBL cell line in RPMI supplemented with 10% human AB serum, 100 IU/mL IL-2, and 1% penicillin and streptomycin. We performed ex-vivo cytotoxicity with NK cell receptor blocking antibodies by a conventional 2-h europium-TDA release assay to explore NK cell susceptibility from primary osteosarcoma to be lysed by NKAE. In addition we explored different strategies (irradiation, gemcitabine and spironolactone) to increase osteosarcoma NK cell cytotoxic susceptibility.

Results

We found ULBP3, Fas and CD112 were highly expressed (ratio MFI ≥10) in 13/19 of the primary cell lines. Specific antibodies blockade shown Fas-FasL and NKG2D pathways have a main role in the NK cell antitumor activity. We found spironolactone upregulated NKG2D and DNAM-1 ligands expression. Finally we have developed an in vivo orthotopic and metastatic osteosarcoma xenograft to explore successfully ex vivo therapies.

Conclusions

CD112, NKG2D ligands and Fas are expressed in metastatic osteosarcoma cells. Although these tumours shown heterogeneity to NK cell lysis, NKG2D/NKG2DL and Fas/FasL pathways were responsible for NK cell elimination. The upregulation of NKG2D ligands mediated by spironolactone could enhance NK cell mediated lysis ex vivo and in vivo.

Conflict of interest

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New Drugs/Experimental Therapeutics

A SIMPLE FORMULA BASED ON CYSTATIN C FOR INDIVIDUAL CARBOPLATIN DOSING IN CHILDREN

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Objectives

As carboplatin clearance is linearly related to glomerular filtration rate, the principle of renal function-based dosing is widely accepted although not always practiced. The prediction of carboplatin clearance could be improved by adding plasma cystatin C to other patient characteristics routinely used for dosing. We aimed to evaluate the usefulness of cystatin C as a predictor of carboplatin clearance in children and develop a simple model that can be used for dosing.

Methods

We performed a population pharmacokinetic analysis on 78 clearance studies performed in 30 children with a wide spectrum of solid tumors, using non-linear mixed effect modeling. The influence of six covariates (sex, age, body weight, height, BMI, BSA, creatinine and cystatin C) on carboplatin pharmacokinetics was evaluated. The final model was validated using bootstrap analysis.

Results

A two-compartment model was fitted to the time-concentration data. The best equation was: carboplatin clearance = $2.63 \times (\textit{cystatin C}/0.695)^{-0.637} \times (\textit{body weight}/15.72)^{0.79}$ with clearance in L/h, cystatin C in mg/L and weight in kilograms. The mean parameters obtained from the 1,000 bootstrap runs were almost identical to the estimates obtained from the original dataset, indicating the model is robust. Observed carboplatin concentrations were accurately predicted by the final model. The correlation between observed and predicted clearance was almost perfect ($R^2 = 0.92$; $P < 0.001$). Bias (%MPE) and imprecision (%MAPE) of the final model were 1.8% and 15.6% respectively.

Conclusions

A model based on cystatin C and weight gives the best prediction of carboplatin clearance in children. This simple model can be used for individualized dosing of carboplatin.

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New Drugs/Experimental Therapeutics

CARBOPLATIN DOSING IN CHILDREN USING ESTIMATED GLOMERULAR FILTRATION RATE: EQUATION MATTERS

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Objectives

Renal function-based carboplatin dosing results in more consistent drug exposure than flat dosing. We aimed to validate the Newell dosing equation using estimated glomerular filtration rate (GFR) and study which renal function marker most accurately predicts carboplatin clearance in children.

Methods

In 30 children with a wide spectrum of solid tumours, 78 carboplatin clearance values were obtained from individual fits using NONMEM. Observed carboplatin clearance was compared with predicted clearance calculated according to the Newell dosing equation using three different GFR estimates, one creatinine-based (eGFR-Schwartz), one cystatin C-based (eGFR-CKiD1) and one based on creatinine and cystatin C (eGFR-CKiD2). Bias and precision of the predictions was examined.

Results

Both CKiD equations were accurate with a bias of 1.7 (95%CI -1.7 to 5.1) and -3.3 (95%CI -7.0 to 0.35) ml/min for respectively eGFR-CKiD1 and CKiD2, whereas the bias of eGFR-Schwartz significantly differed from zero (-16.2; 95%CI -21.5 to -10.9 ml/min). eGFR-CKiD1 gave the lowest bias and imprecision, the other two eGFR equations showed overprediction of carboplatin clearance as reflected by negative bias and higher mean prediction error values. The proportion of variance in observed clearance that can be explained by the predicted clearance was lowest for Schwartz (R^2 = 0.58), the explained variance was 0.65 for both CKiD equations.

Conclusions

The two cystatin C-based CKiD equations outperform the widely used creatinine-based Schwartz equation in predicting carboplatin clearance. We recommend the use of estimated GFR based on cystatin C for carboplatin dosing in children unless a gold standard GFR measurement is available.

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New Drugs/Experimental Therapeutics

ASSOCIATION OF HEMORRHAGIC CYSTITIS WITH GSTM1 AND CYP2C9 GENOTYPES IN PEDIATRIC PATIENTS RECEIVING BUSULFAN BASED CONDITIONING REGIMEN PRIOR TO HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Objectives

One of the complications of Busulfan (BU) based myeloablative conditioning regimen especially in combination with cyclophosphamide (CY) in children prior to hematopoietic stem cell transplantation (HSCT) is occurrence of hemorrhagic cystitis (HC). In this study we explored the association of genetic variants in GSTM1 which is involved in metabolism of BU and CYmetabolites, CYP2C9 (involved in formation of sulfolane and activation of CY), and ALDH3A1 (enzyme detoxifying CY metabolites) in relation to the incidence of HC before day 30 post-transplant.

Methods

Sixty six pediatric patients (33 females, 33 males) recruited at St.Justine's hospital, Canada were retrospectively analyzed. All patients were genotyped for *GSTM1* null, *CYP2C9**2, *3 and *ALDH3A1**2 alleles. HC was defined as the presence of hematuria (both microscopic and macroscopic) for more than a week from the initiation of the conditioning regimen up to 30 days post-transplant. All patients received MESNA as prophylaxis for HC.

Results

Cumulative incidence of HC was 19.7% and BK virus was detected in 85% of the HC cases. We observed higher incidences of HC in carriers of both functional *GSTM1* and *CYP2C9* (36%, n=25) compared to those carrying non-functional allele in either or both of these genes (9.7%, n=41). Significant correlation between age, weight and incidence of HC was also seen. In multivariate analysis including conditioning regimen, age, weight, gender, *ALDH3A1**2 genotype, BU steady state concentration levels only combined *GSTM1* and *CYP* genotype status was independently associated with HC with hazards ratio of 4.2(1.3-13.6).

Conclusions

In view of these observations, we hypothesize that normal *GSTM1* and *CYP2C9* function indicates either higher formation of sulfolane from BU or CY toxic metabolites. Functional *GSTM1* genotypes indicates increased formation of GST conjugates for BU intermediary compounds and simultaneously might deplete GSH levels, to be available for other conjugating enzymes (GSTA1, P1 and T1) predominantly involved in toxic CY metabolites elimination.

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New Drugs/Experimental Therapeutics

INAPPROPRIATE CARBOPLATIN EXPOSURE IN CHILDREN AFTER FLAT DOSING

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Objectives

Although the concept of renal function-based carboplatin dosing is well-established in children, this dosing method is not routinely practiced. Failure to correct for renal function results in variable carboplatin exposure, with the risk of adverse effects and suboptimal treatment. We set out to determine carboplatin exposure in children after flat dosing and compared this with targeted exposure.

Methods

In 30 children with a wide spectrum of solid tumors, the area under the concentration-time curve (AUC) was calculated after 78 courses of carboplatin using NONMEM. Observed AUC values were compared with target values, calculated as 1.325 mg/mL.min per 100 mg/m^2 of protocol dose. Bias, precision and accuracy within 20% of target AUC were calculated.

Results

Median observed AUC as a percentage of target AUC was 89% (range 43%-236%). AUC within 20% of target was achieved in 42% of courses (Figure). This proportion was slightly lower in infants (27%) than in older children (44%; *P*=0.139). In infants, most measurements fell below 80% of the target value (62%), as opposed to 23% underestimation in older children
(*P*=0.001).

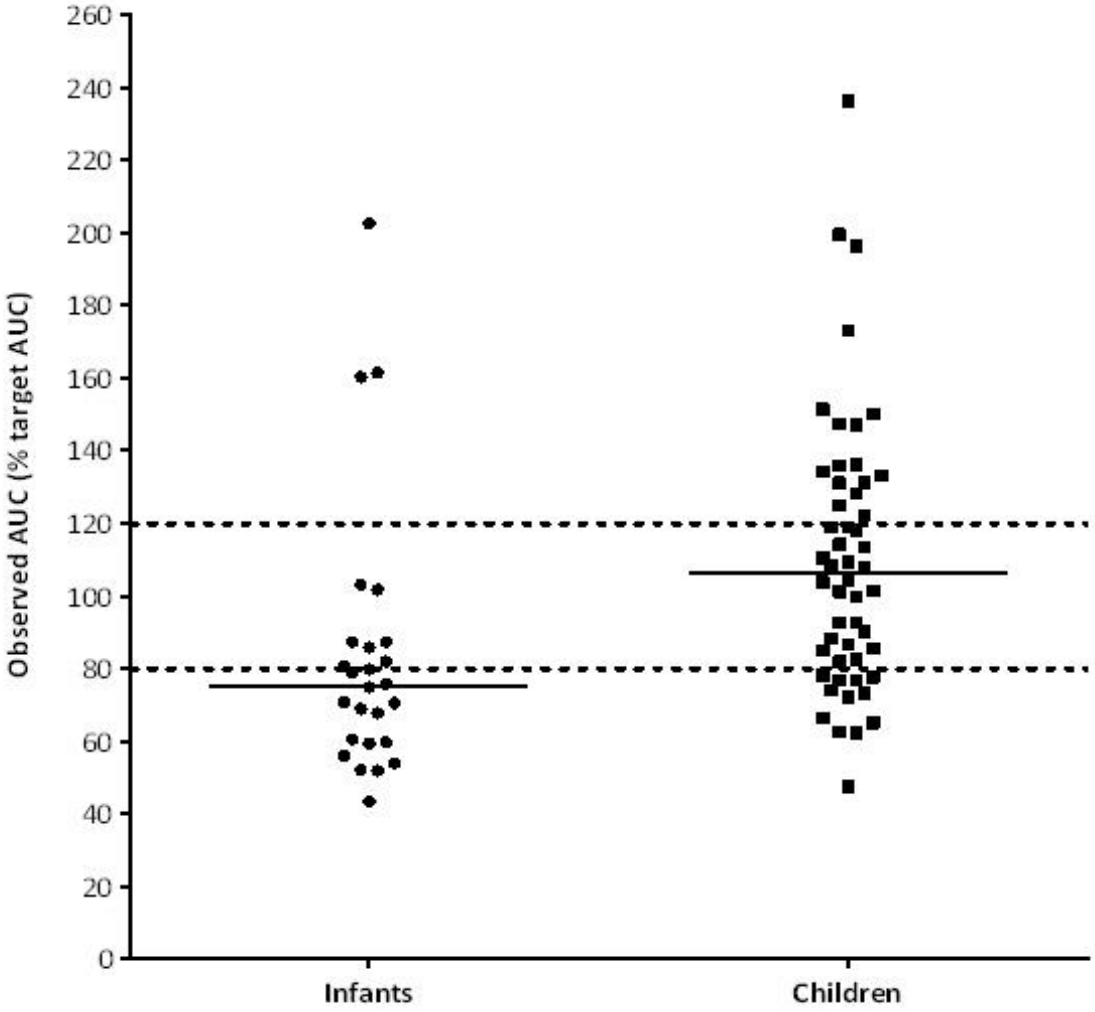

Figure. Observed AUC as percentage of target AUC for infants and older children

Conclusions

Dosing based on body surface area or body weight results in highly variable carboplatin exposure, particularly in infants, with the risk of toxicity as well as a lower cure-rate. This once more underscores the importance of renal function-based carboplatin dosing in children.

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New Drugs/Experimental Therapeutics

NOVEL FORMULATIONS TO TARGET OXIDATIVE STRESS IN PRECLINICAL MODELS OF RETINOBLASTOMA

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Objectives

Overall survival for patients with intraocular retinoblastoma (RB) is excellent; however, globe salvage in advanced disease and survival for patients with metastatic disease remains poor. While whole genome sequencing of retinoblastoma revealed that epigenetic deregulation is essential for tumor development, the presence of double-stranded DNA breaks and G-to-T or C-to-A transversions indicates a possible role for oxidative stress in tumorigenesis. Congruent with this finding, a targeted drug screen of retinoblastoma cells utilizing a library of over 300 anti-neoplastic agents revealed activity of histone deacetylase inhibitors (HDACi). This study evaluated the efficacy of HDACi in preclinical models of RB, optimized the ocular formulation and characterized the pharmacokinetic and toxicity profile of this class of new agents in the retinoblastoma arsenal.

Methods

Panobinostat and vorinostat were selected for characterization. We developed an ocular formulation using FDA approved adjuvants, identifying a topical and intravitreal formulation for ocular delivery. We performed pharmacokinetics and compared the vitreal penetration to systemic dosing. Due to differences in the epigenomic landscape of retinoblastoma mouse models compared with human retinoblastoma, we utilized the human orthotopic xenograft for efficacy studies, monitoring intraocular pressure (IOP) as a proxy for disease progression. Eyes with progressive disease underwent enucleation.

Results

Comprehensive preclinical testing following a standardized approach demonstrated a significant ocular survival advantage with HDACi compared to systemic and subconjunctival chemotherapy. Topical delivery of panobinostat resulted in improved intraocular penetration compared with intravitreal, subconjunctival and systemic dosing. Retinal toxicity following HDACi administration was minimal.

Conclusions

Panobinostat, an HDACi, is a promising targeted therapy for retinoblastoma. Topical application is effective at penetrating the vitreous, and may be useful in a protracted, outpatient dosing regimen. Pediatric phase I testing of oral panobinostat is ongoing and will inform future plans for a clinical trial with this drug in retinoblastoma patients.

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Nursing

PSYCHOSOCIAL CONCERNS EXPRESSED BY CHILDHOOD CANCER SURVIVORS IN ACCRA, GHANA

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Objectives

This study seeks to determine the psychosocial concerns expressed by childhood cancer survivors and what interventions can be instituted by health workers to help address these issues.

Methods

Twenty Ghanaian childhood cancer survivors aged 13 to 35 years were interviewed after consent had been obtained from them. A questionnaire was administered to them during the months of February and March 2014.

Results

Twenty five percent completed treatment less than 5 years ago and 50%, 5-10 years ago. All knew their diagnosis of cancer with 75% having been told at diagnosis. Most support had been from parents and family. Survivors (85%) remember treatment affecting their ability to play and take care of themselves. It affected the finances of all the families with all the mothers having to stay at home to look after them. Over 80% felt stigmatized by friends and it affected their schooling and social life. All the children remember friends who died and this has affected them. All the survivors are concerned about their future ability to marry and have children. 75% of them feel they are stronger and better off than their siblings and peers. Fifty percent still worry about a return of cancer but 50% expressed optimism believing that they were completely healed. 75% felt they were now well adjusted to life.

Conclusions

Easing the financial burden of families in developing countries is a necessity. Clinical psychologists should be involved to help children cope with the psychosocial effects including stigmatization. Measures should be instituted in POUs in developing countries to address bereavement as these children often suffer from the loss of friends they have made. Age appropriate information should be made available to survivors addressing issues related to sexuality and reproductive health. Clubs where survivors can interact could be set up where possible.

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Nursing

A TASK FOR THE PHD NURSE IN A TIME OF GREAT TURNOVER OF NURSES IN PEDIATRIC ONCOLOGY

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Objectives

The overall aim is to meet the demands of an evidencebased childhood cancer care; to promote good quality of care and patient safety and also greater job satisfaction and lower turnover of nurses.

Methods

A position has been created at the pediatric oncology center and the appointed PhD nurse is initiating quality improvement projects and supervising bedside nurses in performing them.

Results

A number of projects have been performed. For example, since 2002 lidocaine has been given together with the hypotonic, and painful, injection solution of PEG-asparaginase. Despite the change to an isotonic solution in 2008 the same routine continued. A general feeling of parents and staff that lidocaine caused pain resulted in a study aiming to compare children's/parents' perceptions of intramuscular PEG-asparaginase given with and without local anesthesia with lidocaine. All participants (N = 14) preferred to continue without lidocaine and it is no longer given before PEG-asparaginase injections. Another project started due to discussions between nurses and physicians about gastronomies. The opinion of the nurses was that gastrostomies should be offered more often. However, physicians were hesitant referring to the high risk of complications. A retrospective review of medical records identified gastrostomies and gastrostomy-related complications in children and adolescents with cancer at the center. Gastrostomy-related complications were very common, but few were severe. Furthermore, an ongoing project aim to compare milk and molasses enema with the more established enema with docusate sodium and sorbitol regarding efficacy on constipation and the degree of discomfort for the child with cancer.

Conclusions

The new position enables a scientific approach in small quality improvement projects performed by bedside nurses. The competence of the PhD nurse is utilized in nursing care and while care is evidencebased the job satisfaction of bedside nurses is improved.

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Nursing

INFRINGING ON AUTONOMY – AN ETHICAL CONCERN EXPERIENCED BY NURSING STAFF

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Objectives

A study regarding ethical issues and ways to deal with them has been conducted in pediatric cancer care. Ethical issues are common in pediatric care and arise in connection with value conflicts within an individual and/or between individuals, concerning which of the possible options should be chosen. Each child's specific situation might lead to disagreements about treatment and care. Furthermore, in pediatric care, children's growing autonomy has to be considered.

The purpose of this presentation is to describe one of the ethical concerns which were identified in our study and experienced by nursing staff when caring for children with cancer.

Methods

Physicians, registered nurses and nurse aides working at a children's hospital in Sweden answered a questionnaire. Qualitative content analysis was applied to the open-ended answers.

Results

To infringe on a child's autonomy is not to give the child a chance to decide upon care related concerns by her/himself or to oppose the child's wishes and perform actions and caring procedures that the child does not want. Nurse and nurse aide participants described children's autonomy as something that can be violated and they experienced powerlessness in these situations. Inflicting suffering and limiting truth-telling are subcategories to infringing on autonomy.

Conclusions

Health care professionals' experiences of ethical concerns when, caring for children with cancer, seem to produce strong feelings and moral confusion among nursing staff. Not wanting to inflict suffering on the child and feeling prevented from telling the truth about the circumstances of the child's illness are some examples of nursing care responsibilities that often are connected to medical treatment decisions.

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Nursing

EXPERIENCE OF PEDIATRIC PROCEDURAL SEDATION AND ANALGESIA IN A TERTIARY CARE HOSPITAL OF PAKISTAN FOR ONCOLOGY PATIENTS

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Objectives

Procedural Sedation Analgesia (PSA) in children is well recognized clinical discipline in developed countries. The aim of this is to describe the experience of PSA from a resource limited country.

Methods

We collected data from our Pediatric PSA database from January 2011 – December 2013. Ketamine and Propfofol IV were used. Success of sedation defined as successful completion of the procedure. Complications defined as hypoxia >1min pulse oximetry less than 90%, apnea>20 sec, cardiac arrest, hallucination & vomiting. All procedures were done according to ASA & AAP guidelines.

Results

1900 diagnostic and therapeutic procedures performed under PSA. Indication were Intra-thecal (IT) 1287, Bone marrow aspiration (276), Intra-thecal (IT) + Bone marrow aspiration + tryfine (261), PIC line insertion (71) and Abdominal mass biopsy (5). Median dose of Ketamine was 0.5mg/kg and Propofol was 3mg/kg respectively.1880 procedures was successfully performed. Adverse events occurred in 20 (0.88%) patients. Complications were 10 transient de-saturation (0.44 %) which resolved by increase flow of O2 and repositioning of airway. 6 apnea (0.26%) which resolved by bag mask ventilation & 3 post sedation hallucination (0.13%) which recorded. 1 sedation failure (0.044%) No cardiac arrest or need of endotracheal intubation.

Conclusions

The Co-administration of small dose of Ketamine and Propofol were found to be safe and effective in children requiring PSA.

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Nursing

THE LIFE OF THE PRESCHOOL AGED CHILD WITH CANCER IN SWEDEN

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Objectives

The majority of children who receive a cancer diagnosis are in the 1-to-6 year age group. Survival rates are high, roughly 75%, but treatment is aggressive and requires long and frequent hospital admissions and causes adverse side effects. Health care focus is shifting from surviving childhood cancer to living with it on a daily basis. The young child's experiences are crucial to providing evidence based care. The aim of this study was to explore the everyday life of preschool aged children as expressed by the child and their parents during the first year post diagnosis

Methods

Interviews were conducted with children and their parents connected to a paediatric oncology unit in Southern Sweden. A qualitative content analysis of interview data from three time points, shortly after diagnosis, six months and one year post diagnosis were made.

Results

A dramatic change in the young child's everyday life was described, with experiences of feeling like a stranger, under attack and lonely. Experiences over time of gaining control, making a normality of the illness and treatment and feeling lonely were described. This process may be seen as a striving for an everyday life.

Conclusions

Nurses have a major role to play in the process of striving the child goes through by giving and updating information, making them participary in their care and assuring access to both parents and peers. Ongoing contact with preschool is vital. Addressing these issues and updating them regularly can assist the young child in their transition to living with cancer. Longitudinal studies with young children are vital in capturing their variety of experiences through the cancer trajectory and necessary to ensure quality care.

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Nursing

THE EFFECTIVENESS OF INTERVENTION ON CHEMOTHERAPY-INDUCED ORAL MUCOSITIS IN HOSPITALIZED PEADIATRIC ONCOLOGY PATIENTS: A SYSTEMIC REVIEW

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Objectives

The objective of this review was to determine the best available evidence of vitamin E and granulocyte-macrophage colony-stimulating factor on chemotherapy-induced oral mucositis in hospitalized paediatric oncology patients.

Methods

Databases were searched from 1979 till July 2013. The databases to be searched for published studies in English included: Academic Search Complete, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials, EBSCO Medline, EMBASE, PubMed, Science Direct, Proquest, Scopus Database and Proquest dissertation and theses.Two reviewers used standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument to independently evaluate methodological validity of these papers.

Results

The review included five articles that were published from 1976 to 2013 with a total of 314 participants. The five included articles were four RCTs and one quasi-experimental study. The average percentage of topical applied vitamin E was 4.1% in three studies the intervention with topical application of vitamin E had the lowest proportion of severe oral mucositis. Two of five articles presented the results in number of participants with oral mucositis, and other three articles counted the days with oral mucositis. The results of the duration of oral mucositis were not comparable in intervention groups of five included studies.

Conclusions

This review identified five articles that tested the topical application and systemic application of vitamin E and GM-CSF on chemotherapy-induced oral mucositis in hospitalized paediatric oncology patients. It demonstrated that topical application of vitamin E was effective on relieving of oral pain and treating of severe oral mucositis caused by chemotherapy.

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Nursing

THE NARRATIVE EXPERIENCE OF CHILDHOOD CANCER: A SYSTEMATIC REVIEW AND CRITICAL APPRAISAL

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Objectives

With improvements in childhood cancer outcomes has come increased interest in the experience of the child under treatment. However, an analysis of the qualitative literature across health-care institutions is lacking. We sought to systematically review and appraise evidence describing narrative experiences of children receiving cancer treatment to identify gaps in understanding and inform interventions to improve quality of life (QOL).

Methods

Electronic searches were conducted in PsycINFO, MEDLINE, EMBASE, and CINAHL (from database inception to June 2013) for primary qualitative studies. Article inclusion criteria were (1) patient population (0-21 years) receiving active cancer treatment and (2) cancer experience described by the patient. Two independent reviewers assessed articles for relevance and methodological quality, and extracted data.

Results

Of the 3103 articles identified, 16 with 254 children from 8 countries were included in analysis. Five overarching themes were identified: a family turned upside down (the changed child, the changed family, a changed trajectory); coping strategies (social support, normalization, sustaining hope, spirituality); child in flux (awareness of mortality, protector of loved ones, need for autonomy, reorganization of priorities); managing treatment (information needed, negotiating lifestyle changes, negotiating treatment effects, managing hospitalization); and fluctuating realities (preparing for the worst while hoping for the best, celebrating high-points amidst of low-points, fighting treatment and not cancer).

Conclusions

Cancer has profound impacts on the lives of children living with the disease. The current qualitative evidence suggests day-to-day life, interactions with family, and developmental trajectories are affected. Qualitative research related to intimate relationships and living with uncertainty is needed to broaden understanding of the impact of cancer on children. Age-appropriate and innovative interventions within a culturally diverse and primarily out-patient treatment environment may address identified child psychosocial and educational needs to improve QOL. Interventions should focus on relationships, normalize the child experience, address long-term effects, and better direct healthcare providers.

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Nursing

ADVANCING NURSING EDUCATION, PRACTICE, AND RESEARCH: THE ROLE AND FUTURE DIRECTIONS OF THE PEDIATRIC ONCOLOGY GROUP OF ONTARIO (POGO) NURSING COMMITTEE IN ONTARIO, CANADA

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Objectives

In 1989, the POGO Pediatric Oncology Nursing Committee was formed to address issues in the delivery of childhood cancer care, and to facilitate professional development activities. Ongoing evaluation is iterative, with aims to ensure accountability, stimulate partnerships, and timely accomplishment of goals. The objective of this presentation is to provide an overview of the Committee's activities and future directions.

Methods

Led by the Chair, the Committee and its taskforces meet in person, correspond via email and telephone, and participate in various POGO-led projects. The committee relies on active participation of its members, knowledge exchange, and sharing of local resources. Each member may lead or provide feedback on any Committee project. Data for this evaluation were collected through follow-up with current Committee/taskforce members as well as selected POGO Staff and Fellows; and through a retrospective review (1989 to 2014) of the nursing roles, meeting minutes, email communications, publications, and research database.

Results

To date, 50 nurses have served as Committee members. Collectively, they have led 5 research projects (e.g. workforce, telepractice); planned 6 education events; and contributed to numerous clinical projects (e.g. drug safe handling; symptom management; and nursing role/curriculum development). The Committee has published 2 peer reviewed articles, developed 7 guidance documents, and presented at 11 peer reviewed conferences. The Committee also promotes research opportunities. Presently, 5 nurses have been awarded PhD Fellowships or seed grants, which have produced 9 peer reviewed publications. Nurses have taken a leadership role in 16 studies related to the delivery of care. Future directions include recruiting new members, planning and implementing additional projects, and strengthening translation efforts and collaborative networks.

Conclusions

The POGO Nursing Committee has been instrumental in advancing the role of nurses in Ontario. These collective efforts may serve as an example to others seeking to optimize the delivery of childhood cancer care.

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Nursing
NURSING MANAGEMENT FOR PREVENTING OF PERIPHERAL CHEMOTHERAPEUTIC EXTRAVASATION: EVALUATING AN INTERVENTION PROGRAM ON THE EDUCATIONAL OUTCOMES OF NURSES CARING OF ONCOLOGY CHILDREN

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Background: There is a growing understanding that good nursing practice is the cornerstone in preventing of extravasation when administrating chemotherapy; one of the shortcomings is lack of understanding or practice of oncology nurses; causes the devastating complication of extravasation. Therefore, good oncology nursing care for children and close monitoring of complications is essential for successful Chemotherapy. This study evaluated the theoretical and practical requirements of the oncology nurses, and the clinical implication of the intervention program as a training for nurses to eliminate the weak points related to safe administration of chemotherapy and prevention of extravasation.

Methods: The study was conducted in the Pediatric Oncology Department at Children Hospital, Ain Shams University Hospital in Cairo, Egypt, using a quasi- experimental research design with pre/post intervention assessments. Data was collected using a self-administered questionnaire sheet and an observation checklist (pre/post format) and developed an intervention educational program about nursing management and for reducing the risks of chemotherapeutic extravasation in oncology children.

Results: Most of the nurses in the study sample were in the age group 25 to less than 30 years (40.0%) and the majority (60.0%) have a nursing school diploma. Only nine nurses (17.0%) have previously attended training courses. the program had a significant positive impact on nurses' knowledge and performance, especially in relation to objectives for minimizing extravasation, types of chemotherapy extravasation, and precautions to follow. Conversely, after application of the program. Meanwhile, no statistically significant increases were noticed in the scores of knowledge related to recommended documentation of extravasation.

Conclusions: The study demonstrated that implementation of an intervention program about preventing chemotherapy extravasation had led to a higher educational and practical outcomes during administration with preventive measures of extravasation as a complication of chemotherapeutic administration among cancer children.

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Nursing

Hospital Infantil Teleton Oncologia (HITO) and Dana-Farber/Boston Children's Cancer and Blood Disorders Center Nurses Partner to Improve Pediatric Oncology Care

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Purpose/Objective:

Nurses are the largest workforce in health care and have a significant influence on patient outcomes. Research has demonstrated the positive association between specialized nursing education and lower mortality rates among children with cancer (1). Nursing partnerships, such as the collaboration between Hospital Infantil Teleton Oncologia (HITO) and Dana-Farber/Boston Children's Cancer and Blood Disorders Center (DF/BCHCC), promote optimal patient care through specialized nursing education and clinical training. The transfer of knowledge between nursing at HITO and DF/BCHCC via an observership exchange program model has proven to be effective.

Materials and Methods:

An ongoing collaboration of nursing staff between HITO and DF/BCHCC consists of a formal curriculum tailored to roles of the nurse leader, staff nurse and other specialties. Nurses from HITO spent three months at DF/BCHCC conducting site assessments and observation of practice throughout key areas prior to HITO opening in December 2013. Nursing staff from DF/BCHCC travel to HITO to provide training and education. Nurses specialized in Oncology, Hematopoietic Stem Cell Transplant, Intensive Care, Emergency Care, Infection Control, Surgery, Leadership and Education partnered to develop a program to meet the needs of HITO staff and provide on-site teaching and mentorship.

Results:

Data is being collected through voluntary surveys from nurses who have and are participating in the collaboration. To sustain the training and education model, a combination of online, teleconferencing and ongoing exchange visits will be conducted.

Conclusions:

Educational programs for oncology nurses throughout developing countries can improve pediatric cancer care and build capacity through ongoing partnerships. HITO and DF/BCHCC nursing programs are committed to continue to exchange information and pursue initiatives to ensure optimal nursing care.

Reference:

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Document not received

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Nursing

ROLE OF NURSING CARE IN MANAGEMENT OF RELAPSED HODGKIN LYMPHOMA PATIENTS DURING HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT- SINGLE CENTER EXPERIENCE FROM PAKISTAN

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Objectives

The main objective of this study was to assess the nursing care issues in pediatric patients of relapsed hodgkin lymphoma (rHL) during their inpatient stay for high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT).

Methods

We retrospectively reviewed nursing notes of all pediatric patients of rHL treated at Shaukat Khanum Memorial Cancer Hospital Lahore during April 2011 to March 2014. All of them were treated with BEAM chemotherapy (BCNU, etoposide, cytarabine and melphalan). Strict protective isolation was observed during admission. Data including age, gender, paying status and duration of hospital stay were recorded. Common problems encountered during hospitalization were thoroughly studied.

Results

Of 16 patients reviewed, 13 were male. Median age at diagnosis of rHL was 15 years. All patients except one received free treatment. Patient to nurse ratio during hospitalization was 1:1. Median duration of hospital stay was 24 days (range: 20-38 days). Symptoms persisting for 7 days or more included diarrhea (56%), oral mucositis (44%), nausea (31%) and fever (6%). Oral intake was markedly reduced in 56% patients (n=9), main contributing factors were oral mucositis (n=8), nausea/ vomiting (n=8), abdominal discomfort (n=4) and disliking for hospital food (n=3). Consistent nursing practices included regular oral care and motivational counseling for dietary improvement. Psychological disturbances were encountered by 62% patients (n=10), notable reasons were isolation, home sickness, fear of disease progression and side effects of chemotherapy. Frequent counseling sessions by attending nurses were conducted with active listening, employing play therapy (n=8) and provision of animated movies (n=8) and story books (n=7).

Conclusions

This study elaborated physical and psychological issues faced by pediatric patients while undergoing HDC and ASCT. Individual assessment and dedicated efforts by nursing staff can facilitate these patients to cope with the problems encountered during prolonged hospitalization for intensive chemotherapy.

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Nursing

THE ROLE OF PEDIATRIC ONCOLOGY NURSE AS AN EDUCATOR IN THE "ANYO HOUSE" A HOUSE FOR SHELTER AND EDUCATION

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Objectives

Pediatric oncology nurses are knowledgeable resources for healthcare providers caring for children with cancer. We describe a pediatric oncology nurse educator developed program in Indonesia that aims to provide information to all stakeholders and reinforce important components of the children's care. This educational program is an important element of the child's pediatric oncology treatment.

Methods

Since June 2013, a monthly formal structured learning activity was designed and executed, coordinated by a pediatric oncology nurse educator. This free educational program was presented to families of children with cancer and members of the health sector: nurses, dieticians, medical students, pediatric nurses, and a donor. The educational venue was the 'Rumah Anyo' (Anyo House) of the Indonesian Anyo Foundation. Speakers represent several disciplines i.e., medical oncologist, dietician, pediatrician, general medicine, senior oncology nursing and also a cancer survivor.

Results

Topics included food for healthy life style, optimization of early detection of child development, myths and facts about breast milk, bio energy power, palliative care, effects of chemotherapy in children with cancer, and the optimization of nutrition in children receiving cancer treatment. Teaching was provided in an hour blocks including lectures, discussion, open-ended questions, and questions and answers. At the end of each session, participants completed a checklist evaluation.

Conclusions

From the results of the educational sessions that the nurse coordinated, guidelines have been created through consultation and discussion with the child's health practitioner for managing chemotherapy side effects and providing good nutrition for children during treatments. There has also been collaboration with a donor to develop motivation and continued education for children who stay in 'Rumah Anyo'. There remain several family support-related strategies that should be improved in the development of this education program in this special community setting and are being addressed by the nurse educator.

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Nursing

HOSPITAL-BASED HOME CARE PROGRAM FOR CHILDREN WITH CANCER: DEVELOPING PALLIATIVE CARE AT HOME

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Objectives

A hospital-based home care program for children with cancer was established in 2008 to develop and provide medical treatment and nursing care in the children's own homes. Since 2011, the hospital-based home care program also delivers palliative care including end-of-life care, to ensure the quality and continuity of care for the child at home according to the families' needs. Providing palliative care is a complex and challenging task and our purpose is to describe the feasibility of delivering hospital-based palliative care at home.

Methods

Children with any type of cancer and who lives within a radius of 50 kilometres from the hospital are eligible for the hospital-based home care program. Two nurses employed at the department provide the home visits e.g. intravenous chemotherapy, supportive and palliative care. Descriptive analysis was performed on hospital records.

Results

Between January 2012 and December 2013, a total of 107 children received home visits and 14 (9 girls) of these received palliative care at home (median age 9 years; range 2-20 years). Ten children with brain tumor, 4 children with solid tumor and one child had ALL. Number of home visits per child were 6 (median; range 1-22) and lasted for 30-40 minutes (median; range 10 to more than 60 minutes). Six children died at home. When needed, the home care nurse provided the home visits in collaboration with the nurse and doctor responsible for the child's treatment, a community-nurse, and a nurse-specialist in pain relief. Evaluation will be performed in 2014 by assessing quantative data and qualitative interviews with the families and the health care professionals.

Conclusions

It is feasible to provide hospital-based palliative care to children in their own homes. The results can be useful when considering the provision of palliative care based at a hospital department.

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Nursing

INVESTIGATION AND ANALYSIS OF SPECIALIZED NURSING KNOWLEDGE OF NURSES IN DEPARTMENTS OF PEDIATRIC HEMATOLOGY AND ONCOLOGY IN 14 CHINESE HOSPITALS

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Objectives

To investigate the present specialized nursing knowledge of nurses in departments of pediatric hematology and oncology in 14 Chinese hospitals and analyze its influence factors.

Methods

Researchers designed investigation form based on literature review, enrolled 182 nurses from 14 Chinese 3A hospitals by convenient sampling, and collected data through SurveyMonkey online investigation system (http://www.surveymonkey.com/)

Results

The average scores of 63.6% parts of specialized nursing knowledge were higher than 3.5, which mean ‘less understanding’. Nurses with different experiences and titles demonstrate different levels with respect to total score, disease-related, therapy-related, symptom-related, operation-related, occupational protection-related and nursing education-related knowledge ($p<0.05$).

Conclusions

Nurses in departments of pediatric hematology and oncology show a relatively lower level of specialized nursing knowledge, especially in the palliative care-related knowledge. Nurses with different background demonstrate different acquisition of specialized nursing knowledge. Researchers suggest paying more attention to the importance of specialized nursing knowledge, in order to substantiate the connotation of nursing, elevate the nursing value, and promote the professional care of children with hematology and oncology.

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Nursing

NURSING CONSIDERATIONS IN THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) WITH VINORELBINE AND NIMOTUZUMAB

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Objectives

Brain tumors are the leading cause of mortality in childhood cancer. The DIPG is a tumor that affects the brainstem. It manifests exclusively in children and teenagers. These patients have a survival rate, after one year of diagnosis, under 10%, with median survival of 6-9 months. Radiation therapy is the standard palliative treatment, because of its location, surgical management is not indicated. Without radiotherapy, the median survival of these patients is 20 weeks.

The objetive of this study is to evaluate tolerance and acute side effects in patients who suffer DIPG, and are under ambulatory treatment with Nimotuzumab and Vinorelbine.

Methods

Review the cases of patients treated in our unit with Nimotuzumab and Vinorelbine, as well as radiotherapy.

Results

Concomitant use of Nimotuzumab plus Vinorelbine along with radiotherapy (weekly during induction treatment, and every two weeks during maintenance period) has shown a decrease in the number of hospital admissions, increased quality of life and survival rate (up to 24 months, with progression-free survival after six months, in 90% of patients).

Conclusions

Combination of radiotherapy and Nimotuzumab plus Vinorelbine is well tolerated by patients, and can be administered on ambulatory basis without the need for hospital admissions due to neutropenia, fever, nausea and vomiting, etc.

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Nursing

COMPLICATIONS IN SURGICAL WOUND HEALING IN CHILDREN AND TEENAGERS WITH BRAIN TUMORS UNDER TREATMENT WITH BEVACIZUMAB (AVASTIN®) AND DEXAMETHASONE

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Objectives

During treatment of brain tumors, with surgery and/or radiotherapy, it is necessary to combine drugs, in order to control symptoms and working towards eradication.
Dexamethasone is a drug frequently used when dealing with cerebral edema, but its long-term administration produces Cushing Syndrome, causing increased skin fragility.
New therapies look to inhibit angiogenesis of these tumors.
Bevacizumab causes regression of tumor vascularization, normalized residual tumor vasculature and inhibits tumor neovascularization, preventing tumor growth. Because of this, healing time is longer.
The objective of this study is to present management and results, from nursery experience, in complications observed during healing process in surgical wounds in three patients treated in our unit. They were treated with Avastin® and Dexamethasone at the same time.

Methods

Cases of patients treated with Avastin® and long-term Dexamethasone were registered and reviewed. It was found that three of them had dehiscensia in surgical wound. One case presented worn septum. Diagnosed diseases were disseminated Oligodendrogliomatosis craniospinal progression (1 case) and Diffuse Intrinsic Pontine Glioma (2 cases).

Results

In two of these cases, after one month of treatment with Avastin®, there was abdominal dehiscensia and catheter head was exposed. Treatment with silver sulphadiazine and povidone iodine ointment helped, but it was necessary to complete healing with surgery closure. In one case, Vacuum Assisted Closure was used and considerably improved until success. In another patient, worn septum unabled the possibility to rebuild tissue.

Conclusions

Bevacizumab has been a breakthrough in clinical practice. The effects are observed after short time and after a single dose treatment. That is why its use is well accepted, as it has been very useful in the improvement of the neurological symptoms of our patients, although it is not free of significant side effects.

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Nursing

BIOMARKERS OF OXIDATIVE STRESS IN CHILDREN TREATED FOR LEUKEMIA

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Objectives

Central nervous system (CNS) treatment for children with acute lymphocytic leukemia(ALL) is necessary to prevent disease recurrence in the brain, but associated with cognitive problems in almost 40% of survivors. CNS biomarkers that can identify children most at risk could increase our understanding of treatment-related neurotoxicity. The purpose of this study was to investigate relationships among F_2-Isoprostanes, a well-established biomarker of oxidative stress, and two oxidized glycerophospholipids [phosphatidylcholine (PC) and phosphatidylinositol (PI)] in the cerebral spinal fluid (CSF) in children with ALL.

Methods

A within subjects repeated measures design was used to investigate relationships among the CSF biomarkers during the first 18 months of ALL treatment. Seventy-nine newly diagnosed children with ALL, and treated on Children's Oncology Group protocols participated. CSF samples were collected with each lumbar puncture required per protocol for intrathecal chemotherapy.

Results

F2 isprostanes and glycerophospholipids increased significantly during CNS treatment compared to diagnostic CSF levels. The highest concentration of F_2-Isoprostanes during induction was significantly correlated with highest levels of oxidized PC (r = .320, p = 0.003) at the same treatment phase. During post-induction the highest concentration of F_2-Isoprostanes was significantly correlated with oxidized PC (r = .356, p = 001) and oxidized PI (r = .290, p = 0.005). Highest concentration of F_2-Isoprostanes during continuation was also significantly correlated with oxidized PC (r = .420, p < 0.001) and oxidized PI (r = .319, p = 0.003).

Conclusions

The significant increase in F2-isoprostanes and oxidized PC and PI provides evidence for their use as measures of oxidative stress in the brain. Both oxidized PC and PI were significantly correlated with F2 Isoprostanes, an established biomarker of oxidative stress. In the future these measures may become important markers of underlying methotrexate-induced neurologic injury.

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Nursing

PORTFOLIO OF ENHANCING RESILIENCE FOR ADOLESCENTS AND YOUNG ADULTS WITH CANCER

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Purpose

The purpose of this study was to evaluate the adolescents and young adults (AYAs) with cancer' views of the usefulness of portfolios to improve their resilience.

Methods

Each patient's portfolio included two sheets to find self and project their goal of the future. The examples of the portfolio were shown to get them an idea of what was expected. One of the authors supported them to work with the questions in the sections that built the content in the portfolio. The Resilience Scale was used before and after the portfolio.

Results

A total of 14 patients aged 12 to 21 years were participated. We found that most of them were middle and high levels of resilience and about a half of them increased their inner resilience score ("I am" factor), a person of hope, faith, confidence, and optimism. All of them found the portfolios worthwhile and useful. The rest of the participants show that they were no change or the low level of resilience after the portfolio.

Conclusions

Using a portfolio can be enabling tool in pediatric oncology nursing to help the AYAs with cancer enhance their resilience. Some of them may need to support for finding self and having their purpose. Future studies are needed to improve the validity of this research.

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Document not received

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Nursing

DELIVERING END OF LIFE CARE FOR CHILDREN AND YOUNG PEOPLE IN A RURAL COMMUNITY

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Objectives

The aim was to develop a Paediatric Palliative Care Nurse Bank (PPCNB)to deliver end of life care for children and young people dying from malignant disease.A previous audit had shown that 50% of parents caring for their dying child in the hospital setting would have taken them home if 24hour nursing support could have been provided.The initiative involved the development, education and training of a nursing bank to provide a fast and flexible response to support families who wish their child to die at home.

Methods

The first step in the process involved explaining our ideas at a senior nurses meeting and gaining management support. Interested paediatric nurses were then recruited in order to to develop a database of staff. Education and Training consisted of an initial series of Study Days followed by a rolling programmme of continuing education and debriefing sessions enabling staff to improve their knowledge and skills in palliative care and symptom management.

Results

The service has so far been utilised for 3 families caring for their dying child at home. The feedback from families and the nurses has been extremely positive.Families have described feeling more in control and reassured by the presence of familiar, experienced nursing staff. The training element of this development has ensured that nurses have supplemented their core skills. These skills have been transferrable to their own areas of practice.

Conclusions

The vision and commitment has been that children,young people and families have safe, accessible, sustainable, high quality end of life care in the home. The development of the PPCNB as a unique service in rural Wales has improved care for families at a vulnerable time and increased confidence, knowledge and skills for nursing staff.

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Nursing
EMOTIONAL EXPERIENCES OF PARENTS CARING FOR THEIR CHILDREN WITH CANCER
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Objectives
The Japanese government decided to improve relationships with pediatric cancer centers in 2013. This resulted in 15 centers cooperating with regional hospitals. However, the system has just started and almost all pediatric cancer patients still receive medical examinations in neighborhood hospitals. Childhood cancer results in considerable stress on families. These stressful events are usually unparalleled in importance to those facing them. The support of professionals is essential for families to adapt to their new lifestyles. Thus, the purpose of this study was to explore the emotional experiences of parents caring for their children with a cancer diagnosis.
Methods
Data were collected through semi-structured interviews and analyzed using qualitative inductive methods. Participants were recruited from a pediatric oncology hospital in Japan. The local ethics committee approved this study.
Results
11 parents (9 women and 2 men) were interviewed. At the time of diagnosis, parents commonly experienced very strong emotions such as feelings of shock, disbelief, anger, loneliness, and powerlessness. It was difficult for the parents to appreciate the implications of their child's disease immediately; however, over time, they managed to grasp the reality of their child's health condition. The timing of when the information is delivered to the parent is one of the most important things to consider. It is also necessary for medical professionals to assess the parents' health simultaneously in order to provide care for both the child and the family.
Conclusions
Pediatric nurses have an important role to play in the provision of information, and they need to be vigilant regarding the individual needs of parents. Medical professionals need to provide comprehensive information that meets the needs of all of the individuals concerned. Better care of ill children needs to be accompanied by lasting relationships between parents and health-care professionals.

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Nursing

JOB ANALYSIS IN ONCOLOGY NURSING AND TASK FORCE PLAN IN THE AMBULATORY CHEMOTHERAPY UNIT: IS AUTOMATING CHEMOTHERAPY PREPARATION WITH ROBOTIC TECHNOLOGY USEFUL?

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Objectives

To analyse the time spent and efficacy with nursing procedures in the ambulatory chemotherapy unit, after the establishment of the automated chemotherapy preparation with Robotic technology.

Methods

In 2012, 16.661 chemotherapy applications were performed in 177 working days, (94 patients/day) in the 'Ambulatory Chemotherapy Unit' (Monday-Friday, 8a.m.-4p.m.) of the Istanbul University, Institute of Oncology. Since July 2012, automated chemotherapy preparation with Robotic technology have been used. Eight nurses worked in the unit. In June 2012, on 6 different days, on three time periods during the day (8-10a.m., 10 a.m.-1p.m., 1-4p.m.), the time spent in nursing procedures were assessed in detail (21 variables) by two independent observers using a chronometer. The median number of patients recieving ambulatory chemotherapy/day during the study period was 78. All nurses were educated for all procedures previously and interviewed.

Results

Using the Robotic technology, all 8 nurses were actively involved in nursing procedures. Prior to robotic technology, 2 of the 8 nurses were involved only in preparation of chemotherapy drugs with no active patient procedures . The median time spent specifically for nursing procedures before,during and after chemotherapy was 31 min, 32 sec./patient, this increased to a median of 2 hours 31 min 48 sec if an adverse reaction occurred. Excluding lunch/specified breaks, each nurse was expected to work actively for 6 h 25 min/day. The median time spent by a nurse for each patient was 40 minutes. For 78 patients/day, each nurse had to actively work for 6 hours 45 min; 20 minutes more than expected. However the extra time of active work was less than prior to robotic technology.

Conclusions

The robotic technology helped increase the safety and accuracy of chemotherapeutic drugs and increased the time spent by a nurse in active nursing procedures of each patient, which led to a better satisfaction of the patients.

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Nursing

MULTIDISCIPLINARY PEDIATRIC ONCOLOGY TRAINING IN BOTSWANA

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Objectives

About 80% of the 160,000 children who develop cancer live in low & middle income countries (LMIC) where survival is considerably less than in resource-rich settings. A major challenge in treating pediatric cancer in LMIC is a lack of trained providers. Baylor College of Medicine (BCM) and Texas Children's Cancer and Hematology Centers (TXCH) have had a partnership with Princess Marina Hospital (PMH) since 2007 as the only center in Botswana treating children with cancer. PMH has a full time pediatric oncologist and a care coordinator from BCM/TXCH. Staff including nurses, pharmacists, dieticians and social workers receive very little, if any, pediatric cancer-specific training.

Methods

We conducted a multidisciplinary workshop to improve cancer care in Botswana. Two nurses and one pediatric resident from PMH were invited to BCM/TXCH for intensive training prior to the workshop. They served as instructors along with the pediatric oncologist, care coordinator, a local nursing instructor and two visiting educators from TXCH. The novel curriculum designed for this workshop included: an overview of pediatric cancer and treatment; supportive care; chemotherapy safety and administration; pain management; family-centered care; and palliative care. Training strategies included case studies, didactic lectures and open forum discussion.

Results

The one week workshop was attended by 28 participants representing eight public and private institutions from throughout Botswana. Eight disciplines were represented including physicians, surgeons, pathologists, nurses, social workers, dieticians, pharmacists and nursing instructors. Pre and post-tests demonstrated the curriculum's effectiveness in relaying key principles to learners. Participant evaluations strongly supported the need for this type of training.

Conclusions

Training opportunities in pediatric oncology are limited in LMIC. Standardized, sustained multidisciplinary education is vital to providing the highest level of oncology care. This curriculum can be adapted to other LMIC. Long term success is dependent on local capacity building of all aspects of pediatric cancer care.

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Nursing

CANCER – LIFE CHANGES AND SO DO THE RULES

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Objectives

The diagnosis of cancer and immunosuppressive cancer treatment requires a thorough change of lifestyle from patients and their families. Outside the hospital, where professionals provide a sense of security, parents need to know how to protect their child and themselves without overly restricting everyday life. This is where the hospital staff steps in with a structured instructional program designed to provide security in caring for the patient at home and raise awareness for signs of potential emergency situations.

Methods

For about four years now, nurses at our hospital have been running once-weekly formal instructional sessions, the nursing clinic, to be attended when a patient is about to be discharged from hospital after the first in-patient stay. Sessions last about 1-2 hours. If needed, instructions may also be arranged outside the clinic hours. The nursing staff is trained to integrate instructions into their nursing routine.

Results

The program has been well accepted; e.g., out of a total of 124 newly diagnosed patients in 2013, 62% have taken advantage of the nursing clinic, while 38% represent patients who had no systemic chemotherapy and some families who declined.

Ideally, both parents take part in the instructional session. Quite frequently, however, only one parent will be able to attend. Mostly, this is the person who will be caring for the patient at home.

Pediatric patients tend to take an interest in the nursing clinic the older they get. Usually, patients are 12 years or older when they decide to actively participate.

Conclusions

The instructional sessions allow parents and their children well-structured everyday living and in consequence a better quality of life at home. Moreover, heightened awareness of emergency signs assures fast intervention in situations that cannot be managed at home, e.g., severe febrile episodes in neutropenia and other situations that require direct communication with the treatment center.

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Nursing

"CHILDREN WITH CANCER: A GUIDE FOR EDUCATORS": THE CREATION OF A SCHOOL BASED RESOURCE BOOKLET

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Objectives

There are approximately 1,000 children undergoing active cancer treatment in Ontario, Canada each year. Many of these children are school aged. A cancer diagnosis presents unique challenges for school administrators and educators to maintain and facilitate this vital aspect of a child's life. As part of their role, Pediatric Oncology Group of Ontario (POGO) Interlink Community Cancer Nurses work collaboratively with educators and families to support schools in the education of children with cancer. To supplement and enhance the sharing of information, a program specific resource booklet entitled 'Children with Cancer: A Guide for Educators' was created.

Methods

Literature regarding school reintegration was reviewed. The content of a well established program of educational support provided through POGO Interlink Nurses via telephone consultation, school meetings and classroom presentations were considered. Consultation with school administrators, educators, physicians and nurses contributed to the content of the booklet.

Results

The booklet is a school based resource that outlines general information about childhood cancer, treatments and practical strategies for supporting children and families throughout the cancer experience. It guides educators by delineating the phases of treatment and outlining special academic and social considerations for when a child is diagnosed with cancer, when a child returns to school and in the event that a child's cancer recurs. Information and emotional support needs of the child, family, siblings, classmates and faculty are addressed. Colourful illustrations are used throughout the booklet to enhance content and clarity.

Conclusions

POGO Interlink Nurses began to distribute the resource booklets to enhance their support of Ontario schools in January 2014. Although formal evaluation is not planned until 2015, anecdotally the document has been well received by administrators and educators as a welcome resource in understanding and facilitating the educational needs of children undergoing cancer treatment.

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Nursing

COMBINATION MORPHINE AND KETAMINE IN HIGH RISK NEUROBLASTOMA PATIENTS RECEIVING CH14.18/CHO ANTIBODY/IL2 MAXIMISES ANALGESIA, MINIMISES SIDE EFFECTS AND OPTIMISES IMMUNOTHERAPY DELIVERY

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Objectives

To obtain optimum pain control in patients receiving CH14.18/CHO antibody on the HR-NBL-1/SIOPEN protocol, with minimal side effects.

Methods

Neuroblastoma patients receive CH14.18/CHO antibody with or without aldesleukin. It is a monoclonal antibody that binds to GD2 receptors on the neuroblastoma cells and induces the killing of tumour cells by the patients own immune response.

This treatment is significantly toxic. Patients experience sudden onset pain during the administration of the antibody, therefore concomitant PCA/NCA morphine treatment is a necessity.

Pain assessment scoring identified that patients were not adequately analgised despite significant morphine dose escalations, and consequent side effects. Antibody infusions were interrupted to optimise pain management. This led to prolonged immunotherapy infusion times.

Multidisciplinary team discussion led to the introduction of a low dose ketamine infusion as an adjunct to opioid analgesia. Ketamine provides good analgesia while preserving airway patency, ventilation and cardiovascular stability.

Results

The combination of morphine and ketamine was successful in controlling pain with far fewer side effects. Optimal pain management allowed immunotherapy delivery without any interruption. Ketamine and morphine co-analgesia is now standard for our patients receiving immunotherapy.

Conclusions

The combination of morphine and ketamine increased the patients' pain tolerance of CH14.18/CHO antibody without the side effects of high dose opiates. This permitted a substantial increase in the number of cycles delivered without delays or breaks and maximised the therapeutic impact of immunotherapy.

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Nursing

LITERATURE REVIEW OF NURSING FOR INFANTS WITH RETINOBLASTOMA AND THEIR FAMILIES

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Objectives

This study aimed to gain insight on nursing research in Japan by literature review of nursing care abroad for infants with retinoblastoma (rare eye cancer) and their mothers. Treatment for retinoblastoma was developed in recent years.

Methods

PubMed and CINAHL databases were explored, covering the last two decades, and 22 papers were selected for review. Based on a literature map developed, nursing care were assessed.

Results

The first paper was published in 1993, and zero to three papers were identified for each year thereafter. The nursing care provided was classified into three topics: nursing for treatment, nursing for visual impairment, and nursing for hereditary cancer. In nursing for treatment, brachytherapy, enucleation of the eye, and chemotherapy were covered. The studies also investigated nursing to prevent long-term psychological issues and long-term effects after treatment, and to coordinate community and school for the children coping with school, as the cure rate had increased. Particularly, in case of hereditary cancer, nursing care for counseling the family was important.

Conclusions

Because the long-term survival rate for infants with retinoblastoma continues to increase as hereditary cancer research advances, papers discussing support for post-treatment problems from a long-term perspective have now appeared. The results suggest the significance of further studies on continuing care for children with familial retinoblastoma and visual impairment , and their family in Japan to improve the quality of life after treatment.

Document not received

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Nursing

APPETITE, SENSES AND JOY OF LIFE – A NUTRITION PROJECT

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Objectives

The project is towards children admitted to the paediatrics oncology ward at Aalborg University Hospital. The purpose of the project is to ad focus on nutrition to reduce the weight loss induced by chemotherapy. And also minimize the need for tube feeding formula and Parenteral Nutrition.

Our intend is to change the hospitalised child's perception of food, to generate new knowledge and create the settings for, how the meal that favours the children's needs and wishes, can be implemented into the paediatrics ward.

Methods

The project is an interdisciplinary project in co- operation with the paediatric oncology ward, the hospital kitchen and the company Unisans. Both parents and children have been included in the project with interviews regarding wishes and needs concerning the children's diet. It has been studied, when the children's nutritional value is most threatened.

A new kitchen has been build, where the families can cook and a new food concept has been developed with better content and more exciting food serving. In addition, a new pamphlet with inspiration has been developed.

Food shops where parents and children have been cooking with a sense coach and chefs from Unisans were a part of the project. The "food shop" turned up every 14 days.

Results

All of the results have not yet been calculated, but we can conclude that a number of success criteria's have been fulfilled.

Greater fellowship, joy in the eating situation, children who wanted to cook and participate in social gatherings including food. The children and teenagers have become more outgoing and eat more of the food served.

Conclusions

We expect that the project will help improve the children's psychosocial development. In the future, the experiences from this project can be used when designing new eating environments in paediatric wards

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Nursing

DECISION-MAKING IN PARENTS OF CHILDREN WITH SICKLE CELL ANEMIA (SCA) CONTEMPLATING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Objectives

Sickle cell disease is the most common inherited blood disorder in the United States, affecting an estimated 90,000-100,000 individuals. Despite improved supportive care in the past 20 years (hydroxyurea and chronic transfusions) the only known cure for SCA is HSCT. HSCT for SCA carries a 10-15% mortality risk. This risk, associated with potential morbidities and lack of studies directly comparing supportive therapy against HSCT, contributes to the controversy of supportive care versus HSCT for SCA.

Our center is a comprehensive hematology/oncology/BMT program, including a pediatric hemoglobinopathy specialty-center. Since 2000, the BMT program has transplanted only 16 children with SCA: with 100% (16/16) OS and 94% (15/16) DFS, although we have consulted many more families.

Methods

A PubMed search of the past 20 years of research was performed to identify SCA parent/patient interest and decision-making process for families contemplating HSCT therapy. We aimed to identify key concepts related to HSCT for SCA interest; decision-making factors; educational material needs, and options for improving consultation services and informed consent.

Results

Only four studies surveyed HbSS and HbSβ^0 patients/families, although the focus varied. Surveys assessed: decision-making process regarding treatment choices or declination, patients' and parents' attitudes towards HSCT, factors associated with patient/parent interest in HSCT, and parents' attitudes towards risk acceptance of HSCT. Key themes identified were providing risk/benefit information and assessing both parental and patient interest when offering HSCT.

Conclusions

In conclusion, limited research and unanswered questions exist regarding interest and decision-making for SCA families regarding HSCT. Our next step is to implement either a survey or focus group to capture information specific to our center, then incorporate findings into HSCT/SCA educational materials and the HSCT consultation process. Specific interests also include the role of the referring/primary physician and outreach into the SCA community.

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Nursing

KNOWLEDGE AND ATTITUDES OF THE NURSING TEAM ON THE TREATMENT OF PEDIATRIC CANCER PATIENTS WITH MEDICAL CANNABIS

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Objectives

Lately, there has been an increase in using medical cannabis on pediatric cancer patients. At Rambam Medical Center, we started using cannabis 3 years ago, as a request of parents of a 15 years old girl at the end of life, in order to alleviate pain, improve her mood and increase her appetite.The use of cannabis raised some ethical issues among our team members. As a result of parents' requests and the need to improve supportive care, we analyzed the knowledge and attitudes of the nursing staff (31 nurses) towards cannabis and in particular in relation to its use by pediatric cancer patients.

Methods

We composed a questionnaire that checked knowledge and attitude towards medical cannabis. The questionnaire consisted of demographic details and questions of knowledge and stance. Questionnaire I was given out without any prior exposure to the subject. As part of a staff meeting, the team heard a lecture and demonstration about medical cannabis and its benefits. About a month afterwards, questionnaire II was answered to check if there was any change in knowledge and attitude. 98% answered the 1st questionnaire and 80% on the 2nd.

Results

No significant changes between the averages of the staff's attitude in questionnaire I (2.55) and questionnaire II (2.71) were found. As to the question of attitude for use of cannabis, about 84% of subjects supported that idea. As for the issue of knowledge, there was a significant difference between questionnaire I (13.55) and II (22.22).

Conclusions

Results show that teaching the staff about the advantages of medical cannabis enriched their knowledge and changed their negative attitudes. The knowledge about cannabis increased significantly so it would help us to build a future medical training program about cannabis for children with cancer.

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Nursing

10 YEARS FOCUS ON CENTRAL LINE CARE

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Objectives

To evaluate ten years focus on central line care

Due to an increased number of central line infections in 2004, a structured education program for nurses, patients and parents was developed. The program was evaluated in 2007 and showed a decrease in the number of Central Venous Catheters (CVC) removed due to infection from 20 % to 15 %, but still a need of focus on follow up on the training of patients and parents. All newly employed nurses are trained during the first two weeks and will receive their certification within the first 2 months after employment. The training of patients and parents is performed by certificated nurses and supported by written guidelines and photos. The education is documented on a checklist in the patient's medical record.

Methods

The certification of nurses in central line care is renewed every year by a practical and theoretical test. Training of patients and parents is evaluated by audit on the checklist in the medical record and by interview with patients and parents if a CVC related infection occurs.

Results

At almost every recertification of the nurses some habits needs to be changed to ensure that our guidelines are strictly followed. A recent audit on the education of the patients and parents unfortunately still showed lack of consistent follow up.

Conclusions

Education of nurses, patients and parents is important, it needs to be ongoing and constantly improved. Future plans on improvement for the education of patients and parents: A patient CVC booklet will be developed. Follow up on the patients and parents training will be scheduled during the whole treatment period. New ways of information: video, app and also new ways of education such as group sessions with special trained nurses will be developed and the individually training will be improved with shared responsibility.

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Nursing

ACUTE PEDIATRIC ONCOLOGY - SCENARIO TRAINING

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Objectives

Children undergoing treatment for cancer are at continuous risk of developing life-threatening complications. Treatment-related complications may develop acutely, within *minutes* or hours. Early recognition, assessment and treatment of such complications are crucial to reduction in morbidity and mortality.

In 2012 we conducted a questionnaire for doctors and nurses targeting their knowledge and skills in emergency situations with the child, specifically addressing ABC handling, teamwork and safe communication. The staff expressed great uncertainty and lack of knowledge in how to handle the critically ill child.

The purpose was to test if the doctors and nurses experienced increased skills in handling the critically ill child with a special emphasis on ABC algorithm, safe communication and team work after scenario training in common oncological emergency situations such as sepsis and anaphylactic reactions.

Methods

Prior to scenario training staff were lectured in use of the ABC algorithm, team work and safe communication. Real time scenario training was conducted in the department in a patient room so the situation appeared as authentic and practice-oriented as possible involving one doctor and three nurses. After completing the scenario exercise debriefing was held.

Results

Overall, all 16 participants reported an increase from below average to above average in self-evaluated skills in relation to ABC algorithm, teamwork and safe combination, where the greatest improvement in skills were within the use of the ABC algorithm.

Conclusions

The emergency scenario training has significantly improved self-evaluated skills in care of the oncological child. Common standards, targeted training and education and the implementation of emergency carts and emergency tables, have improved work processes with clear roles and communication. Our aim in the future is to create an education- and scenario training program in early warning signs and treatment of oncological emergencies, and to test the staffs' skills prior and after completion of the program.

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Nursing

IMPACT OF STRUCTURED EDUCATION AND TRAINING FOR FAMILIES AND STAFF ON RATE OF INFECTION OF CVAD IN CHILDREN WITH CANCER

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Objectives

Introduction: Central venous access devises (CVADs) are central to the modern treatment/management of paediatric cancer patients. Infection is a serious, potentially life threatening complication of CVAD.1. To identify if the implementation of structured education and guidance for staff and families in the year 2000 has had an impact on infection rates. 2. To identify if CVAD care has been maintained when there was no longer a full time lead person responsible for the management of CVADs since January 2013.

Methods

A retrospective study was carried out for a period from January 2000 to November 2013 to identify the rate infection of CVADs. This period was then divided into two, one from Jan 2000 to December 2012 when a full time Advanced Nurse Practitioner(ANP) was in post and the second, Dec 2012- Nov 2013 when a full time ANP was no longer in post. Data was obtained from unit CVAD, microbiology and theatre data base. Evidence based educational methods, training programmes, policies, guidance and patient information booklets, were introduced in January 2000

Results

During the study period there has been a steady increase in the number of CVADs in situ from 50 to 70 patients per year. There has been a decrease in the rate of infection over this study period from 4% to 1.5%. The Decrease has continued into the second period where the full time ANP was no longer in post.

Conclusions

This audit demonstrates the implementation of structured education and training for families and staff has resulted in decrease in the rate of infection of CVADs despite the increase in the number of patients with CVADs. The decline in the infection rate has continued during the absence of full time ANP signifying that the education and training packages have now become a culture of the unit.

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Nursing

THE USE OF CHILDREN'S EMOTIONAL MANIFESTATION SCALE (CEMS) IN PEDIATRIC ONCOLOGY DAY- HOSPITAL PATIENTS

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Objectives

To identify the nursing interventions able to improve the compliance to treatment in children with cancer admitted to the day-hospital.

Methods

We used the Children's Emotional Manifestation Scale (CEMS), that considers 5 variables: facial expression, verbalization, activity, interaction and cooperation and assigns for each item a score from one to five, for a total score ranging from five to twenty-five.

Over 8 months, 100 pts were evaluated by CEMS at: first admission (1) and/or subsequent admission (2). Pts were divided in < 5 years (40 pts) and > 5 years (60 pts).

Results

The study showed that the score is different at point 1 and 2 .

At first admission the most effective intervention was sound for pts < 5 years and play for pts > 5 years, with a score of 18 and 8, respectively.

At second admission , the most effective intervention was distraction for pts < 5 years and explanation of the procedure with listening to the patient's request for pts > 5 years, with a score of 19 and 5, respectively.

Conclusions

This study could help the nursing staff to better manage the children with cancer admitted to the day-hospital.

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Nursing

ENGAGE, EDUCATE, STUDY AND EVALUATE: SUCCESSFULLY REDUCING CENTRAL VENOUS CATHETER-ASSOCIATED BLOODSTREAM INFECTIONS IN PEDIATRIC CANCER

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Objectives

Central Venous Catheters (CVCs) are indispensable for chronic or acutely ill patients requiring long-term and/or complex therapies. CVCs carry a high level of mortality and morbidity directly related to the risk of infection. There have been substantial strides toward reducing CVC associated bloodstream infections (BSIs). These efforts have included implementation and adherence to CVC insertion and maintenance bundles along with ongoing education and monitoring. Treatment for most children and adolescents with cancer includes the use of a CVC. Despite the ubiquitous use of CVCs, few prospective studies have been conducted to address infection prevention strategies for pediatric oncology patients. The purpose of this presentation is to provide an overview of CVC types and selection, infection prevention strategies and interventions which include engagement and education of frontline staff from the Children's Hospital Los Angeles as well as other interventions for consideration.

Methods

Dedicated approaches to engage frontline staff utilizing multiple methodologies for education and accountability of CVC care; auditing and observations of care, root analyses for all CVC associated BSIs; implementation of reliability interventions and completion of a pilot study were accomplished.

Results

There remains sustained reduction in CVC associated BSI rates as a result of staff engagement, education, CVC care and BSI evaluation and implementation of reliability interventions. Furthermore, completion of a CVC infection prevention pilot study highlighted key risk factors for study to propose further valuable interventions.

Conclusions

Ongoing evaluation of education, monitoring and random observations of CVC care, critical analysis of each CVC associated BSI and interventions employed are necessary to sustain improvements. Additionally, rigorous study of key risk factors and critical mediators in pediatric oncology patients such as underlying malignancy, CVC type, patient acuity/clinical indicators are imperative for further strategic interventions such as a dedicated CVC team, chlorhexidine bathing regimens and oral care bundles.

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Nursing

EFFECT OF HEALTH EDUCATION: PARENTAL ASSESSMENT OF (KAP) KNOWLEDGE, ATTITUDE AND PRACTICE OF PEDIATRIC ONCOLOGY PATIENT

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Objectives

The aim of study was to find effect of health education on parent's attitude in care of pediatric oncology patient. Improved knowledge and quality care has effect on incidence of Febrile Neutropenia and hospital admission and long term event free survival.

Methods

Study samples consisted of 50 parents of pediatric oncology patient. The questionnaires were made in local language (Hindi) for the assessment of parental knowledge, attitude and practice about (4c's) clean food, clean water clean environment and clean hands.

Results

Diagnosis of cancer affected life of 90% of parents (N=50) questioned, 10% parents had no prior knowledge of the disease before coming here, 96% of patient reported improved is understanding of disease after health education, 95% of patient were aware of importance of clean food, clean water and clean environment, 64% of parents reported that care of siblings of oncology patient was affected after their child was diagnosed with cancer.

Conclusions

Health education is important part of holistic care of oncology patient. Most of our patients were of low socio economic status with very little knowledge of hygiene and personal care. Health education improves care and quality of life of oncology patient by decreasing rate of infection and need for hospitalization.

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Nursing

THE INFLUENCES OF SCHOOL REENTRY SUPPORT ON RELATIONSHIPS THAT ADOLESCENTS WITH CANCER SHARE WITH PEERS AND TEACHERS

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Objectives

Supportive relationships with peers and teachers, particularly the social support offered by these relationships, are especially important to adolescents with cancer. The purpose of this study was to clarify what forms of school reentry support for adolescents with cancer were related to the perceived social support. It was posited that adolescents with cancer would perceive supportive relationships with peers and teachers as high level of social support.

Methods

The questionnaire survey recruited 62 dyads of adolescents with cancer and their guardians. The questionnaire for adolescents had questions on perceived social support. The questionnaire for their guardians had questions on demographic information and school reentry support. Their guardians were interviewed to supplement the results of the questionnaire survey after completing their questionnaire.

Results

The questionnaire data from 37 dyads and the interview data from 3 guardians were analyzed. The questionnaire survey revealed that peers' visits, and their understanding of hospital experiences and how to interact with adolescents with cancer, were related to perceived social support from peers. Teachers' understanding about physical appearance, academic performance, and hospital experiences, as well as their status as a liaison between the hospital and school were related to perceived social support from peers and teachers. The interview survey found that adolescents with cancer could establish supportive relationships with peers and teachers when school reentry support led to 'adolescents' recognition that they are members of the local school,' 'peers' and teachers' understanding about the long-term recovery process of adolescents,' and 'adolescents' own awareness that they are struggling with the disease.'

Conclusions

Healthcare professionals should provide information to peers and teachers emphasizing adolescents' hospital experiences, and also encourage adolescents with cancer to regard their cancer experience as an opportunity to grow, which would help adolescents with cancer establish supportive relationships with peers and teachers.

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Nursing

CENTRALIZATION OF PAEDIATRIC ONCOLOGY NURSING EDUCATION IN THE NETHERLANDS: AN INCREASE OF THE SURVIVAL RATES?

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Objectives

In the Netherlands approximately 550 children are annually diagnosed with cancer. These children are diagnosed and treated in 5 paediatric oncology centres (POC's) and 2 centres for allogenic stem cell transplantation. Treatment also takes place in secondary paediatric unites (Shared Care). About 75% of all children with cancer can be cured since 1990.

The education and training of paediatric oncology nurses of the POC's and Shared Care is not according an existing and recognised competency framework. Training on the job is the method so far.

Since 2009 there are major developments in the care for children and young people with cancer. Centralization of care is leading in this, not 7 hospitals but one National Paediatric Oncology Centre, the Princess Máxima Centre.

Methods

This study has a qualitative descriptive design.

Results

The current education of paediatric oncology nurses consists of: 4 years for the Bachelor Nursing degree (BN), 1 year Specialisation on Paediatric Nursing and training on the job in paediatric oncology nursing.

To provide care at the highest level nurses should be highly qualified. Education and training is essential.

In addition to centralization of care is centralization of education and training required for paediatric oncology nurses in the Princess Máxima Centre and the Shared Care.

A start can be made with an outflow of students from the BN with a Paediatric Oncology Profile.

Intensive cooperation is necessary between the study BN, internship's paediatric nursing and paediatric oncology nursing.

Conclusions

Only with one Paediatric Oncology Centre, the Princess Máxima Centre, in which specialised nursing care and nursing education and training are brought together at the highest level, the ambition of an increase in survival rates of more than 90% can be realised. Together with the highest possible quality of life during and after treatment.

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Nursing

A STUDY OF THE JAPANESE LITERATURE ON GRIEF CARE IN RELATION TO PEDIATRIC NURSING

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Objectives

To review Japanese studies on grief care in relation to pediatric nursing from the past 10 years and to ascertain the future direction of that research.

Methods

The keywords childhood cancer, grief care, and hospice were used to search for articles from 2004 to 2014 in a database of Japanese medical literature. Articles mentioning grief care were categorized and analyzed.

Results

The recipients of grief support were most often family members. The personnel providing grief care were most often nurses, followed by medical personnel. Grief care involved the need for grief care, difficulties of grief care, training in grief care, forms of grief care, and the grieving process.

Conclusions

Many studies have examined care for the bereaved, most of whom were family members, but few studies have examined care for other individuals such as nurses and children with cancer. The survival rate of children with cancer will improve in the future. A major issue that needs addressing is the mounting evidence of the need for grief care for children, and particularly those in the same ward as children who have died.

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Nursing

PAIN EXPERIENCED BY CHILDREN WITH CANCER: NURSE EXPERIENCE IN A RESOURCE LIMITED SETTING

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Objectives

To highlight pain experienced by children with cancer.

Highlight Challenges encounter

Methods

An observation qualitative study was carried out. Through practice observing and children interaction

Results

Children with cancer felt pain during drawing of blood for investigations. Children also felt pain during fixing of branulars for administration of chemotherapy. When they have to receive injections for other treatments. During wound dressing. Pain from cancer itself especially during tumour progression.

Challenges

Lack of trained personnel to handle children with cancer**.**

Lack of training opportunities and facilities to care for paediatric cancer.

Lack of equipment and supplies like, POTTS, catheters for chemotherapy administrations

Conclusions

Managing paediatric oncology pain reduces cancer suffering and improves quality of life.

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Nursing

EXPANDING PAEDIATRIC ONCOLOGY CARE INTO THE HOME: BUILDING NURSING COMPETENCE AND CONFIDENCE TO FACILITATE THE ADMINISTRATION OF SUBCUTANEOUS CYTARABINE AT HOME

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Objectives

A review of services provided by the "Monash Children's at Home" community nursing program indicated that many patients would benefit by expanding the nursing scope of practice to include the administration of subcutaneous cytarabine during treatment for acute lymphoblastic leukaemia (ALL). The general paediatric nurses indicated they lacked the confidence and competence to deliver this chemotherapy in the home. This project aimed to expand paediatric home-based outreach services to include the delivery of low complexity chemotherapy for paediatric ALL patients.

Methods

Staff attended the current foundations day offered for oncology nurses, as well as a ‘fit for purpose’ training module developed specifically to support this scope of practice This included training in chemotherapy safe handling, clinical trials and cell biology, and focused on the agent to be delivered. Nursing procedures for home administration of cytarabine were developed. Nurses were rostered to the oncology outpatient department for competency assessment.

Results

Fourteen paediatric community nurses have completed the competency program, providing a sustainable level of care. Nineteen children have so far been able to have their cytarabine delivered in the home. This has resulted in 133 hospital bed days saved, reduced 85 day oncology admissions and negated 48 inpatient weekend ward admissions. Travel distance saved across all families is estimated at 1,752 km.

Conclusions

This project illustrates the potential wide ranging benefits of implementing small, localised service improvement projects to families, staff and health services. By increasing the scope of practice and confidence of staff, the project has improved the care pathway for children and their families, with less hospital visits and more time at home. For the health services, it has freed up bed days and allowed the service to expand its level of care in the community. A fit for purpose model of training also encourages participation from services outside the oncology department.

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Nursing

PHYSICAL ACTIVITY SURVEY IN ADOLESCENTS WITH CANCER

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Objectives

Decreased physical activity has been well documented in childhood cancer patients, yet little is known about the adolescent's desire to engage in physical activity during treatment or the perceived barriers to these activities. Surveys were administered to 1) identify the exercise activities adolescents performed before diagnosis and what activities they are interested in during treatment as well as 2) to identify barriers for exercise during cancer treatment.

Methods

Participants (n=43) were enrolled across six pediatric oncology centers in the United States and Canada. Participants were between 13-18 years, newly diagnosed with cancer, receiving chemotherapy with a planned treatment of at least 3 months, able to independently complete a written survey and able to provide assent/consent. Enrolled participants completed the Amherst Health and Activity survey describing their participation in physical activities before diagnosis and during month 2 of treatment, as well as physical activities that they would be interested in participating in during therapy.

Results

Adolescents' physical activity levels decreased during therapy, although interests remained high. Participation in calisthenics was 70% pre-diagnosis, 21% participation during therapy, with 51% expressing interest in this activity. Walking was reported as a 58% participation rate pre-diagnosis, 42% during therapy, with 51% expressing interest. Basketball was reported as the most commonly participated in team sport during therapy (16.3%). Interest was expressed for participation in basketball (42%), laser tag (37%), volleyball (32%), football (28%) and soccer (28%). Personal barriers to exercise were also reported.

Conclusions

Research has consistently shown that physical activity levels decrease during therapy. This study found that although activity levels declined, many adolescents still reported having an interest in being physically active during therapy. Awareness of the adolescents' interest in physical activity as well as the perceived barriers may assist healthcare professionals with engaging childhood cancer patients in maintaining more active lifestyles during therapy.

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Nursing

PERCEPTIONS OF CANCERFIGHTCLUB – AN INTERACTIVE INFORMATIONAL AND SOCIAL NETWORKING WEB-BASED PLATFORM FOR YOUNG ADULTS WITH CANCER

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Objectives

Young adults with cancer are increasingly turning to online resources to meet their cancer-related needs; however, research is needed to explore their perceptions of these online resources. As a cancer survivorship platform, CancerFightClub (CFC) was created with the goals of providing young adults with cancer online access to support and resources. The study objectives were to: (a) explore the extent to which CFC addresses their practical, psychosocial and informational needs; and (b) explore how CFC could be enhanced**.**

Methods

A qualitative descriptive study was conducted with a purposive sample of young adults treated for cancer at a university-affiliated tertiary hospital in Montreal, Quebec, Canada. A one-time, face-to-face, semi-structured interview was completed for all participants. Data were audio-recorded, transcribed and thematically analyzed.

Results

Twelve participants of mixed age (range 19-39 years), gender (9 female), and first cancers (brain tumor, lymphoma, testicular, and breast) entered into the study. Participants expressed great interest in CFC; describing CFC as “important” and “definitely needed”. They felt reassured in knowing they were not alone, as they were able to connect to a young adult cancer community — thus appeasing their feelings of isolation. CFC additionally provided a space where participants felt that they could find the information they needed without the information they wanted to avoid. Opportunities for enhancing CFC were recommended by facilitating direct peer connections, initiating diagnosis-specific discussions, providing support to family members, and raising awareness of CFC early-on.

Conclusions

CFC’s regional online support community might contribute towards reducing young adults’ feelings of isolation, and provide a resource that meets some of their needs. The positive reception to CFC helps to champion the continued development and use of such online support platforms for young adults. The cancer community should be made more aware of online-based support websites in order to refer their young adult patients to such helpful resources.

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Others

MAJOR ACHIEVEMENTS OF THE EUROPEAN NETWORK FOR CANCER RESEARCH IN CHILDREN AND ADOLESCENTS (ENCCA)

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Objectives

Building an effective European research arena by facilitating, fostering and coordinating regional, national and joint European pediatric and adolescent oncology programs and actions between European Member States to develop a virtual European Pediatric Oncology (PO) Institute

Methods

The European Network for Cancer Research in Children and Adolescents (ENCCA) project was funded by the European Union's FP7 program in 2011. ENCCA is driven by 34 leading organizations in 11 countries (18 structured work package activities) and interacts with the SIOPE community, aiming to resolving fragmentation in translational research and biobanking, enhancing drug development, improving the clinical trial framework and population-based cancer registries and addressing special needs of patient groups with reference to age and given cancer diagnosis, including ethical aspects in clinical research.

Results

Having established the European Clinical Research Council as integrated platform for leukemia and tumor group chairs and presidents of national PO groups together with the European Parents& Patients Advisory Committee, ENCCA helped SIOPE to become the unique voice of European stakeholders resulting in a major impact on the new European Clinical Trials Regulation. ENCCA has designed an “Advanced Biomedical Collaboration Domain 4 ENCCA” (ABCD-4-E) which is a cloud-based solution for the “European Virtual Institute”, and has created a roadmap towards the federation of pediatric cancer biobanking resources. Eight clinical trials are embedded in ENCCA, in addition to new methodological approaches and innovative trial designs. One of ENCCA’s highlights is the development of the survivorship passport prototype for survivors. ENCCA triggered the establishment of new links of the PO community including patients/parents organizations to Industry and European regulators (EMA).

Conclusions

Actions undertaken so far are the basis for a sustainable EU Virtual Institute devoted to improve outcome and the quality of treatment of pediatric cancer and the quality of life of survivors.

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Radiation Oncology (PROS)

IMPROVING THE DELIVERY AND SAFETY OF PROTON BEAM THERAPY

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Objectives

In proton beam therapy production of secondary neutrons and its contribution to the risk of second malignancy is debatable. We hypothesized we could improve proton safety by decreasing neutron production. We simple methods to minimize neutron production.

Methods

The narrow proton beam produced by the accelerator needs to be laterally spread out to provide coverage of the target and use passive, active and pencil beam methods to achieve this. The amount of neutrons depends on the amount of high Z material intercepted in the path of the beam. Using a 12 cm snout and a 10 cm circular aperture at a 16 cm range and 10 spread out Bragg peak (SOBP) with 100 MU. Neutron readings were taken using a WENDI-II (Wide Energy Neutron Detection Instrument) neutron detector at a distance of 28 cm from the snout tip and 41 cm perpendicular to the snout tip on both the left and right sides. Five readings were collected per side. Various wobble (field) sizes and snouts were employed to compare neutron dose as wobble shape and size was compared to aperture size.

Results

Passive scanning averaged 71.05 mR. Active scanning averaged 52.68 mR. When the wobble was adjusted to mimic the aperture via only allowing a 1cm overlap, the reading was 30.02 mR. Analysis of wobble shape showed decreasing neutron measurements as wobble sized decreased. When a real pediatric craniospinal field was treated via our 30 cm nozzle with an average wobble and an optimal wobble (30 x 16 versus 27 x 8 respectively) using a 7.5 cm deep 5 SOBP beam, the neutron reading fell from 47.0 mR to 28.87 mR.

Conclusions

Active scanning significantly decreased secondary neutron production relative to passive scanning. Wobble size directly impacted neutron production. It is possible to minimize neutrons via achievable methods using existing hardware.

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Radiation Oncology (PROS)

IMPACT OF IMAGE-GUIDED RADIATION THERAPY (IGRT) ON PEDIATRIC RADIATION ACTIVITY

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Objectives

To determine the impact of Image-Guided Radition Therapy (IGRT) on time and factors associated with magnitude of set-up displacement in pediatric population

Methods

The clinical data of 42 children treated between 2010 and 2013 in our institution were analyzed : 21 with IGRT (2DkV or CBCT) and 21 patients without IGRT (2DMV control). Time of session was calculated for the 2 groups. The setup errors were assessed by displacements in the superior-inferior (SI), anterior-posterior (AP), and medial-lateral (ML) directions and divided in minor (3 to 5 mm) and major (> 5 mm).

Results

1069 sessions were delivered and 475 imaging were performed. In IGRT group, 321/ 583 (55%) sessions were realized with CBCT (72.6 %) and 2DkV (27.4%) before irradiation versus 154 / 486 (27%) sessions with 2DMV. The mean time per session was 15 minutes for 2DMV group and 25 minutes for IGRT group. For children between 3 and 10, mean time of session with IGRT increased of 149% compared with session with 2D MV. In contrast, mean time of irradiation was similar whatever the irradiation modality. Minor displacements were found for 12.9% and 8.7% while major displacements for 4.1% and 0,3% respectively for group with CBCT and with 2DKV. Major displacement was found in 0.6% of cases if control was realized twice a week versus 4.6% for daily control. Major displacement concerned mainly the AP direction 8.1% vs 3.4% for SI and 0.85% for ML direction and children between 3 and 10 years old.

Conclusions

In pediatric population, IGRT control induced an increase of 40% for time of treatment. These results showed that using daily CBCT improved detection sensitivity and correction of residual errors exceeding 5 mm especially for children between 3 and 10 years old.

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Radiation Oncology (PROS)

THE EMOTIONAL AND PSYCHOLOGICAL IMPACT ON RADIATION THERAPISTS OF TREATING CHILDREN IN A LARGE REGIONAL CANCER CENTRE, CANADA

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Objectives

The aim of this study was to determine the psychological effects and difficulties that radiation therapists (RTs) experience while treating children. This study was intended to provide some information in order to assist RTs in their occupation, and complement the sparse literature on this topic

Methods

A survey was conducted in order to capture data on the emotional effects and opinions of RTs in one Cancer Centre. The questionnaire was inspired from the limited literature around this issue. The study converged on the reactions of RTs while children received radiation treatment and the impact on the RTs emotional state around this component of their practice. The questionnaire was distributed electronically via email. The answers were provided on a Likert scale for most questions.

Results

62 of the 104 RTs completed the survey of 20 questions. The questionnaire showed that gender and age played no major role in the RTs ability to cope mentally. Half of the RTs had children themselves; and of these, 66% indicated that having children made it somehow more difficult to cope emotionally with paediatric patients. Seventy-five-percent of all RTs indicated that the emotional state of parents or care givers of the affected children played a key role in the anxiety they felt during a child's treatment. Eighty-one percent of RTs stated that treating children caused higher anxiety levels than treating adults. Finally, our survey suggests that time constraints played a large part in the RTs stress level during treatments.

Conclusions

Overall, treating children did not cause much more distress than treating adults. Also, as a result of the survey, a new tool for RTs, describing the cognitive stages in children, was created in order to help RTs treat paediatric patients.

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Radiation Oncology (PROS)

PROTON RADIATION FOR TREATMENT OF CHILDREN LESS THAN 18 MONTHS OF AGE

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Objectives

Radiation therapy (RT) may be delayed, omitted, or reduced in dose for very young children in efforts to reduce toxicity. Proton therapy allows sparing of normal tissues, and may improve outcomes by allowing multidisciplinary treatment delivery to be delivered with maximal safety.

Methods

10 patients requiring RT at age less than 18m were enrolled on a prospective registry. Radiation was delivered after induction chemotherapy and/or surgical resection where indicated based on diagnosis, but radiation was not delayed due to age. Radiation was planned after CT simulation and fusion of pre and post-operative imaging. The tumor bed, clinical target volume, and organs at risk were contoured with Eclipse planning software. Doses are reported in radiobiologic-equivalent-weighted absorbed dose (cGyRBE).

Results

The patient population at the time of RT ranged from 9-17m (median 13.5m), and 6 (60%) were female. Six patients had CNS tumors (medulloblastoma (1), ATRT (2), ependymoma (2), PNET (1)), with other diagnoses including neuroblastoma (2), undifferentiated sarcoma (1), and non-CNS rhabdoid tumor (1). Radiation treatment site included infratentorial brain (6), abdomen (2), and head/neck (2). Radiotherapy was delivered using passive scattered proton beams for 8 patients, and pencil beam scanning for 2. Dose ranged from 2160-5400. All patients received daily general anesthesia. No patient experienced greater than grade 1 (CTCAEv4) acute radiation-related toxicity. With a maximum follow-up of 22 months (range 1.4-22), all patients are alive, one with disease recurrence outside the radiation field. No patient has experienced serious (grade 3-4) long-term toxicity related to radiation.

Conclusions

Although radiotherapy for very young children must be undertaken with caution, proton therapy has potential to reduce normal tissue dose and maximize safety. Based on this series, proton radiation appears safe in the acute setting, even for extremely young children, and may improve outcomes compared to paradigms that eliminate RT. Long-term monitoring for late effects is paramount in this population.

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Radiation Oncology (PROS)

FEASIBILITY OF BREAST SPARING DURING WHOLE LUNG IMRT IN CHILDREN WITH WILMS TUMOR LUNG METASTASIS: A DOSIMETRY STUDY

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Objectives

We have demonstrated the feasibility and dosimetric advantages of whole lung IMRT in children. Several reports implicated whole lung irradiation (WLI) to be an important cause for the higher rate of secondary breast cancer in Wilms tumor (WT) survivors. We conducted a dosimetry study to estimate breast doses in girls receiving WLI.

Methods

WLI plans using standard AP-PA (S-RT), IMRT and breast sparing IMRT (BS-IMRT) treatment plans were performed (ADAC system) using 6MV x-rays in 10 girls (median age 4yrs). The doses to the breasts, breasts+5mm expansion, lung PTV, whole heart (WH), right ventricle (RV), left ventricle (LV) were compared. The PTV for IMRT included entire lung volume +1cm margin, mediastinum and vertebrae. Heterogeneity corrections were applied. The RT dose was 12Gy/8fr. The organ-volumes (V) receiving specific RT doses (Gy): V_{12}, V_{10}, V_8 were estimated and compared.

Results

The mean breast dose with S-RT and IMRT was 9.2Gy (8.9-9.6Gy) and 10.6Gy (10.1-11.0Gy) respectively. The mean dose to the breasts+5mm expansion with S-RT and IMRT was 10.4Gy (10.2-10.7G) and 11Gy (10.8-11.2Gy) respectively. Following BS-IMRT the mean breast dose was 3.2Gy (2.8-3.4Gy) ($P<0.0001$) and mean breast+5mm expansion dose was 4.9Gy (4- 5.5Gy) ($P<0.0001$). The mean dose coverage to 95% of lung PTV was 95% of prescription dose with BS-IMRT and 98% with IMRT. The $V_{11.4}$, V_{10} and V_8 respectively for WH, LV and RV for S-RT was 96-100% and for IMRT and BS-IMRT was: WH 45% (<0.0001), 66% (<0.0001), 82% (<0.0001); LV 40% (<0.0001), 65%(0.0004), 84%(<0.0001); RV 21%(<0.0001), 54%(<0.0001), 77%(<0.0001).

Conclusions

This dosimetry study demonstrates that BS-IMRT can result in significant sparing of breast tissues in girls with WT without compromising on improved lung volume coverage and cardiac protection compared to S-RT. BS-IMRT may be considered for young girls with limited volume lung metastases.

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Radiation Oncology (PROS)

RADIOTHERAPY OF CHILDHOOD RHABDOMYOSARCOMA: EXPERIENCE OF EGE UNIVERSITY HOSPITAL

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Objectives

Radiotherapy (RT) is frequently used in the treatment of RMS to contribute local-regional control. The planning and delivery of RT needs to be carefully organized in order to obtain maximum control with minimum late effects , regarding the small ages of the patients, tumor sites surrounded with critical organs, the need of high radiation doses to eradicate RMS. In this presentation we evaluated the results of RT in 38 children with RMS.

Methods

From January 2000 to October 2012, RT was used in 38 cases with RMS. Median age was 8 years (2-18) and M/F ratio was 2.4/1. Histological subtypes were embryonal in 17, alveolar in 16, botryoid in 1, mixt type in 4. Localization of tumors were pelvic in 16 cases (3 paratesticular, 7 vagina-bladder), head and neck in 10 (7 paramenengial), trunk in 7, extremities in 5 cases. From 2000 to 2006 patients were treated with SIOP/MMT-89 protocol (11 cases) and IRS III-IV was used after 2006 (27 cases). RT doses were 41-45 Gy for subclinical disease, 45-59 Gy for macroscopic tumors. External RT was used in 33 cases whereas brachytherapy alone was used in 3 cases and a combined external RT and brachytherapy was used in 2 cases.

Results

Median follow-up time was 30 months (5-100 months). Local-regional relapses were occurred in 11 while distant metastases were occurred in 10 patients. Unfortunately 14 patients were succumbed to progressive disease. Disease free survival rate at 3 years was 61% and overall survival rate 64%. Grade III/IV late effects of RT were detected in 8 patients (growth delay of bone and soft tissue in 6, renal atrophy in one and azospermia in one patient).

Conclusions

RT is effective treatment modality in the local–regional control of childhood RMS. Careful planning of RT is extremely important for maximum benefit. Long-term late effects need to be monitored in the pediatric age group.

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Radiation Oncology (PROS)

FIFTEEN-YEAR EXPERIENCE IN CRANIOSPINAL IRRADIATION FOR THE MANAGEMENT OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS

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Objectives

Medulloblastoma (MB) is the most common malignant brain tumor of childhood. Craniospinal irradiation (CSI) is central to the management of these tumors. The purpose of this study is to assess the prognostic factors for survival in MB patients treated with postoperative CSI.

Methods

The study was conducted for patients with primary MB treated with CSI from August 1996 through May 2012 at 2 Institutions.Inclusion criteria included a minimum follow up of 6 months. Forty-eight patients (standard risk, N=31; high risk, N=17) met such criteria. Median CSI doses were 23.4Gy (13 fractions) and 36 Gy (20 fractions) for standard and high risk patients, respectively. The tumor bed received 50-60 Gy. Radiation therapy (RT) techniques used were two dimensional RT (N=11), three dimensional RT (N=15), volumetric modulated arc therapy (VMAT; N=3), and tomotherapy (N=19).Starting at the beginning of CSI, the intent was for standard-risk patients to receive eight weekly doses of vincristine. High risk patients underwent chemotherapy before RT. Adjuvant chemotherapy began approximately 6 weeks after patients completed RT.

Results

The median age at diagnosis was 8 years (range, 2-43) and the median follow-up 39 months (range, 7-198). Overall, 16 patients died.Two and three-year overall survival was 84% and 77%, respectively. There were 19 relapses. Two and three-year disease-free survival was 69% and 63%, respectively. The most common acute toxicity was hematological (87 %), being grade ≥3 in 19 (39 %) cases.In the univariate analysis, older patients (>8 years old) associated with higher risk of mortality (HR: 6.09; *P*=0.003) and high risk patients associated with higher risk of relapse (HR: 2.67; *P*=0.047).

Conclusions

Older patients associated with higher risk of mortality and high risk patients associated with higher risk of relapse.Further research is necessary to assess a better treatment approach in these patients in order to improve the outcome.

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Radiation Oncology (PROS)

PREPARATION AND BEHAVIORAL TRAINING FOR PEDIATRIC PATIENTS TREATED BY PROTON BEAM THERAPY

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Objectives

Sedative care including anesthesia is often administrated for younger children during proton beam therapy (PBT). However, daily sedation contains something problem: manpower of specialist is required, anesthetic risk cannot be fully eliminated, and treatment time becomes prolonged. Besides, radiotherapy including PBT is associated with no pain, and daily treatment is doing same thing again for patients. Therefore, we consider PBT without anesthesia is possible even for pediatric patients who can communicate in some measure and have tried to administrate treatment training (preparation) for PBT not to use anesthesia.

Methods

From April 2010 to December 2012, 40 pediatric patients were treated by PBT in our institute. 24 of the 40 patients aged 2y 11m to 7y 4m were applied preparation and training for PBT as follows:At first, a patient look over the treatment room, and treatment fixator was made. Whole body fixation is made for pediatric patients, and treatment mask was prepared if necessary. During treatment planning and dosimetric measurement, patients come to treatment room every day, and simulated treatment with the fixator.The preparation was continued after the start of PBT.

Results

Fifteen of 24 patients could successfully receive PBT without sedation. The median age of 15 patients were 5y 8m (range: 3y 9m to 5y 8m). Sedative drugs were administrated to 9 patients at first, but became non-necessary for 5 of the 9 patients with daily training during PBT. The age of the 5 patients were ranged from 3y 9m to 5y 5m.

Conclusions

Preparation seems useful to perform PBT without sedation even for younger pediatric patients. Generally, PBT requires longer treatment time than photon radiotherapy. The preparation may be able to apply photon radiotherapy.

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Radiation Oncology (PROS)

REVIEW ON 63 CHILDHOOD CANCER PATIENTS TREATED WITH ACCELERATED RADIATION THERAPY AT BACH MAI HOSPITAL, VIETNAM FROM JULY 2009 TO JULY 2013

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Objectives

To review clinical and epidemiological characteristics of childhood cancers treated by accelerated radiation therapy at The Nuclear Medicine and Oncology Center, Bach Mai Hospital, Vietnam from July 2009 to July 2013.

Methods

Materials: 63 childhood cancer cases were underwent radiation therapy at The Nuclear Medicine and Oncology Center, Bach Mai Hospital, Vietnam from July 2009 to July 2013.

Methods: retrospective study

Results

Average age was 7,51 years old; youngest: 2, oldest: 15. The ratio male/female is 2,5/1. brain tumors (63,5%), wilms tumor (12,7%); bone tumor and soft tissue sarcoma (11,1%); leucemie with CNS infiltration (7,9%). Other kinds of tumors were less common. Clinical symptoms varied depending on cancer types: Intracranial tumors: 92,5% patients had headache and 85% had nausea or vomiting; other symptoms were hemiplegia (40%), cerebellar syndrome (25%). Wilms tumor: lumbar pain (75%), hematuria (50%), abdominal palpapble tumor (37,5%). Sarcoma: ischemia syndrome (85%), bone pain and limited movement (42,9%); infection syndrome (28%). Radiation doses changed depending on the natural of disease, stages and risk factors. Radiation side effects were reported mainly in the course of treatment such as headache (50.8%); nausea and vomiting (36.5%); fatigue (42.9%); anorexia (46%); hair loss (31%).

Conclusions

Accelerated radiotherapy in the combination of surgery and chemotherapy is an effective and safe method for the treatment of childhood cancers in pediatric patients (under 15 years old).

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Radiation Oncology (PROS)

SHOULD PERCENTAGE NECROSIS INFLUENCE THE DECISION FOR ADJUVANT RADIOTHERAPY AFTER SURGICAL EXCISION IN EWING SARCOMA?

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Objectives

To determine the indications of adjuvant radiotherapy after surgical excision in Ewing sarcoma.

Methods

94 consecutive patients of non metastatic Ewing sarcoma were analysed. Patients underwent appropriate surgical resection after receiving neoadjuvant chemotherapy. Excised specimen was analysed for chemotherapy induced percentage necrosis and divided as < / > 90 % necrosis. Post operative adjuvant radiotherapy was decided on a case to case basis irrespective of percentage necrosis.

Results

One patient had involved margins. Necrosis was available in 80 patients. 25 had < 90 % and 55 had > 90 % necrosis. 23 of these patients received radiotherapy (9 < 90 %, 14 > 90%). All patients were available for follow up. The OS of all patients was 68 % at 5 years. Currently 62 patients are alive (follow up range 33 to 90 months, median 61 months). There was no difference in OS in patients who received radiotherapy (57%) and those who did not (75%) p = 0. 133. In the cases with < 90 % necrosis the OS in patients who received radiotherapy was 56 % as against 49 % in those who did not p = 0. 760. In the cases with > 90 % necrosis, the OS in patients who received radiotherapy was 57 % as against 85% in those who did not p = 0. 043.

Conclusions

Our data suggests that the decision to offer adjuvant radiotherapy after surgical excision in Ewing sarcoma is multifactorial and independent of percentage necrosis after chemotherapy.

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Radiation Oncology (PROS)

BEVACIZUMAB AS A TREATMENT FOR RADIATION-INDUCED NECROSIS (RIN): A PEDIATRIC CASE REPORT

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Background:

RIN is a serious complication of radiation treatment for brain tumors. This damage results from local cytokine release, increase in capillary permeability and extracellular edema, and loss of the myelin covering of neurons. If allowed to progress, radiation necrosis can lead to small vessel occlusive disease and bleeding from friable small vessels. These changes combine to cause a definable worsening in patients' neurological signs and symptoms. Steroids are the standard of care treatment for brain RIN despite limited efficacy. Bevacizumab has been used in adults as a strategy to treat cerebral RIN

Purpose:

Describing the use of Bevacizumab in a child with this complication.

Material and Methods:

10- year- old boy, who presented with a 4-week history of a progressively increasing headache, vomiting and left faciobrachiocrural paralysis. Magnetic resonance imaging (MRI) showed a supratentorial right temporoparietal lesion. Following complete resection of the tumor, histopathological examination revealed anaplastic ependymoma. He received conventional radiotherapy (5940 cGy in 180 cGy fractions). After 12 months of radiation therapy, the patient reported severe neurocognitive impairment problems and urinary incontinence. The MRI revealed images suspected of RIN and confirmed by a stereotactic biopsy .After non effective steroid treatment, bevacizumab was administered for 2 cycles (7.5 mg/kg, at three-week interval)

Results:

The child showed clinical neurological improvement and MRI revealed an important reduction in post-gadolinium and T2-weighted sequence analysis

Conclusions:

Bevacizumab efficacy in the treatment of CNS RIN in adults justifies consideration of this treatment option for children who suffer RIN secondary to the treatment of brain tumors .

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Radiation Oncology (PROS)

DAILY CBCT-IMAGING OF PEDIATRIC RADIOTHERAPY PATIENTS CAN REDUCE THE RISK OF SECONDARY CANCER

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Objectives

Image-guided radiotherapy (IGRT) allows for accurate setup of patients for treatment, and in some cases daily IGRT makes reduction of PTV-margins possible. However, daily x-ray images also add to the integral dose delivered to the patient, and in pediatric cases many centers will limit IGRT due to the risk of secondary cancer. In this study we demonstrate that daily CBCT-imaging in combination with margin-reduction can reduce the total dose to the patient.

Methods

Thorough analysis of all uncertainties in our local radiotherapy process have shown that a PTV-margin as low as 2 mm can be used for small cerebral targets, when daily CBCT-imaging is applied. A 4-year old male ependymoma patient was planned and treated to 54 Gy over 30 fractions with a 3 mm PTV-margin. A second plan was prepared using a standard 5 mm PTV-margin. Care was taken to obtain similar target coverage and conformity index. The increase in integral dose from 3 to 5 mm margins was determined and compared to doses from CBCT-scans.

Results

Using tabulated data from vendor and published effective dose factors for children, we find that one CBCT-scan delivers an effective dose of 0.25 mSv. For 30 CBCT-scans this equals 7.5 mSv of added dose. Comparing the two dose plans, the plan with the 5 mm-margin gives an extra effective dose of about 31 mSv compared to the 3 mm-plan. The margin reduction thus reduces the effective dose 4 times more than the entire IGRT-procedure adds.

Conclusions

This case demonstrates that treating with standard radiotherapy margins without daily IGRT can result in a higher total effective dose, and thus risk of secondary cancer, than if reduced margins are used in combination with daily IGRT.

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Radiation Oncology (PROS)

SHOULD FRACTIONATED FULL DOSE RADIOTHERAPY REMAIN THE STANDARD FOR TREATMENT OF METASTATIC SITES IN RHABDOMYOSARCOMA?

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Objectives

The current standard of care for patients with metastatic rhabdomyosarcoma includes full dose radiotherapy to each metastatic site. We wished to question this practice, which can cause side-effects and is often logistically challenging, by studying the pattern of failure in our pediatric and teenage patient population.

Methods

The McGill University Health Centre cancer registry was queried for patients diagnosed with rhabdomyosaroma aged 19 or less from January 1990 until January 2014. Twenty-nine patients were found and, of these, six had metastatic disease. Five of the six were treated with standard chemotherapy together with radiotherapy to the primary and metastatic sites with doses and fractionation according to site (36-50.4 Gy in 1.8 Gy fractions; 15 Gy in 1.5 Gy fractions for whole lung radiotherapy). Time to progression was calculated from the end of radiotherapy until radiological or pathological evidence of disease progression.

Results

Median age for the five patients was 13 years (range 12-18). Three were girls (60%). All had alveolar histology and unfavorable primary sites (100%). Median number of metastatic sites treated was 2 (range 1-5). Three patients developed progressive disease outside the treated field (60%). One patient died from treatment-related complications without evidence of disease progression. Median time to progression was 14.3 months (range 1.9-88.6). One of the five patients remains progression-free at 88.6 months post radiotherapy.

Conclusions

Radiotherapy to metastatic disease sites prevented in-field progression in in all five patients with metastatic alveolar rhabdomyosarcoma. However, failure at sites outside of the radiotherapy volume occurred in 60% of patients and overall survival was very poor despite aggressive treatment to all sites of disease. Radiotherapy clearly has an important role in the management of patients with metastatic disease. Future studies should address radiotherapy dose and fractionation in the context of a need for better systemic control in this patient population.

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Radiation Oncology (PROS)

REDUCING DOSE TO THE PANCREAS IN PEDIATRIC ABDOMINAL IRRADIATION WITH HELICAL TOMOTHERAPY

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Objectives

In children, irradiation of the pancreas and its tail was shown to increase the likelihood of secondary diabetes mellitus. We compare conformational radiotherapy (CRT) and helical tomotherapy (HT) for sparing the pancreas in children with abdominal irradiation.

Methods

We selected children with abdominal tumors treated in our institution who received ≥10Gy to the abdomen. Treatment plans were calculated using CRT (XiO, Elekta) or HT (TomoTherapy Treatment Planning System) in order to reduce the dose to the pancreas as low as possible while maintaining the same PTV coverage and the same dose-constraints to the other Organs At Risk (OAR). Dosimetric values were compared using Wilcoxon signed-rank test. The results were considered significant at the 0.05 level.

Results

The dose distribution of 20 clinical cases with a median age of 8 years (range 1-14) were calculated with different doses to the PTV: 5 medulloblastomas (36Gy), 3 left-sided and 2 right-sided nephroblastomas (14.4Gy to the tumor + 10.8Gy boost to para-aortic lymphnodes), 1 left-sided and 4 right-sided or midline neuroblastomas (21Gy) and 5 Hodgkin lymphomas (19.8Gy to the para-aortic lymphnodes and spleen). Using CRT or HT, similar target coverage was obtained. The doses to the other OAR were similar or better with HT. HT significantly reduced the mean dose to the Whole Pancreas (WP) and Pancreatic Tail (PT) in general (WP: 19.67Gy [SD 4.03] with CRT vs 12.56Gy [SD 5.05], p=0.0001). The mean dose to PT was reduced in 17/20 patients with >10 % difference and ranges -20% to -40% according to tumor location, reaching significance in midline and right-sided tumors, not in left (on 4 cases).

Conclusions

Using helical tomotherapy, it is possible to reduce the dose to the pancreas and its tail while maintaining a good PTV coverage and OAR sparing in children with abdominal irradiation.

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Radiation Oncology (PROS)

A COMPARATIVE STUDY ON DOSE DISTRIBUTION OF PROTON BEAM THERAPY, AND CONFORMAL RADIOTHERAPY, AND INTENSITY-MODULATED RADIOTHERAPY FOR PEDIATRIC BRAIN TUMOR.

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Objectives

The purpose of this study is to evaluate the effectiveness of proton beam therapy (PBT) for pediatric brain tumor compared to conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT).

Methods

From 2009 to 2012, 13 pediatric patients with brain tumor, who were treated by PBT in our institute, were evaluated. Seven patients of the 13 had ependymoma and 6 had germinoma. Localized irradiation and whole ventricle irradiation was performed for ependymoma and germinoma, respectively. The IMRT and 3D-CRT treatment plans were generated and optimized using the same practical treatment planning CT of PBT to compare dose distribution of PBT. The planning target volume (PTV) was identical among PBT, IMRT and 3D-CRT for each patient which was covered by 95 % iso-dose line at all plans. The dose-volume histogram (DVH) for normal brain were calculated and compared

Results

At localized irradiation case, PBT could reduce 14 to 63% (median 38%) of normal brain dose compared to 3D-CRT, and 6 to 62 % (median 38%) compared to IMRT. And whole ventricle radiation case, PBT could reduce 17 to 24% (median 22%) of normal brain dose compared to 3D-CRT, and 9 to 25 % (median 21%) compared to IMRT.

Conclusions

PBT could reduce the dose of normal brain compared to 3D-CRT and IMRT.

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Radiation Oncology (PROS)

PROTON BEAM IRRADIATION IN CHILDHOOD: FIRST EXPERIENCE AT THE WEST GERMAN PROTON THERAPY CENTRE ESSEN (WPE)

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Objectives

Proton beam therapy (PT) is of increasing interest in pediatric oncology. The West German Proton Therapy Centre Essen (WPE) started treatments in May 2013. In September 2013, a registry was started to collect prospective data on children (<18 years) during and after PT.

Methods

Between June 2013 and March 2014, data on 26 children (sixteen males, 10 females, aged from 1.5-14.2 years (median 6 years)) were collected. Diagnoses were CNS (n=20) and sarcomatous tumors (n=6), respectively. Tumor sites were brain/head and neck (n=22), spine (n=2) and pelvis (n=2). In 16 children, parallel chemotherapy was applied. Karnofsky performance status (KI) was below 80% in 13 patients at first presentation. Total PT doses ranged from 45 to 70 Gy (median 45 Gy). Side-effects were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system.

Results

Median follow-up (FU) was 4.3 months (range 1.8-8.4 months). In the majority of children, only grade 1 side-effects were observed as Erythema, Fatigue, Pain, Nausea, Fever and headache. In 2 patients, grade 2 pain and fever was observed. 1 patient presented with grade 3 oral Mucositis. At the end of PT, KI was scored 90-100% in 13, and below 80% in 13 children. Late side-effects were evaluable in 11 patients (FU> 90 days). One of them presented with a grade 3 keratitis. Otherwise, no or only mild late side-effects were documented: Fatigue, focal alopecia or skin reaction. At last FU, 7 patients presented with KI of 90-100% and 4 patients below 80%.

Conclusions

Current prospective and standardized data from WPE registry suggest excellent feasibility with only moderate early side-effects during and after intensive local PT in the majority of children. However, longer FU time and larger patient cohorts are needed to define the potential role of PT in pediatric oncology.

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Radiation Oncology (PROS)

EARLY EXPERIENCES OF THE ADVISORY CENTRE FOR PARTICLE THERAPY IN PEDIATRIC ONCOLOGY IN GERMANY

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Objectives

Particle therapy (PT) is of increasing interest when modeling individualized oncological treatment concepts in childhood. The number of particle facilities is continuously increasing worldwide. Still, technical equipment and clinical indications treated with PT are diverging widely, and experts in this field are rare. Therefore, advising on PT is of increasing demand.

Methods

The advisory centre for PT in pediatric oncology offers support to referring centres, treating facilities and affected families. Support is provided in close collaboration with the respective radiation reference centre of the multidisciplinary trials of the German Society for pediatric oncology and hematology (GPOH) to ensure adequate treatment modality according to study protocols. Advising is given to define appropriate indications, to implement PT in new protocols or to push financial coverage by insurances. Until now, PT is considered in 9 interdisciplinary treatment protocols.

Results

Between January 1st, 2012 and December 31, 2013, 465 children and adolescents (<21 years, 57.8% males, 42.1% females) were presented to the advisory board. Age ranged from 0.1 to 19.9 years. Diagnoses were brain tumors (62.4%), sarcomas (22.8%) and miscellaneous (14.8%). In 44% advice was requested by radiation reference centres, in 39% by hospitals, in 13% by patients or family members, in 3% by PT centres and in 1% by other institutes. In the majority of inquiries, PT was recommended as first choice (59%). However, due to limited availability of PT-slots, external photon radiotherapy was proposed alternatively or exclusively in 50%. In 19% other treatment options were proposed.

Conclusions

The number of inquiries shows high demand in advisory services concerning PT. Efforts were made to establish PT in the multidisciplinary protocols to ensure evaluation and homogeneous approaches for PT. In future, advising activities will continue and data evaluation of the study groups accompanied by PT experts from the reference centre.

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Radiation Oncology (PROS)

CLINICAL RESULTS OF PROTON THERAPY IN PEDIATRIC ONCOLOGY: SYSTEMATIC REVIEW OF LITERATURE

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Objectives

To systematically review the clinical results of proton therapy (PT) in pediatric oncology reported in the literature.

Methods

Two radiation oncologists searched independently in the Pubmed database the articles regarding PT in pediatric oncology, published between 01/01/1990 and 28/02/2014. The key words used, combined with Boolean operators AND/OR, were: “proton therapy”, “pediatric cancer”, “ependymoma”, “medulloblastoma”, “PNET”, “craniopharingioma”, “glioma”, “rhabdomyosarcoma”, “pediatric sarcoma”, “Ewing sarcoma”, “germ cells tumors”, “osteosarcoma”, “AT/RT”, “retinoblastoma”, “neuroblastoma”, “Hodgkin lymphoma”. Only articles reporting local control (LC), overall survival (OS) and late toxicity in series with ≥10 patients were selected. Reviews, editorials, congress abstracts and papers not in English language were excluded. The process was critically reviewed by other two researchers.

Results

Fourteen out of 104 selected articles were consistent with selection criteria. The median follow-up was limited (19-72 months). Four articles concerned chordoma (5-years(y)-LC=60%-81%; 5y-OS=60%-89%) and chondrosarcoma (5y-LC=80%-100%; 5y-OS=75%-100%), two soft tissues sarcomas (LC=59%-75%; OS=64-69%), one Ewing sarcoma (3y-LC=86%; 3y-OS=88%), one medulloblastoma/PNET (3y-LC=92%, 3y-OS=86%), one ependymoma (3y-LC=83%; 3y-OS=95%), one craniopharingioma (LC=93%; OS=80%), one low-grade glioma (LC=78%; OS=85%), one AT/RT (LC=100%; OS=90%), one germ cells tumors (LC=100%; OS=100%) and one neuroblastoma (3y-LC=82%; 3y-OS=75%).

Late toxicity was usually of low-to-moderate grade. For intracranial or skull base malignancies the most reported toxicities were neuro-endocrinopathies (3%-50%), ototoxicity (3%-13%) and bone asymmetry (0-41%). Major events as brain necrosis or cerebrovascular problems were rare (≤7%). The cognitive function remained stable in comparison to the baseline. For peripheral tumors, dermatitis and vertebral asymmetry were the most frequent side effects observed.

Conclusions

The evidence of PT efficacy in pediatric oncology is limited. The clinical results reported confirm that PT can achieve similar LC rates as historic photon cohorts, while late toxicity appears to be reduced. These evidences are consistent with the results of dosimetric studies suggesting the potential clinical advantage of this technique.

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Rare Tumours

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN: A TERTIARY CARE CENTER EXPERIENCE FROM INDIA

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Objectives

Hemophagocytic Lymphohistiocytosis (HLH), although rare, is being increasingly diagnosed nowadays. We discuss the clinical profile and treatment of patients diagnosed with HLH at our center over 2 years.

Methods

We retrospectively analyzed the patients diagnosed with HLH based on HLH 2004 criteria between January 2010 - December 2013. Search for secondary causes was performed in all patients. Patients who were <5years or with significant family history were evaluated for familial HLH.

Results

Out of total 31 cases diagnosed, Male: Female ratio was 3:1. Median age was 5 years. 5 children had parental consanguinity and 4 had previous sibling death. Presenting features included fever and hepatosplenomegaly(31), bleeding manifestations(6), lymphadenopathy(6), skin rash(4), shock(5), jaundice(11), CNS manifestations(8), renal failure(5), liver failure(1) and arthritis(1). All had pancytopenia. Other laboratory parameters include hemophagocytosis in bone marrow(23), hyperferritinemia(27), hypertriglyceridemia(26) and hypofibrinogenemia(26).

Secondary cause was identified in 12 patients. Infectious causes include EBV(2), typhoid(2), malaria(1), tuberculosis(1), juvenile rheumatoid arthritis(1), Pseudomonas(1), fungal(1) and CMV(1). Malignant causes include Hodgkin lymphoma(1) and anaplastic large cell lymphoma(1). Mutation analysis was positive in 6 out of 13 children evaluated. 2 children had FLH-3(MUNK13-4), 1 each had FLH-4(STX11), FLH-2(Perforin) and Griscelli syndrome. A 8 weeks old child was heterozygous for MUNK 13-4; however sequencing for other mutations could not be done.

Treatment given was according to HLH 2004 protocol. All received steroids, while only 17 received cyclosporine. 3 underwent stem cell transplant (2 Umbilical cord blood, 1 matched sibling bone marrow). 1 survived while 2 patients succumbed to secondary complications. Overall 17 patients expired (54%), 8 survived, 3 were lost to follow up and the rest are undergoing treatment.

Conclusions

Diagnosis of HLH should be considered in patients presenting with fever, hepatosplenomegaly and pancytopenia. Despite early and aggressive treatment we have encountered mortality in more than 50% of our patients.

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Rare Tumours

LANGERHANS CELL HISTIOCYTOSIS: A SINGLE CENTER EXPERIENCE

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Objectives

To evaluate patients with Langerhans cell histiocytosis (LCH) who were diagnosed and treated at our center.

Methods

The medical records of patients with LCH were rewieved. The clinical characteristics, treatment details and responses were analyzed retrospectively.

Results

There were 30 patients with LCH. The median age at diagnosis was 5.8yrs (3.4 month-15.8yrs), M/F ratio was 1.0. Complaints were: mass (47%), back/limb pain (47%), rash (20%), ataxic walking (13%), polyuria-polydipsia (3%), lymphadenopathy (3%). *Single system involved LCH (SSIG-LCH) (77%, n:23);* involvement sites were bone (87%), skin (4%), lymph node (4%), lung (4%). Surgery was performed in 52%, chemotherapy consisted vinblastin, prednisolone ± methotrexate, mercaptopurine was given in 48%, radiotherapy (RT) was given in 17% of cases. Out of primary relapse (n:1) occured, and treated by RT. Primary relapse (n:1) occured, and CR was achieved by cisplatin, interferon, vinblastin. The median follow-up time was 7.8yrs (1 week -18yrs), 15-years OS rate was 100% and 1-year and 15-years EFS rates were 95% and 88% respectively .*Multisystem involved LCH (MSIG-LCH) (23%, n:7);* involvement sites were bone (86%), skin (86%), lung (57%), pituitary gland (14%). In four patients had lung involvement as a risky organ (RO). Surgery was performed in two, chemotherapy consisted vinblastin, prednisolone ± methotrexate, mercaptopurine was given in all 7, and RT was given in two patients. Refractory disease (n:2) and out of primary relapse (n:1) occured in three patients. These three cases treated with cisplatin, interferon, vinblastin, prednisolone, CR achieved in two. The median follow-up time was 31month (8.5m-17y), the 2- and 5-years OS rates were %71 and EFS rates were 43%.

Conclusions

In MSI-LCH group age tends to be younger than SSI-LCH group, and these patients particularly had RO involvement. These patients need more intense therapy.Cisplatin containing chemotherapy is an effective treatment option for relapse/refractory LCH patients.

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Rare Tumours

FOLLOW-UP OF CHILDREN WITH GENETIC MUTATION FOR ADRENOCORTICAL TUMORS IN WESTERN PARANÁ-BRASIL

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Introduction:

The Adrenocortical tumors (ACT) is a relatively rare tumor accounting about 0.1 % of malignancies. Despite its rarity, the South and Southeast regions of Brazil the incidence (ACT) is 15 times higher than the worldwide, about 3.4-4.2 casos/1.000.000 approximately. This incidence is considered an endemic problem in southern Brazil mainly in children under 5 years old. In a study conducted by Dr. Bonald Figueredo, through genomic screening of newborns, it was possible to identify the genetic mutation (R337H TP53 gene) in newborns of Paraná since 2005. The risk of developing the tumor in patients with mutation in Paraná is around 9.9 %, as shown penetrance studies conducted by the same author in cases of ACT in Paraná.

Objective:

Follow-up healthy children carry the germline TP53 mutation R337H for ACT, and refer early to a center for the Children's Oncology suspected cases.

Methods:

Follow-up was performed in 29 children from the study by Pelé Pequeno Príncipe Research Institute, by collecting blood sample from the "heel prick" (DNA) specific to the ACT, with positive results for genetic mutation since 2006 until 2008. This monitoring was conducted at the outpatient clinic of Pediatrics of the University Hospital of the West of Paraná, Cascavel.

Results:

Of the 29 children, 18 were female (62.0 %) and 11 males (38 %). And of these, three (10.3%) developed TCA, with clinical manifestations and initial hormonal level compatible with tumor development.

Conclusion:

The clinical follow-up of healthy children with genetic mutation for ACT, in order to proceed with the investigation as early as possible in suspected tumor manifestation, will benefit those that eventually have tumor development and will increase the chance of cure.

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Rare Tumours

FUNCTIONAL INHIBITION OF IGF1R IN ADRENOCORTICAL TUMORS CELLS PROMOTES CELLULAR DEATH AND CHANGES GENE EXPRESSION OF WNT/BETA-CATENIN PATHWAY COMPONENTS

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Objectives

In preview analysis of 60 pediatric adrenocortical tumors (ACT), we observed a significant association of *IGF1R* high levels with tumor relapse and metastasis, especially in those with Weiss score ≥ 3. Interestingly, *IGF1R* expression presented correlation with some important genes from the Wnt/beta-catenin pathway, which could suggest some interaction between both pathways. The aim of the study was to evaluate IGF1R function in adrenocortical carcinoma cell line NCI-H295A.

Methods

The cells were treated with a specific IGF1R inhibitor (OSI-906) and performed cell proliferation and apoptosis assays. In addition, we investigated gene expression of components from IGF (*IGF1R*, *MAPK3*, *MAPK1 PI3K*) and Wnt/beta-catenin (*CTNNB1*, *SFRP1*, *APC*, *AXIN1*) pathways after the treatment by quantitative RT-PCR.

Results

The OSI-906 treatment significantly decreased cell proliferation (concentrations between 125 and 3000 nM) ($P < 0.0001$) after 48 and 72 hours, reaching 40% of reduction. The IC_{50} values were 2,636.7 nM ± 235.5 at 48 hours and 1,990.4 nM ± 777.3 at 72 hours. The apoptosis rate increased in a dose-dependent manner, reaching 70.8% of dead cells with 1000 nM ($P < 0.0001$; IC = 62.4 – 79.3). In addition, OSI-906 reduced gene expression of *CTNNB1*, *SFRP1* and *MAPK1* ($P = 0.034$; $P < 0.05$ and $P = 0.009$, respectively) and increased *IGF1R* ($P = 0.016$) after 6 hours. At 24 hours, it was observed significant low levels of *SFRP1* ($P < 0.05$) and *PI3K* ($P < 0.0001$).

Conclusions

The treatment with OSI-906 in adrenocortical carcinoma cells reduced cell proliferation and increased apoptosis rates in a dose-dependent manner, suggesting IGF1R as a potential therapeutic target. In accordance with the correlation observed in pediatric ACT, the inhibition of IGF1R function induced gene expression changes in Wnt/beta-catenin components, suggesting an association between both pathways.

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Rare Tumours

MENINGEAL SARCOMA IN CHILDREN: A SURVEY FROM THE FRENCH SOCIETY OF PEDIATRIC ONCOLOGY (SFCE)

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Objectives

Describe the outcome of a population of meningeal sarcoma in children from the SFCE.

Methods

Retrospective study on patients harboring a meningeal sarcoma (MS) based on the French registry of pediatric tumor and pediatric oncologists questionnaires. Patient characteristics and treatments were collected. Pathology and imaging were centrally reviewed.

Results

Between 08/1989 and 05/2010 12 pts from 6 French centers, 3 months-14.5 years of age (mean: 3.3) were treated for a MS. Mean follow-up is 12 years (3 to 24 years). Tumor locations were: frontal (3), parieto-occipital (2), parietal (1), temporal (1), occipital (1), thalamic (1), pontocerebellar angle (1), cerebellar tentorium (1), cistern ambient (1). No metastase was observed. The first treatment was surgery in 10 cases, chemotherapy in 2. Resection was total in 6 cases, partial in 6. The pathological central review concluded to: high-grade undifferenciated sarcoma (8), chondrosarcoma (2), fibrosarcoma (1), myxoid desmoplastic tumor (1). 9 patients received 2 to 10 courses of chemotherapy (median 5). The number of patient alive is equal whatever the age (< or > 10 years) and tumor size (< or > 5 cm). 4 out of 6 pts who received radiotherapy are alive versus 1 out of 4 without radiotherapy. The 5-year EFS and OS are 50%. The median EFS in case of total resection is 39 months versus 16 in case of partial resection.

Conclusions

In this short series of very rare cancers, age and tumor size do not seem to be prognostic factors while total resection and radiotherapy seem to be essential. The role of chemotherapy is unclear.

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Rare Tumours

INFLAMMATORY MYOFIBROBLASTIC TUMOURS IN CHILDREN-MASQUARDING PAEDIATRIC SOLID TUMOURS

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Objectives

Inflammatory myofibroblastic tumors (IMT) are rare, benign lesions most often seen in lung of young adults but can occur in children, in various sites.They mimic, clinically and radiologically, malignant tumors—especially sarcomas and lymphomas. The aim was to review the clinical, radiological and pathological data of children with diagnosis of IMT reffered to our department.

Methods

This retrospective study was carried out at the Department of Medical and Paediatric Oncology, Regional Cancer Centre, Sher-i-Kashmir Institute Of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir,India,from January 2012 to December 2013.

Results

Among 288 paediatric solid tumours registered during the study period, 5 (1.73%) had the diagnosis of inflammatory myofibroblastic tumours.There were 3 male and 2 female children(M:F ratio 1.5:1).The mean age was 5.32 years (range 2 to 9 years).The main symptoms were abdominal distension and pain in 60% (3 cases),breathlessness and cough in 20% (1 case) and right axillary area swelling in 20% (1 case).On Computed tomography of chest and abdomen,1 patient had mediastinal widening with impression of lymphoma,two patients were labelled as having retroperitoneal sarcoma,and 1 patient had an ileal growth with impression of burkitt lymphoma.In one patient with right axillary swelling,lymphoma was suspected. In 3 patients complete surgical excision was done (1 with axillary mass and 2 with abdominal disease).One patient with retropritonel mass had residual disease and received chemotherapy followed by complete second surgery.In case of mediastinal IMT,surgery was followed by local radiotherapy.Only 1 patients (20%) initial histopathology was diagnosed as IMT (retroperitoneal lesion),otherwise it was only after review with immunohistochemitry from an oncopathologist that diagnosis of Inflammatory myofibroblastic tumour was made.At present 4 patients are disease free and 1 patient with mediastinal IMT has residual progressive disease.

Conclusions

On presentation, IMT can constitute a formidable challenge, from diagnosis through to treatment.

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Rare Tumours

MEDICAL TREATMENT OF CAPILLARY HEMANGIOMAS IN YOUNG CHILDREN

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Objectives

Hemangiomas, common congenital lesions in infants and children are benign tumors that arise when islands of angioblastic tissue fail to connect with the developing vascular system. Capillary hemangiomas in young children are difficult to treat. The treatment of capillary hemangiomas is needed for both cosmetic and medical reasons including maceration and erosion of the epidermis, infection and risk of occlusive amblyopia when located in periocular site.

Methods

Between April 1996-February 2014, 270 patients, whose age ranged between 5 days to 7 years with capillary hemangiomas were followed. There were 196 girls, 74 boys. (F:M=2.6:1)

Results

Among 270 patients 10 had multiple cutaneous lesions. Based on imaging studies of cranial and abdominal sites, there were no detected visceral hemangiomas. Most of the hemangiomas were located on head and neck in 148 (55%) cases and followed by 52 (19.6%) on the trunk, 44 (16.6%) on upper extremities, 20 (7.5%) on lower extremities, 8 (3%) on perineum, respectively. Medical management of hemangiomas included observation, corticosteroids, systemic beta blocker, local beta blocker, Interferon Alpha and sirolimus 49%, 6%, 12%, 13%, 20%, 1.3%, respectively.

Conclusions

Systemic steroids are tolerated well. Treatment with Interferon alpha 2-a is expensive, is used for vision threatening hemangiomas that are resistant to steroid treatment. Systemic propranolol has been effective and a reduction occurred in both radiographic and amblyogenic astigmastism. As the treatment does have potential complications, particularly cardiac, patients need to be monitored closely. Sirolimus have been effective in sizable hemangiomas resistant to steroids and systemic propranolol. It is highly recommended that patients should be monitored carefully.

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Rare Tumours

GASTROINTESTINAL CANCER IN CHILDREN AND ADOLESCENTS - A SINGLE INSTITUTION EXPERIENCE

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Objectives

To describe types and clinical course of gastrointestinal cancer in children and adolescents treated in our Institution.

Methods

Retrospective analysis of medical records of patients with gastrointestinal carcinomas treated between 1996 – 2013 was performed. Gender, age, tumor type, stage, treatment and it's results were analyzed.

Results

Out of 3,316 patients treated 14 (0.42%) were diagnosed with gastrointestinal tumors. There were 8 boys and 6 girls, aged 12 – 18 yrs, (median 15 yrs 10 m). Distribution of tumors was as follows: colorectal – 9 pts, pancreas – 4, stomach - 1. Two patients had FAP, 2 patients with ulcerative colitis developed colorectal carcinoma. Most patients presented with advanced disease at diagnosis (42 % stage III and 35% stage IV). All patients underwent primary surgery, followed by adjuvant chemotherapy. Adult chemotherapy regimens specific for disease type were used in first line treatment. At progression/relapse chemotherapy was modified individually. Radiotherapy was implemented in 2 patients, targeted therapy - in 1 patient.

8/14 (57%) are alive, disease free from 3 to 120 months, median 14 months. Six patients died all from disease with time to death ranging from 3 to 32 months, median 5 months.

Conclusions

Insidious onset and advanced stage at presentation are hallmarks of digestive system carcinomas in childhood and adolescence. Early diagnosis has a crucial role. Individuals who are at risk based on carcinoma associated conditions should be closely monitored.

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Rare Tumours

MANAGEMENT AND FOLLOW UP OF UROTHELIAL NEOPLASM OF THE BLADDER IN CHILDREN. A REPORT FROM THE TREP PROJECT

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Objectives

Urothelial Neoplasms of the Bladder (UNB) are rarely found in paediatric patients. As part of the TREP (*Tumori Rari in Età Pediatrica*) project - an Italian network dedicated to very rare tumours - we present a nationwide series of patients with UNB with the aim to establish treatment and follow up guidelines.

Methods

From 2008 to 2013, 9 patients (age range 6-13 years) with UNB were registered. According to pTNM System, tumours were classified pTa: non-invasive, pT1: evidence of subepithelial invasion, pT2: muscle invasion, pT3: invasion of perivesical tissues, pT4: invasion of extravescical organs. According to 2004 WHO Grading System we distinguished PUN-LMP, papillary urothelial neoplasm of low malignant potential (grade 1); LG-PUC, low grade-papillary urothelial carcinoma (grade 1 or 2); HG-PUC, high grade-papillary urothelial carcinoma, (grade 2 or 3).

Results

In all nine cases ultrasound showed a broad-based area or a polypoid lesion attached to the internal wall of the bladder (maximum diameter from 0.5 to 2.9 cm). All lesions were classified as pTa; 8 were considered G1-PUNLMP and 1 G2-HG-PUC. All lesions were completely resected by transurethral resection (TUR). In 3 children a single dose of intravesical chemotherapy was administered. One child had a recurrence one year after diagnosis and was treated by a new TUR and intravesical mytomicin. All patients are in complete remission (median FU 26 months). Follow up was performed differently in each patient and it was mostly based on ultrasound, cystoscopy at 2 months to 1 year interval and cytology.

Conclusions

We show that, in absence of defined guidelines, the management of children with UNB can be very heterogeneous and may include unnecessary and potentially toxic treatments. In consideration of the good prognosis, follow up should not be very intensive and the number of cystoscopies may be reduced.

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Rare Tumours

PRIMARY PULMONARY TUMORS IN CHILDREN - 20 YEARS EXPERIENCE OF SINGLE CENTER

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Objectives

Primary pulmonary tumors in children are rare. Individual or single center experience is therefore limited. The aim of our study was to evaluate patients with primary pulmonary tumors at our institution during period of the years 1994 – 2013.

Methods

Between 1994 and 2013 we treated 27 children with primary pulmonary tumors. We retrospectively reviewed medical records and histological material of these patients.

Results

Twenty-seven patients (19 girls, 8 boys) were treated for primary pulmonary tumor. Median age at time of diagnosis was 8.7 years (range, 23 days to 19 years). The presenting symptoms were pneumonia (9x), cough (7x), fever (3x), wheezing (4x), dyspnea (2x), back pain due to bone metastasis (1x), failure to thrive (1x). CT scan was performed in all patients. Surgical procedure was pneumonectomy in three cases, lobectomy in 18 patients, segmental resection in four and biopsy in two patients. Nine histologic types of tumor were observed – twelve benign (seven inflammatory myofibroblastic tumors - IMT, two hamartomas, one invasive fibroblastic tracheobronchial tumor - IFTBT, one cystic histiocytoma, one fibro-histiocytic tumor), eight neuroendocrine tumors (typical carcinoid – NET) and seven malignant (four pleuropulmonary blastomas, one rhabdomyosarcoma and two mucoepidermoid carcinomas). All patients with malignant tumor received combined chemotherapy. At median follow-up of 12 years (range, 10 months to 20 years) 24 patients are alive without signs of disease, three patients died (11,1%) - one patient with pleuropulmonary blastoma and both patients with initially metastatic disease (mukoepidermoid carcinoma; carcinoid).

Conclusions

Primary pulmonary tumors are rare and their histopathology heterogenous. Estimated incidence in Czech Republic is 1.2:100 000 of live births. Prognosis of benign tumors after complete surgical resection is excellent, whereas malignant tumors are still associated with significant mortality.

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Rare Tumours

MUCOEPIDERMOID CARCINOMA IN CHILDREN: A SINGLE INSTITUITIONAL EXPERIENCE

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Objectives

To determine the clinicopathologic features and outcome of children with mucoepidermoid carcinoma.

Methods

Retrospective clinical, histopathologic and molecular findings were reviewed in patients with mucoepidermoid carcinoma at Texas Children's Cancer Center between 2000 and 2013.

Results

There were 9 females and 4 males. The mean age was 10.8 years (range 7-19 years). The tumors were located in the submandibular gland (4 cases), parotid gland (4 cases), soft or hard palate (2 cases) and tracheobronchial (3 cases). All patients with salivary gland and palate tumors presented with asymptomatic fluctuant mass while patients with tracheobronchial mass presented with persistent lower respiratory tract infection. The median duration of symptoms was four months. Among eleven patients with salivary gland and palate tumors, initial tumor biopsy was performed in six cases, while in five other patients gross total removal was attempted. Eight of eleven patients required additional surgical extirpation. Three patients required postoperative radiation therapy because of positive margin (2 cases) and mandible bone marrow involvement (1 case). Three patients with tracheobronchial tumors underwent bronchoscopy with tissue biopsy prior to total tumor removal by pulmonary lobectomy. Histological grades were low (1), intermediate (9) and high (3). Nine of ten informative cases were positive for *MECT1/MAML2* fusion transcripts by RT-PCR. There were no deaths, metastasis or recurrence in this series with a mean follow-up of 30 months. No patient was treated with chemotherapy.

Conclusions

In children and adolescents, MEC has a female predilection. Low to intermediate histological grades were more common as in adults. Complete excision is the treatment of choice with excellent outcome. The role of radiotherapy is unclear but maybe considered only in patients with positive surgical margin or incomplete resection.

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Rare Tumours

THYMIC CARCINOMA IN CHILDREN: A REPORT FROM THE EUROPEAN COOPERATIVE STUDY GROUP FOR PEDIATRIC RARE TUMORS (EXPERT)

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Objectives

Thymic carcinomas belong to a group of rare thymic epithelial tumors arising from the anterior mediastinum and constitute 0.2 to 1.5% of all malignancies in adults. These tumors are extremely rare in children and no therapeutic guidelines has been established.

Methods

The clinical data and therapeutic characteristics of pediatric patients with malignant thymic tumors treated between 2000 and 2012 who were registered in the EXPeRT database of the cooperating national rare pediatric tumors working groups from France, Italy, Germany, United Kingdom and Poland.

Results

Twenty patients with thymic carcinoma, median age 14 years were enrolled into study. All patients were under 18 years old. Four children presented with autoimmune and paraneoplastic symptoms associated to tumor presence: myasthenia gravis, polymyositis, nephritic syndrome, and systemic lupus erythematosus associated to a hypertrophic pulmonary osteoarthropathy. Complete primary resection was performed in one patient, resection with microscopic residue was made in 3 cases and incomplete resection with macroscopic residue- in four patients. Chemotherapy with various regimens was administered to 17 children; 14 of them as neoadjuvant chemotherapy. Eight received additional radiotherapy. Fifteen children died. 5-year overall survival for the 20 patients with thymic carcinoma is 21.0±10,0%.

Conclusions

This study confirms very poor prognosis for pediatric patients with thymic carcinoma independent on the therapeutical management. Multidisciplinary and multicenter approach is necessary in order to make a common assessment.

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Rare Tumours

BREAST MASSES IN CHILDREN AND ADOLESCENTS

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Objectives

The overwhelming majority of breast masses in children and adolescents are benign and self-limited. They have a variety of etiologies. Knowledge of the clinical and sonographic features allows the clinicians to guide appropriate management of these patients. In this paper we evaluated the breast masses in children and adolescents.

Methods

All children less than 18 years diagnosed with breast mass admitted to our center between March 2012 and March 2014 were analyzed for age, gender, complaint, history of malignancy, sonographic and pathological findings, diagnosis, retrospectively.

Results

Thirty-seven patients (29 girls and 8 boys) admitted with breast mass within last two years. The mean age was 14.6 years (range 5-18). Eleven patients had pain, 3 patients had nipple discharge, 2 patients had bloody nipple discharge. Two patients had family history of breast cancer. Ultrasonography was applied to all patients. According to BI-RADS (Breast Imaging Reporting and Data System) classification, 4 patients had category 3 and 2 patients had category 4 masses. Four patients had operation of mass excision. Two of these patients were BI-RADS 4, and the remaining two patients were in BI-RADS 3 category. Furthermore three of operated patients' masses were more than 5 cm. Histopathologic diagnosis of these 3 patients were juvenile fibroadenoma. Pathologic diagnosis of fourth patient who had malignancy history was pseudoangiomatous stromal hyperplasia. The other patients diagnosis according to clinical and sonographic features were: Fibroadenoma 11 patients, gynecomastia 8 patients, breast abscess 6 patients, premature thelarche 3 patients, mammary duct ectasia 2 patients, accessory breast 1patient, fibrocystic change 1 patient and adenosis 1 patient. Patients followed up with ultrasound and none of them developed malignacy.

Conclusions

The prevalence of breast cancer in the pediatric age group is extremely low so a conservative approach of clinical and sonographic follow-up is more commonly adopted in children.

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Rare Tumours

GENOME-WIDE APPROACH TO IDENTIFY GENE TARGETS OF PANCREATOBLASTOMA

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Objectives

Pancreatoblastomas (PBL) are unusual malignant neoplasms of the pediatric pancreas that may also rarely affect adults. Somatic alterations in the APC/beta-catenin pathway, including inactivating mutations in APC and activating mutations in CTNNB1, and loss of chromosome 11p have already been reported in the majority of PBLs. However, mainly due to its rarity, little is known about additional genetic changes that are responsible for the pathogenesis of PBL. To explore the genetic alterations underlying the pathogenesis of PBL, we performed whole transcriptome and exome analyses in 2 cases of PBL. Additional 6 cases of PBL were used as validation cohort.

Methods

Total RNA and DNA were extracted from fresh frozen tumors of the PBL patients. According to manufacture's protocol, mRNAs and exons were captured, and whole transcriptome/exome analyses using Illumina HiSeq 2000 were performed. DNA from matched germline samples were used as controls. All the candidate fusions and somatic mutations were validated by RT-PCR and Sanger sequencing.

Results

Across the coding regions of two cases, a number of candidate mutations and several novel fusion genes were identified. Similar to the other pediatric solid tumors, recurrent mutations were almost not detected in PBL, except for the CTNNB1 mutations (S33F and T41A). These CTNNB1 mutations were confirmed as somatic origin. Interestingly, we found a novel fusion transcript which associated with a beta-catenin related gene in one case.

Conclusions

As previously reported, our results revealed that alterations of CTNNB1-pathway could be responsible for the pathogenesis of PBL, and our result suggested that this pathway is a candidate for therapeutic target. To further elucidate pathogenesis of PBL, searching pathways enriched mutations, possibility of involvement of germline mutations, and epigenetic regulations should be assessed.

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Rare Tumours

TREATMENT EXPERIENCE IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

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Objectives

To summarize our treatment experience in patients with Langerhans cell histiocytosis (LCH).

Methods

Medical records of LCH patients were evaluated retrospectively for clinical features, treatment outcome.

Results

There were 20 patients with LCH with median-age-of-diagnosis 37mos (5mos-10yrs) and M/F-ratio 1.5. Nine had single system involved (SSI) LCH, 11 had multisystem involved (MSI) LCH.

SSI-LCH: Spontaneous complete remission (CR) without chemotherapy observed in both skin involved infants. Patient with Rosai Dorfman treated with LCH2 protocol. Surgery was performed in two patients with bone involvement, one of which also received RT. Remaining 4 patients with bone involvement received chemotherapy (LCH2 (n:3), LCH3 (n:1)), one of which was given additional RT. Out of primary relapse occured in three cases, CR achieved by RT in two patients. Median follow-up-time was 77mos (3mos–14.5yrs), 10-yr-OS 100%, 5- and 7-yr-EFS 60%.

MSI-LCH: Involvement sites were skin (n:8), lung (n:7), bone (n:7), liver (n:4), spleen (n:2), CNS (n:4), lymphadenopathy (n:1), gingiva (n:1); 8 patients had risky organ (RO) involvement. CR achieved in three without RO involvement. Five with RO involvement were treated with LCH2 treatment, (1)two died within one month due to progression, (2)one received additional RT and in CR, (3)PR achieved in one and liver transplantation was proposed, (4)one refused treatment at 4th month. Remaining 3 patients: (1)PR achieved with DAL HX90 protocol, then CR achieved with prednisolone, vinblastin, methotrexate, cyclophosphamide; (2)CR achieved with LCH3 and LCH4 protocols in remaining two patients. Primary and out of primary relapse occured in one of them, and treated with 2CdA containing chemo. Median follow-up-time was 49mos (1mo–10yrs), 5- and 10- yr-OS 82%, 5-yr-EFS 44%.

Conclusions

In addition to infants with spontaneous remission of skin involvement, there were infants with MSI-LCH who died early despite treatment. Pulmonary and liver involvements affected survival and outcome adversely. Multidisciplinary new treatment approaches are needed.

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Renal Tumours

TREATMENT OF RELAPSED WILMS TUMOUR (WT) PATIENTS: EXPERIENCE WITH TOPOTECAN

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Objectives

Topotecan has been variably incorporated in the treatment of patients with relapsed WT who have previously been treated with the three or four drugs first line SIOP chemotherapy regimes. However, so far, no large series are available describing the efficacy of topotecan in this setting. Our objective was to describe outcome and to retrospectively investigate the potential role of topotecan in relapsed WT patients.

Methods

Children who were treated with topotecan as part of their chemotherapeutic regimens for relapsed/refractory WT were retrospectively identified and included in our study. Patient charts were reviewed for general patient characteristics, histology and stage at diagnosis, number and type of relapse, treatment schedules, toxicity, response to treatment and outcome.

Results

From 2000-2012, 27 children (median age at relapse 5.5 years, range 1.6-14.5) were treated with topotecan (refractory disease 10%, first relapse 43%, second relapse 30%, third relapse 7%, rest or partial response 10%). Topotecan was given as a single agent or in combination with other conventional drugs, e.g. cyclophosphamide, etoposide, carboplatin, ifosfamide. Sixteen patients had SIOP high-risk (HR) histology at diagnosis (including 11 diffuse anaplastic tumours). All died within 12 months because of progressive disease, except one, who had bilateral nephrectomy after a partial response to topotecan treatment. Eleven patients had intermediate-risk (IR) histology at diagnosis of which three patients displayed objective responses to topotecan. Overall, 5/11 IR patients survived (median follow up of 6 years), three of whom (stage V) had a bilateral nephrectomy after topotecan treatment.

Conclusions

Topotecan showed no effectiveness in the treatment of relapsed WT patients with high-risk histology. In patients with intermediate-risk histology, the role of topotecan might

deserve further attention, to prove its efficacy.

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Renal Tumours

SURGERY OF PATIENTS WITH LIVER METASTASES FROM WILMS TUMORS TREATED IN SIOP PROTOCOLS: SINGLE SURGICAL CENTER EXPERIENCE

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Objectives

Either synchronous or metachronous with renal tumor, liver metastases (LM) are less frequent than lung metastases in patients with Wilms tumors (WT). Persisting LM after initial chemotherapy are proposed to excision. Our purpose is to report on a series of patients operated on for LM in a single pediatric liver surgical center.

Methods

All patients enrolled in SIOP studies 9, 93-01 and 2001, undergoing surgery for LM have been included in this retrospective study. Following points have been emphazised: synchronous (SLM) or metachronous (MLM) occurrence of LM, personal data, side, local stage and histology of renal tumor(s), vascular involvement and presence of lung metastases at diagnosis, number, location in liver of LM, surgical procedures and quality of resection of LM, follow-up and outcome of patients.

Results

Four patients with SML and 6 with MLM (diagnosed 1 to 123 months, average 23) after nephrectomy have been identified. Two had predisposing syndromes. Renal tumor was in right kidney in 6 patients, local stage III in 2, and high-risk histology in 1. At diagnosis 3 patients had caval involvement and 5 (4 SML + 1 MLM) lung metastases. At surgery all metastases, multiple in 6 cases , were in right liver, removed by means of wedge resection in 4 cases, “réglées” hepatectomies in 6 cases. Eight patients had complete (R0) and 2 incomlete (R1) microscopic resection. Three patients (one R1, two R0) had LM recurrence 4 to 12 months after LM surgery, and two of them died. The remaining 8 patients were alive and disease-free with a follow-up of 1 to 9 years.

Conclusions

These results point out the need for screening WT patients for LM after nephrectomy, and the major role of aggressive surgery aiming to microscopic complete excision of LM in their treatment.

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Renal Tumours

PRELIMINARY TREATMENT OUTCOMES UTILIZING SIOP GUIDELINES IN A NOVEL ONCOLOGIC CARE MODEL FOR WILMS' TUMOR IN RWANDA

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Objectives

Wilms' Tumor (WT) is the most prevalent pediatric malignancy at the Butaro Cancer Center of Excellence (BCCOE), a Partners in Health-supported Ministry of Health facility in rural Rwanda. WT has been successfully treated in a few urban centers in Sub-Saharan Africa. There are currently no reports from rural centers on delivery of protocoled care via non-oncologist clinicians. This is the first report of preliminary outcomes using SIOP WT guidelines in this setting.

Methods

Patients treated for WT since program inauguration in July 2012 determined using electronic medical records and paper charts. Patients excluded if missing imaging or pathologic WT confirmation. Extraction performed using Excel with validation parameters. Descriptive analyses and non-parametric comparisons were performed with SPSSv20.

Results

38 patients treated for WT, 61% female (n=23), median age at intake 45 months (range:1-52). 68% (n=26) presented with localized, unilateral mass, 24% (n=9) metastatic, 5% (n=2) localized bilateral, and 3% unknown (n=1). Common metastatic sites were lung (89%; n=8) and liver (67%; n=6). 35 started pre-operative chemotherapy (Vinc/Act-D: 66%, n=23; Dox/Vinc/Act-D: 34%, n=12) and 71% (n=27) had surgery. Post-surgically, SIOP staging: 37% (n=10) I/II, 15% (n=4) III, 11% (n=3) IV, 4% (n=1) V, 33% (n=9) indeterminate/missing. 26 started post-operative chemotherapy (Dox/Vinc/Act-D: 92%, n=24; Vinc/Act-D: 8%, n=2). 21% (n=8) died (median time intake-death: 11 days, range:1-45), 75% (n=6). 17% of treated patients were lost to follow up (n=5). 14 patients completed treatment, 57% (n=8) had post-treatment evaluation. All evaluations showed clinical remission (median follow-up: 12 months, range:10-14).

Conclusions

WT can be successfully treated in a rural, resource-limited setting through a protocoled approach utilizing non-oncologist clinicians. Loss to follow-up remains low relative to comparable settings. Treatment vs. disease-related mortality is difficult to determine, though conservative analysis indicates treatment-related mortality estimates within reported ranges for SIOP PODC protocol. Further studies to determine mortality associated risk factors are needed.

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Renal Tumours

PATIENTS WITH NEPHROBLASTOMA TREATED WITH SIOP 2001 PROTOCOL IN NATIONAL HOSPITAL OF PEDIATRICS, HANOI, VIETNAM – OUTCOME AND CHALLENGES

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Objectives

Our aim is to replicate the result of SIOP 2001 protocol in our hospital and test its applicability in the Vietnam situation

Methods

All eligible patients with inclusion criteria of SIOP 2001 protocol will be enrolled to the study. For intermediate risk group, patients with stage II treated with AV2 regimen, patients with stage III treated with AVD + RT (no randomization). Patients enrolled on study from July 2008 to December 2012 and follow up to 30th June 2013.

Results

80 patients had enrolled to study: 7 died or abandoned during preoperative chemotherapy, 13 had other diagnosis after preoperative chemotherapy. 60 patients had diagnosis nephroblastoma and had full treatment, 2 were lost for follow-up after cease of treatment, and they were in EFS at last examination. After preoperative chemotherapy tumor's volume reduced in 86.5% cases and total volume of tumors reduced by 47.7%, 38.3% of tumors in stage I. 58 patients had been followed up to the end of study: 9 patients died, 13 relapsed. There are 75.9 % of patients in event free survival and 84.5% in overall survival (follow up time 2-57 months, mean 27 months). Imaging diagnosis is corrected with pathological anatomy in 78.3% cases, much lower than SIOP data. The discrepancy may be due to less experience by our imaging specialists compared with SIOP institutions or a true higher incidence of rare tumors in our Vietnamese population. We experienced a higher incidence of 18% of clear cell sarcomas and rhabdoid tumors compared with 4-6% reported by SIOP. Pathological anatomy diagnosis is a difficult work because rapid central review is not available as in SIOP institutions

Conclusions

In National Hospital of Pediatrics, protocol SIOP 2001 had been applied successfully, our treatment outcome is much lower than SIOP data, imaging and pathological anatomy diagnoses are big challenges

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Renal Tumours

WILMS TUMOR: A RETROSPECTIVE STUDY OF 61 CASES IN THE CENTER OF TUNISIA

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Objectives

To compare our results to SIOP 9 study.

Methods

We studied retrospectively 61 children with WT treated at the department of medical oncology of Farhat Hached Hospital, from January 1994 to December 2010. Kaplan Meier method with Log-Rank testing was employed for survival analysis.

Results

The mean age was 3.5 years old, with a sex ratio 0.48. Eighty percent of the children presented a painless abdominal tumor as a first sign. The tumor was mainly unilateral (93%) , right for 56% of them.

Ultrasounds, computed tomography showed an heterogeneous tumor in 52%, with a medium size of 16.5 cm, developed in 48% in the lower pole of the kidney. Venous thrombosis were diagnosed in 6.5%. WT were metastatic in 23%.

Most of the patients received preoperative chemotherapy (98.3%) then enlarged nephrectomy was practiced (only 2 postoperative complications).

Postoperative stage I, II, III were respectively 39%, 41%, 20% and according to SIOP 9 risk classification, there were 28%, 62%, 10% of low, intermediate and high histological risk. Postoperative chemotherapy was received in 84%. Adjuvant radiotherapy was practiced in 16% .

The five-year overall survival was 68%, 80% in localized stages and 46% in metastatic stages. Thirty-four percent relapsed in an average of 9 months. No late sequelae was noticed.

Conclusions

This study shows less overall survival then the SIOP 9, due to a bigger rate of metastatic forms, late diagnosis and the difficulty to respect the time schedule of the protocol .

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SIOP AFRICA / PODC COLLABORATIVE WILMS TUMOUR PROJECT – CHALLENGES AND PROGRESS

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Objectives

Reported survival of Wilms tumour (WT) patients in sub-Saharan Africa is 11 – 50%. Challenges include late presentation, malnutrition, less intense supportive care facilities and failure to complete treatment. We aim to improve care and survival in a feasible and sustainable fashion.

Methods

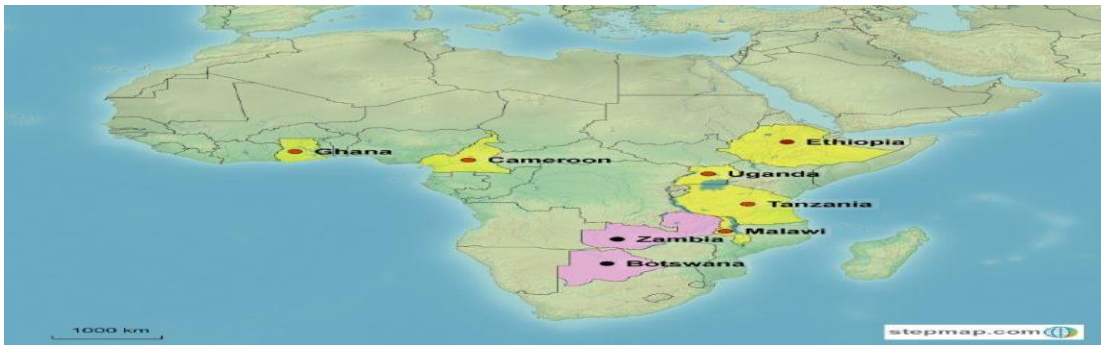
A regional collaborative group has been established with participation of eight institutes in five countries in sub-Saharan Africa. All institutes have had a dedicated childhood cancer unit, established Wilms tumour treatment and external (funding) support for several years. A SIOP PODC adapted treatment guideline for Wilms tumour and supportive care in low income countries was published. It includes an emphasis on the diagnostic role of ultrasonography, preoperative chemotherapy with a reduced dosage for malnourished children and social support to enable parents to complete treatment. This guideline is being implemented as a multi-centre prospective clinical trial, expecting about 200 new patients per year. Research questions include event free survival, reasons of treatment failure, efficacy and toxicity of preoperative chemotherapy and the comparison of surgical staging, local pathology and central review pathology in stratifying postoperative chemotherapy.

Results

A comprehensive uniform treatment protocol, uniform data collection form and central data collection tool are in place. A collaborative agreement has been developed and signed by the different participating units. Local IRB approval has been sought in the different units. A baseline evaluation of outcome has been done for the years 2011 – 2013. World Child Cancer and SIOP have agreed to co-fund for 5 years. Enrolment started in January 2014. The project website is on paedonc.wix.com/wilmsafricaproject.

Conclusions

Prospective use of adapted treatment regimens for childhood cancers along with systematic data collection among regional partners is achievable in Sub-Saharan Africa. We hope to demonstrate in the future, that this leads to improvement in outcomes along with capacity building.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RESULTS OF THE SIOP-2001 TRIAL AND STUDY FOR THE TREATMENT OF NEPHROBLASTOMA AT A SINGLE INSTITUTION IN A DEVELOPING COUNTRY

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Objectives

Evaluate the outcome of patients with Wilms Tumor (WT), treated according to SIOP-2001 strategy.

Methods

A retrospective analysis of 141 consecutive patients with WT diagnosed at our institution between December 2001 and 2013 was performed. Kaplan-Meier survival estimates for overall survival (OS) and event free survival (EFS) were calculated.

Results

115 patients, median age 38.8 months old (3-155) were assessable for analysis. Fine needle aspiration was initially performed on 88 patients (84.6%). Stage distribution was: stage I:33%; II:10.4%; III:27.8%; IV:13.9%; V:14.7%. Six patients (5.2%) were stage III because of tumor spill during surgery. Eleven patients (9.5%) underwent initial nephrectomy. The other patients received preoperative chemotherapy (POC). Adjuvant chemotherapy was given without randomization, using vincristine-actinomycin D for stage II and vincristine-doxorrubicin-actinomycin plus radiotherapy for stage III.

With a median follow up of 52 months, 5-year OS and EFS were 91% and 84.5%. OS according to stage was: stage I:92%; II:99%; III:88%; IV:78%; V:99% (p=0.04). There was no significant difference in EFS (p=0.4).

Seventy-eight patients (85.7%) were intermediate risk, and 11 patients (12%) high risk. Comparing blastemal subtype with intermediate-risk subtypes, the 5-year OS was 100% vs. 88% (p=0.47), and EFS was 100% vs. 80% (p=0.92).

Five-year EFS according to tumor volume after POC was 95% for tumors ≤399ml and 60% for ≥400ml, respectively (p=0.0003). There was no significant difference in OS (p=0.13).

Fifteen patients (13%) relapsed within 2 to 99 months (median 29,9). Eight patients (6.9%) died of progressive disease. There were no treatment-related deaths.

Conclusions

SIOP-2001 guidelines are feasible to be applied in our institution, with excellent results. The 5-year OS and EFS in our series are similar to those reported by the leading groups.

Despite of small number of patients, blastemal subtype showed better outcome when treated with an intensified regimen.

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OUTCOME OF WILMS TUMOR TREATED WITH SIOP WT 2001 (UK VERSION) GUIDELINES: A MULTICENTER EXPEREINCE IN PAKISTAN

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Objectives

To study outcome of children with Wilms tumor treated with SIOP 2001 (UK version) guidelines

Methods

Retrospective chart review of all cases of Wilms Tumors registered at CCH and SIUT from July 2002 to October 2012. Children treated after immediate nephrectomy and those presenting with relapsed disease after chemotherapy were excluded. Only children received pre and post- operative chemotherapy as per SIOP WT 2001 (UK VERSION) guidelines were included. Outcome analysis was done with respect to disease stage at presentation (localized, metastatic and bilateral), post op- staging and risk group. Causes of death were recorded.

Results

131 children were diagnosed with Wilms tumor on pre-op biopsy during study period. The age range was 0.1 - 3 years (median 3 yrs). Male to female ratio was 1.46: 1. Abdominal mass (100%) and hematuria (15%) were most common presentation. At presentation localized, metastatic and bilateral diseases were seen in ,93 (71%), 25 (19%) and 13(10%) respectively. The overall survival with median follow up of 5.5 years for whole cohort with and without abandonment is 64% and 76% respectively. Overall survival among localized disease with and without abandonment is 70% and 80%, for metastatic disease 48% and 55% and for bilateral disease it is 46 and 75%. Overall survival according to post-op stage for localized disease were stage 1 (95%), stage II (71%) and stage III(72%). Survival according to risk group among localized were low risk (100%), intermediate risk (84%) and high risk(76%). Major causes of death were relapses, inoperable tumor with poor response to chemotherapy and sepsis. Abandonment during treatment was a major adverse factor.

Conclusions

Treatment of Wilms tumor with SIOP approach in Karachi has shown good survival. This can be further improved with reduction in abandonment , toxicity deaths and better compliance with protocol

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WILMS TUMOUR IN MALAWI: SURGICAL STAGING TO STRATIFY POSTOPERATIVE CHEMOTHERAPY ?

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Objectives

Wilms tumour postoperative chemotherapy is ideally stratified according to the pathologist's assessment of tumour stage and risk classification (tumour type). In sub-Saharan Africa results are often not available in time to influence therapy and in Malawi surgical staging has been used to stratify postoperative chemotherapy. Here we compare the results from surgical and both local pathology and central pathology review.

Methods

Children diagnosed with a Wilms tumour in Blantyre, Malawi between 2007 and 2011 were included if they had had a nephrectomy and the pathology slides were available. All tumour specimens were assessed in three different ways: the local surgeon documented the surgical stage of the tumour, and the risk classification and pathology stage were assessed both by the local pathologist and by a SIOP central review pathologist in Europe.

Results

Fifty patients had complete data available and were included in the analyses. Tumour risk classification differed between the local and central pathology review in two patients only (4%). Using central pathology review as the 'gold standard'; 60% of patients received the correct postoperative chemotherapy treatment based on surgical staging and 84% based on the local pathology stage and risk classification.

Conclusions

Local pathology capacity building is needed to enable timely assessment and reporting.

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EPIDEMIOLOGY AND OUTCOME OF RARE RENAL TUMORS IN PEDIATRIC POPULATION IN A SINGLE TERTIARY CARE CENTRE IN INDIA

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Objectives

Little data exists on the epidemiology and outcomes of renal tumors other than WIlm's in children. We aimed to study the epidemiological profile of rare renal tumors in pediatric population and their outcome.

Methods

This is a retrospective analysis of 10 years data from January 2004 to December 2013 from Tata Memorial Centre, Mumbai, India. Study included all children who presented to our hospital during this period with renal mass and post operative histopathology or pre operative biopsy suggestive of tumor other than Wilm's tumor. Patients received standard treatment as per the diagnosis and their outcomes were analyzed

Results

We recorded total 38 cases of rare renal tumors in our study. There were 16 cases of clear cell sarcoma of kidney (CCSK), 5 primitive neuroectodermal tumor (PNET), 5 rhabdoid tumor of kidney, 4 renal cell carcinoma (RCC), 3 germ cell tumor (GCT), 2 translocation associated RCC, 2 congenital mesoblastic nephroma and 1 synovial sarcoma. Metastatic disease at presentation was found in total 10 cases (7 cases of CCSK, 1 case of PNET and 2 cases of rhabdoid tumor). Patients with metastatic disease received only palliative and supportive care. Four patients with localized disease had progression on treatment (1 RCC and 3 rhabdoid tumor) and 2 patients (both CCSK) relapsed after completion of therapy. Eleven patients (4 CCSK, 2 PNET, 2 RCC, 2 translocation associated RCC and 1 synovial sarcoma) are disease free at a median follow up of 2 years. Eleven patients were lost to follow up.

Conclusions

The most common renal tumor after Wilm's tumor in our patients is CCSK followed by PNET and rhabdoid tumor. Approximately one-fourth of patients present with metastatic disease. Patients with localized disease have reasonable long term survival when treated with standard treatment.

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COMBINED-MODALITY NEOADJUVANT THERAPY FOR ADVANCED WILMS TUMOR: 10 YEARS EXPERIENCE

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Objectives

Evaluate the effect of combined-modality neoadjuvant therapy using transcatheter arterial chemoembolization (TACE) and systemic chemotherapy for treatment of advanced Wilms tumor.

Methods

From January 2003 to December 2012, 46 patients (25 boys and 21 girls; median 2.9 years, range 0.5–11 years,) of unilateral advanced Wilms tumor were treated with TACE and systemic chemotherapy before surgery. Characteristics of the patients were maximal tumor diameter ≥ 10 cm, involvement of periaortic lymph nodes, inferior vena cava invasion, distal metastasis, or tumor with anaplastic histology. Patients subjected to TACE by Seldinger's method. A catheter was placed into the involved renal artery and chemoembolization emulsion consisted of cisplatin (80 mg/m2), pirarubicin (40 mg/m2), vindesine (3 mg/m2) and iodized oil (5 ml) was infused. Intravenous chemotherapy with vindesine (3 mg/m2 once a week) and actinomycin D (15 g/kg daily in a 3-day course) was administered one week after TACE. Surgical resection carried out 2 or 4 weeks after TACE. Postoperative therapy was according to NWTS IV protocol.

Results

No cardiotoxicity, renal insufficiency, or hepatic dysfunction were found in all patients. Grade I-II marrow suppression developed in 5 patients (10.9%). Tumor volumes were significantly reduced after neoadjuvant therapy. Complete surgical removal of the tumor achieved in 39 patients (84.8%). Surgical stages were stage ?: 20 (42.6%), and stage ?: 22 (46.8%). Four patients had clinical stage IV disease at presentation. Histology results classified as FH in 43 and AH in 3 cases. Gross inspection revealed necrosis of tumor to variable extent in all cases. Total necrosis of tumor was observed in 11 cases (23.9%). Overall Survival and event-free survival were 100% and 97.8% respectively,with a median follow-up of 71.9 (range 15-109) months.

Conclusions

Combined-modality neoadjuvant therapy showed high clinical and pathological response rates for the treatment of advanced Wilms tumor.

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BILATERAL WILMS' TUMOR; FREQUENCY, MANAGEMENT AND OUTCOME EXPERIENCE AT CHILDREN CANCER HOSPITAL - EGYPT

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Objectives

Successful treatment of Wilms' tumor requires meticulous attention to correct staging of the tumor and good communication between the pediatric oncologist, surgeon , radiodiagnosis specialist , pathologyist and radiotherapist.

When combined with adjuvant therapy, nephron-sparing surgery for children with BWT is nearly always technically feasible, with few complications. In addition, it is believed that this operative intervention should be done early, by not more than 12 weeks after the initiation of chemotherapy, because little significant further change in tumor size is likely, and it is important to determine the exact tumor histology.

We aim at evaluating patients' disease characteristics, assessing response and complications of different treatment modalities and survival analysis.

Methods

This is a retrospective study included all patients with bilateral Wilms' tumor (BWT) presented between July 2007 and March 2012 to the Children's cancer hospital- Egypt and they were followed up till March 2013.

Results

There was 25 patients during the selected time period, with age ranging between 4 months and 8.6 years (median = 2.7 years). The male to female ratio was 1:1.3.

All cases had bilateral synchronous renal masses and no recorded cases of metachronous BWT. Using COG staging system, local stage distribution was: 20%, 12% and 68%, for stage I – III respectively, while initial metastatic BWT was diagnosed in 8 cases representing 32% of the cases studied.

With a median follow up duration of 21 months, the 4 years OS was 78.2%, a RFS showed 73.9%. Presence or absence of metastatic disease was the only factor having statistically significant effect on OS and RFS.

Conclusions

The treatment of bilateral Wilms' tumors requires multimodality therapy with individualized decision to ensure cure while preserving as much renal parenchyma as possible. 3 months of preoperative chemotherapy allow to perform renal sparing surgery in most cases.

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IS THREE DRUG CHEMOTHERAPY PROTOCOL FOR ALL STAGES OF WILMS TUMOR A PRACTICAL COMPROMISE FOR SUBOPTIMAL STAGING IN DEVELOPING COUNTRY? IS IT WORTH & SAFE?

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Objectives

The obstacles in management of WT in tertiary cancer centres in developing country such as India are lack of awareness among caregivers in community regarding multidisciplinary management of WT leading to delays in referral for adjuvant treatment post surgery without adequate surgical and pathological details limiting appropriate stage assignment.To overcome these obstacles we started chemotherapy protocol using anthracyclines for all stages.

Methods

WT 10/90 protocol is the pulse intensive arm of NWTS-4 study comprising of vincristine, actinomycin D and doxorubicin. WT patients registered at Tata Memorial Hospital from Oct 1990 to Dec 2006 treated on WT 10/90 were analysed. Univariate analysis (UVA) for relapse free survival (RFS) and overall survival (OS) was performed using Kaplan-Meier method. Multivariate analysis (MVA) was performed using Cox Proportional Hazards model.

Results

147 patients of WT were treated on WT10/90 protocol from October 1990 to December 2006. Median age at presentation was 40 months with 59% males. Majority, 105 (71.4%) were operated outside and referred for adjuvant therapy. Of these, 101 patients were operated upfront, whereas only 4 received anterior chemotherapy followed by surgery. Favorable Histology (FH) was seen in 98.6%. Ten year RFS and OS were 84.7% and 89% respectively at median follow up of 88 months.

Age group (40 months) (p=0.005), histology (p=0.000) were significant for RFS on UVA & MVA. Only histology (p=0.002) was statistically significant on UVA and MVA for OAS. CHF occurred in 3 (2%) while 17 (11.5%) had asymptomatic echo-cardiographic changes. Chronic HBV in 12 (8.2%), skeletal abnormalities in 5 (3.4%), second malignancies in 3 (2.1%) and hypertension in 3(2.1%) were other late effects.

Conclusions

Chemotherapy protocol comprising of three drugs for all stages of WT is a practical compromise to compensate for lacunae in staging and optimal therapeutic planning. Asymptomatic late anthracycline related cardiac toxicity needs to be monitored further for its impact on QOL

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Retinoblastoma

LIFE BEFORE EYE: IMPLICATIONS FOR THE WHOLE CHILD AND FAMILY OF ATTEMPTED EYE SALVAGE FOR UNILATERAL AND SEVERE BILATERAL RETINOBLASTOMA

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Objectives

Primary enucleation is standard care for unilateral retinoblastoma and International Intraocular Retinoblastoma Classification Group E eyes in children with bilateral disease, often curing and enabling careful pathology and genetic testing to evaluate further risks. Families and physicians are increasingly selecting innovative therapies in hope of saving the eye. In countries with limited access to advanced medical care, families seek international treatment. We evaluated physical, psychological and financial impact on the child and family of primary eye salvage for unilateral and severe bilateral retinoblastoma.

Methods

We reviewed treatment course, event free survival, psychological and financial impact, and primary reason for contact among families who approached Daisy's Eye Cancer Fund for assistance.

Results

Secondary enucleation rate was high, particularly among international patients and children with unilateral retinoblastoma. In two cases, parental request for enucleation of a unilateral blind eye was contested by the multidisciplinary team, leading to emotional trauma, extra treatment and delayed surgery. Mortality was most associated with poor follow up due financial limitations, resistance to secondary enucleation and, in developed countries, leptomeningeal metastasis following Intra Arterial Chemotherapy. Of 6 children who had bone marrow relapse following intensive therapy for unilateral retinoblastoma, 3 are alive with no evidence of disease at 2 years follow up. Reports consistent with Post Traumatic Stress Disorder are frequent in both children and parents, but only one child is diagnosed with PTSD. Diagnosis of Autism Spectrum Disorders is frequent. Financial distress is common, with many families unable to pay medical bills. Families seeking international treatment experience increased poverty on return home and lost-to-follow-up rates are high.

Conclusions

Primary enucleation for unilateral and advanced bilateral retinoblastoma saves lives. Significant financial and psychological burdens of eye salvage therapy must be weighed against perceived treatment benefits in the informed consent process, especially when consulting with families in resource-poor countries.

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ONE RB WORLD ONLINE: A VIRTUAL RETINOBLASTOMA CLINIC

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Objectives

Global research collaboration has been identified as key to improving outcomes for retinoblastoma. In 2009, the first retinoblastoma clinical practice guidelines were published in Canada. Optimal resources and expertise for retinoblastoma management were outlined, and serves as a guide to inform health policy, at national, regional and institutional levels. Subsequently these guidelines were adopted by the Kenyan National Retinoblastoma Strategy group. In both countries, a situational analysis of key treatment centers has informed systems of patient referral, educational capacity initiatives, and is predicted to result in enhanced patient care. We now apply this approach on a global scale, with an online virtual retinoblastoma clinic.

Methods

We conducted a survey of Global Retinoblastoma Treatment Centers to identify and document expertise and resources available for the care of children with retinoblastoma worldwide. An online platform was developed to disseminate this information in an interactive and data-rich format.

Results

The virtual clinic connects patient families to caregivers, and documents data on 90 centers in 50 countries. A survey functionality allows further data collection and updates. Knowledge of where and how retinoblastoma children are managed worldwide provides an efficient and rapid path for parents to access urgent care. The website indicates the closest expert center and all the contacts. Paths of referral and multicenter co-management aim to keep the children close to home while optimizing access to advanced therapies when needed. Estimated incidence vs location and capabilities of treatment centres reveals opportunities to increase capacity, collaboration and coverage in various regions.

Conclusions

The One Retinoblastoma World Virtual Clinic connects stakeholders and strengthens capacity to care for the global retinoblastoma population. This first-of its-kind collaboration promotes global standards of care, setting the stage for multicenter clinical trials and other research, thereby accelerating the translation of results from lab to clinic.

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Retinoblastoma

TRILATERAL RETINOBLASTOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives

Rarely, children with hereditary retinoblastoma (Rb) develop trilateral retinoblastoma (TRb): retinoblastoma combined with a histologically identical brain tumor, most commonly located in the pineal gland. Unfortunately many do not survive. The objective of this study was to provide an overview of published cases, and to analyze survival.

Methods

We searched Medline and Embase for TRb cases published from January 1966 through February 2014. This study was performed according to the PRISMA statement. Meta-analysis was performed on survival data.

Results

One hundred and sixty-two TRb patients from 87 studies qualified for meta-analysis. Patients diagnosed with TRb <1995 showed a 5-year cumulative survival rate (CSR) of 4% (95% confidence interval (95%CI): 1%–12%). In the period ≥1995 CSR rose to 45% (95%CI: 31%–59%), along with increased use of (high-dose) chemotherapy and decreased use of radiotherapy for the brain tumors. Pineal TRb showed CSRs of 6% (95%CI: 1%–15%) and 43% (95%CI: 24%–59%) for <1995 and ≥1995 respectively, whereas non-pineal TRb showed CSRs of 0% (95%CI: incalculable) and 53% (95%CI: 28%–73%) for <1995 and ≥1995 respectively. Restricted to actively treated patients, pineal TRb showed CSRs of 43% (95%CI: 27%–58%) and 5% (95%CI: 0%–18%) for asymptomatic and symptomatic disease respectively, whereas non-pineal TRb showed CSRs of 31% (95%CI: 10%–56%) and 35% (95%CI: 12%–59%) for asymptomatic and symptomatic disease respectively. Smaller tumor size showed statistically significant better survival in pineal TRb, but not in non-pineal TRb.

Conclusions

Survival has improved considerably over time. It is difficult to pinpoint the exact reason for this improvement as many factors have changed over the years, but the results of this meta-analysis suggest that early detection and proper treatment of subclinical tumors is the key to success, especially in pineoblastoma. However, patients with larger tumors and clinical symptoms also have a chance to survive, especially in non-pineal TRb.

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BASELINE CENTRAL NERVOUS SYSTEM MAGNETIC RESONANCE IMAGING IN RETINOBLASTOMA: A SINGLE INSTITUTION EXPERIENCE IN EARLY DETECTION OF TRILATERAL RETINOBLASTOMA

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Objectives

To report on frequency, as well as on clinical and imaging findings of trilateral retinoblastoma (TRB) from a single-institution retinobastoma (RB) series where a baseline MRI is adopted as routine investigation in all patients at the time of RB diagnosis

Methods

The RB database was checked in order to identify patients with TRB diagnosis from January 1999 to December 2012. All MRI were reviewed for this study.

Results

107 RB patients were diagnosed over 14 years of regular use of baseline MRI screening. Sixty-two patients had unilateral RB and 45 bilateral RB. MRI revealed the presence of TRB in three patients (2.8%) aged 18, 16 and 10 months, respectively. In one patient the TRB was metachronous and in the other 2 patients was synchronous. TRB occurred in 3 out of 45 (6.7%) bilateral RBs and in one out 15 (6.7%) of familial RBs while no TRB was reported in the unilateral group. None of the patients had received prior chemotherapeutic treatment. Seven benign pineal cysts (6,5%) were diagnosed during the same period.

Conclusions

TRB represents a rare condition occurring, in our series, in 3 (2.8%) of all RB patients; its frequency appeared to be higher in bilateral/familial cases. A synchronous presentation seems most frequent when a baseline MRI is performed. Brain MRI is recommended to be performed in each patient with RB for a timely diagnosis. Further analysis on large series should address how to consider and treat small synchronous pineal lesion suggestive for a pineoblastoma.

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ALTERATION OF MITOCHONDRIAL COMPLEX I PROTEIN IN HUMAN RETINOBLASTOMA

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Objectives

Mitochondria are critical for cellular function in cancer and play an important role in cell differentiation and survival. Deficiency of mitochondrial complex I is the most important factor in cancer cells. The purpose of this study was to determine the expression of mitochondrial complex I and the morphological changes of mitochondria in human primary retinoblastoma tissues.

Methods

Expression of mitochondrial complex I was performed in all the 38 cases by immunohistochemistry and then validated by western blotting on representative cases. Morphology of mitochondria was studied by transmission electron microscopy (TEM) in 5 cases.

Results

Deficiency of mitochondrial complex I was found in 29/38 (76.31%) cases by immunohistochemistry. Western blotting was performed to confirm the immunoreactivity results. Electron microscopy showed numerous degenerated and swollen mitochondria in tumor cells. On statistical analysis, the loss of mitochondrial complex I expression correlated significantly with poorly differentiated retinoblastoma and tumor invasion.

Conclusions

This is the first study to show the expression of mitochondrial complex I in retinoblastoma tumor. Electron microscopy revealed that numerous morphological changes in mitochondria which may be due to changes in mitochondrial protein expression. Correlation between mitochondrial D-loop variations and expression of complex I is being investigated. Investigating mtDNA alterations might be helpful for developing biomarkers in the management of retinoblastoma patients.

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Retinoblastoma

HISTOPATHOLOGICAL ANALYSIS OF CELL DIVISION CYCLE 25 (CDC25) PHOSPHATASE PROTEINS IN RETINOBLASTOMA

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Objectives

Retinoblastoma is the most common childhood intraocular malignant tumor of the developing retina . Cell Division Cycle 25 (CDC25) phosphatase is an essential regulator of the cell cycle machinery, functioning as a positive regulator by activating Cyclin-Dependent Kinases (CDK). CDC25A plays a pivotal role in controlling cell proliferation during development and tumorigenesis. Overexpression of CDC25A is detected in a number of tumors which implies dysregulation in malignant transformation. However, the role of CDC25A in patients with Retinoblastoma is still unknown.

Methods

Prospective analyses of 60 primary enucleated retinoblastoma cases over a period of one year (Jan 2011-Dec 2012). CDC25A protein expression was investigated by Immunohistochemistry in formalin fixed paraffin embedded sections and then validated by western blotting. Cytoplasmic staining was graded as weak/negative (1+), moderate (2+) and strong (3+). Semi-quantitative analysis for expression of CDC25A mRNA was performed by the Reverse-Transcriptase PCR (RT-PCR). Expression of CDC25A was correlated with tumor differentiation and various histopathological high risk factors.

Results

There were total of 45 poorly differentiated retinoblastomas and 15 well differentiated retinoblastomas. Necrosis and calcification was found in 37 (61.6%) and 17 (28.3%) respectively. Massive choroidal invasion, optic nerve invasion and scleral invasion was found in 20/60, 17/60 and 7/60 cases respectively. Immunohistochemistry showed CDC25A expression in total of 38/60 (63.3%) cases. Western blotting was performed to confirm immunoreactivity results on representative cases. mRNA expression was seen in 31/60 (51.6%) cases by RT-PCR. Expression of CDC25A showed statistically significant correlation with poor tumour differentiation and tumor invasion ($p<0.05$).

Conclusions

Our results suggest that increased expression of CDC25A plays an important role in the pathogenesis of retinoblastoma. CDC25A was associated with invasion of ocular coats and poor differentiation. CDC25A expression might be a potential molecular target for novel drug development in tumor biology.

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Soft Tissue Sarcomas

A POSSIBLE ROLE FOR THE HEDGEHOG PATHWAY LIGANDS DESERT AND INDIAN IN RHABDOMYOSARCOMA

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Objectives

To establish the mechanism of activation of Hedgehog (HH) pathway in Rhabdomyosarcoma (RMS). More concretely, to elucidate the role of HH ligands -Sonic HH (SHH), Indian HH (IHH) and Desert HH (DHH)- in the pathogenesis of this neoplasia.

Methods

Real-time PCR, Western blot and immunohistochemistry were used to determine HH ligands levels in RMS cell lines and tumor samples. Genetic inhibition of the ligands was performed by shRNAs in the lentiviral vector pGIPZ. Functional assays were performed in order to determine the effects of genetic inhibition of HH ligands in RMS cells.

Results

The mRNA analysis by real-time PCR showed medium or high IHH and DHH expression in all samples analyzed. Conversely, the expression of SHH was shown to be negligible in the majority of samples. However, approximately 30% of patients showed expression of SHH. Western blot and immunohistochemical analysis coincided with the results obtained by real-time PCR. SHH, IHH and DHH levels were correlated with GLI1 expression. SHH and DHH levels showed a significant direct correlations with GLI-1 expression. For IHH a tendency to correlate was observed but no significant correlation was obtained. Genetic inhibition of IHH significantly decreased cell proliferation.

Conclusions

Our results confirm the extremely low levels of SHH expression in the majority of RMS patients (approximately 70%). Interestingly, we found a prominent expression of IHH and DHH ligands in RMS. Together with the direct correlations observed between these two ligands and one of the targets of HH pathway (GLI1), our results support the possible existence of an autocrine ligand-dependent activation of the Hedgehog pathway in this neoplasia. These results suggest that the development of ligand-specific inhibitors may help to specifically inhibit the pathway in ligand-dependent tumors such as RMS, thereby providing a therapeutic alternative beyond cyclopamine derivatives or GLI-inhibitors.

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INFLUENCE OF CYP2B6 POLYMORPHISM ON OUTCOME OF IRS-V TREATED RHABDOMYOSARCOMA PEDIATRIC EGYPTIAN PATIENTS

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Objectives

Cyclophosphamide is a conventional pro-drug used in rhabdomyosarcoma (RMS) and other malignancies. The highly polymorphic CYP2B6 is suggested as a major contributor in cyclophosphamide bioactivation. Polymorphisms of this enzyme may affect drug bioactivation and hence treatment outcome. The aim of this work was to investigate the impact of the CYP2B6 SNPs G516T, A785G and C1459T, on the outcome for cyclophosphamide treated RMS patients, in order to find biomarkers for personalized therapy.

Methods

Germ line DNA samples from 73 RMS patients presented at Children's Cancer Hospital-57357 from December 2010 till December 2012 were genotyped by RFLP for CYP2B6 SNPs G516T, A785G and C1459T. These patients were enrolled on IRS-V protocol based on cyclophosphamide and followed up till March 2014. Clinical data on survival, demographics, pathology, chemotherapy dose and clinical response were collected. We examined the association between these genotypes and overall survival, failure free survival and achievement of complete response.

Results

The CYP2B6-516 in this population was TT in 36(49.3%), 29 cases (39.7%) were GT while it was GG in 8 patients (11%). CYP2B6 c.785G was GG in 33(45.2%) of cases and AG in 32 (43.8%) while it was AA in 8 patient (11%) and CYP2B6 c.1459T which was TT in 24(87.7%) of cases and CT in 8 (11%) while it was CC in 1 patient (14%). 3-years failure free survival was 59.7±10.4% for those with CYP2B6 c.516TT genotype while it was 42.6±8.2% for those with GT or GG genotypes (*p*-value=0.04). 3years- failure free survival was higher in those with type CYP2B6 c. 785 GG and CYP2B6 c. 1459TT compared to those with a mutant genotype yet it was not statistically significant.

Conclusions

CYP2B6 c.516T can be used as a prognostic biomarker for rhabdomyosarcoma patients receiving cyclophosphamide.

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Soft Tissue Sarcomas

EXPRESSION AND LOCALIZATION OF MHC CLASS-I RELATED CHAIN MOLECULES A AND B IN HUMAN RHABDOMYOSARCOMA CELLS

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Objectives

Natural killer (NK) cells are important effector cells for the first line of defense against tumors. The interaction of the MHC class I-related chain molecules A and B (MICA/MICB) with the corresponding natural killer group 2, member D (NKG2D) receptor triggers the cytotoxic effector activity of natural killer cells and certain T-cell subsets. Thus, the presence of MICA/MICB on the surface of tumor cells contributes to the tumor immunosurveillance. In this study, we investigated the expression and localization of MICA/MICB in human rhabdomyosarcoma (RMS) tumors and cell lines.

Methods

The immunohistochemical detection of MICA/MICB was performed using paraffin embedded samples obtained at surgery. The presence of MICA/MICB mRNA and protein in alveolar (RH30) and embryonal (RD, RMS-YM) RMS cells lines were evaluated by RT-PCR and a Western blot analysis. The surface expression levels of MICA/MICB were determined by flow cytometry.

Results

The immunohistochemical staining showed that 21 of 25 clinical tumor samples were positive for either MICA or MICB, while normal striated muscle cells were negative. In all RMS cells lines, MICA mRNA was detected by RT-PCR, whereas no MICB mRNA was detected in the RH30 cells. The Western blot analysis revealed that the MICA protein was presented in all RMS cells lines, as well as the mRNA, and the MICB protein was presented in the RD and RMS-YM cells. However, the surface expression of MICA and MICB was limited with only MICA being detected on RD cells.

Conclusions

Our results suggest that RMS cells have the ability to produce the MICA and MICB proteins, whereas only RD cells expressed MICA on their cell surface. Therefore, since the lack of MIC expression on the surface of RMS tumor cells may lead to the lack of the tumor recognition by NK cells, some modulators of MICA/MICB expression may be helpful to further activate NK cells.

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ALDEHYDE DEHYDROGENASE 1 (ALDH1) IS A POTENTIAL MARKER FOR CANCER STEM-LIKE CELLS IN EMBRYONAL RHABDOMYOSARCOMA

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Objectives

Recent studies have demonstrated aldehyde dehydrogenase 1 (ALDH1) has been detected as the marker for cancer stem-like cells (CSCs) in adult cancers. In pediatric malignant tumors, however, there have been no studies regarding ALDH1 as a marker for CSCs. In this study, we hypothesized a subpopulation of cells with high ALDH1 activity ($ALDH1^{high}$ cells) would have characteristics of CSCs in rhabdomyosarcoma (RMS), and we examined the characteristics of $ALDH1^{high}$ cells in embryonal RMS.

Methods

We used the human embryonal RMS cell line, RD. Cultured cells were sorted into $ALDH1^{high}$ cells and a subpopulation with low ALDH1 activity ($ALDH1^{low}$ cells) using an ALDEFLUOR assay kit. To demonstrate $ALDH1^{high}$ cells had stronger CSCs characteristics than $ALDH1^{low}$ cells, we performed a colony-formation assay, a WST-8 assay *in vitro* and a tumor-initiating assay using immunodeficient mice *in vivo*.

Results

$ALDH1^{high}$ cells comprised 5.8% of all cultured RD cells in ALDEFLUOR assay. In the colony-formation assay to document the self-renewability of the cells, the number of colonies of $ALDH1^{high}$ cells was higher than that of $ALDH1^{low}$ cells (36.3 vs. 21.3 colonies/well, respectively). With regard to chemoresistance, the survival rate of $ALDH1^{high}$ cells was found to be one-and-a-half times as high as that of the $ALDH1^{low}$ cells following treatment with vincristine. The survival rate of $ALDH1^{high}$ cells was 1.9-fold and 1.8-fold compared to $ALDH1^{low}$ cells when cultured with cyclophosphamide and etoposide, respectively. Tumor-formation was found in one of four mice injected with $1x10^3$ $ALDH1^{high}$ cells, and in two of three mice injected with $1x10^4$ $ALDH1^{high}$ cells, whereas no tumors were found in mice injected with $ALDH1^{low}$ cells at either cell density.

Conclusions

We confirmed the $ALDH1^{high}$ RD cells had characteristics of CSC, including colony-formation, chemoresistance
and tumor-initiation. These results suggest ALDH1 is a potentially useful marker of CSCs in embryonal RMS.

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Soft Tissue Sarcomas

NOVEL SECONDARY SOMATIC MUTATIONS IN EWING'S SARCOMA AND DESMOPLASTIC SMALL ROUND CELL TUMORS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

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Objectives

Ewing's sarcoma (ES) and desmoplastic small round cell tumors (DSRCT) are related small round blue cell tumors driven by an N-terminal containing EWS translocation. Very few somatic mutations have been reported in ES, and none have been identified in DSRCT. The aim of this study is to explore potential actionable mutations in ES and DSRCT.

Methods

Twenty eight patients with ES or DSRCT had tumor tissue available that could be analyzed by one of the following methods: 1) Next-generation exome sequencing platform; 2) Multiplex PCR/Mass Spectroscopy; 3) Polymerase chain reaction (PCR)-based single- gene mutation screening 4) Sanger sequencing

Results

Actionable somatic mutations were identified in four out of 18 patients with advanced ES and two of 10 patients with advanced DSRCT (six out of 28 (21.4%));*KRAS* (n=1), *PTPRD* (n=1), *GRB10* (n=2), *c-MET* (n=2) *and PIK3CA* (n=1). One patient with both PTPRD and GRB10 mutations and one with a GRB10 mutation achieved a complete remission (CR) on an Insulin like growth factor 1 receptor (IGF1R) inhibitor based treatment. One patient who achieved a partial remission (PR) with IGF1R inhibitor treatment later developed resistance demonstrated a *KRAS* mutation in the post-treatment resistant tumor, but not in the pre-treatment tumor suggesting that the RAF/RAS/ MEK pathway was activated with progression.

Conclusions

We have reported several different mutations in advanced ES and DSRCT that have direct implications for molecularly-directed targeted therapy. Our technology agnostic approach provides an initial mutational roadmap used in the path towards individualized combination therapy.

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Soft Tissue Sarcomas

DOES ROUTINE IMAGING IN CHILDHOOD RHABDOMYOSARCOMA IMPROVE PATIENT SURVIVAL?

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Objectives

While routine imaging is often obtained for surveillance of disease relapse or response assessment in children with rhabdomyosarcoma, there is no evidence whether imaging improves patient outcomes. We compared survival in patients in whom relapse was detected on the basis of clinical symptoms versus routine imaging.

Methods

Forty-three children with relapsed rhabdomyosarcoma treated at Texas Children's Hospital from 1993-2012 were identified. Overall survival (OS) time after relapse was compared between two groups: (1) patients presenting with a symptom related to relapse; and (2) patients whose relapse was initially detected by imaging prior to symptoms. Differences in survival time were evaluated with Kaplan-Meier analysis with bivariate adjustment for age, stage, Clinical Group, and histology at diagnosis.

Results

Forty-three children with relapsed rhabdomyosarcoma treated at Texas Children's Hospital from 1993-2012 were identified. Overall survival (OS) time after relapse was compared between two groups: (1) patients presenting with a symptom related to relapse; and (2) patients whose relapse was initially detected by imaging prior to symptoms. Differences in survival time were evaluated with Kaplan-Meier analysis with bivariate adjustment for age, stage, Clinical Group, and histology at diagnosis.

Conclusions

Our results suggest that routine imaging surveillance for relapsed disease in children with rhabdomyosarcoma is not associated with longer patient survival. Validation of these results in a larger study and more limited use of surveillance imaging could reduce medical costs and radiation exposure without compromising patient outcome.

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THE IMPACT OF RESPONSE TO INDUCTION CHEMOTHERAPY ON SURVIVAL AND LOCAL CONTROL IN EMBRYONAL PARAMENINGEAL RHABDOMYOSARCOMA

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Objectives

Disease control remains a challenge in pediatric parameningeal rhabdomyosarcoma (PM-RMS). In this study we set out to identify predictors of failure in PM-RMS.

Methods

We identified 25 patients with localized, non-metastatic embryonal PM-RMS, age 2-18 years, without surgical resection. 24 of 25 patients had complete MRI imaging data. All patients were treated with chemotherapy followed by proton therapy, median dose 50.4 Gy_{RBE} (50.4-55.8 Gy_{RBE}). Tumor volumes were determined prior to initial chemotherapy and prior to proton therapy (after induction chemotherapy). The dimensions of each tumor were measured on MRI and ellipsoid tumor volumes were calculated using the formula $4/3\pi(r1 \times r2 \times r3)$.

Results

Median follow was 3.1 years. Actuarial 3-year FFS and OS were 52% (95% CI, 30% to 70%), and 64% (95% CI, 40% to 80%) respectively. Local failure (LF) predominated, seen in 9 of 12 failures with a 3-year cumulative incidence of LF of 41% (95% CI, 24% to 65%). Median time from initiation of CT to start of RT was 4.8 weeks. Patients with LF had a greater median pre-radiotherapy (pre-RT) volume compared to those with LC (40 cm^3 vs 7 cm^3) and a smaller relative percent reduction in tumor size after initial chemotherapy (6% vs 78%). Both pre-RT tumor volume and relative percent reduction in tumor volume were significantly associated with LF ($p=0.03$ and $p=0.003$, respectively, on univariate Cox regression) and FFS ($p=0.05$ and $p=0.01$, respectively). Other factors including age, sex, initial tumor volume, interval between CT and RT, and intracranial extension were not associated with LF or FFS

Conclusions

Poor response to induction chemotherapy appears to be associated with an increased risk of LF, FFS, and OS in pediatric embryonal PM-RMS

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Soft Tissue Sarcomas

RESULTS OF THE JAPAN RHABDOMYOSARCOMA STUDY GROUP JRS-I LRA0401 PROTOCOL, USING VINCRISTINE, DACTINOMYCIN AND CYCLOPHOSPHAMIDE AND RADIATION THERAPY, FOR LOW-RISK EMBRYONAL RHABDOMYOSARCOMA

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Objectives

Patients with localized, grossly resected, or gross residual (orbital only) embryonal rhabdomyosarcoma (ERMS) had 5-year failure-free survival (FFS) rates of 93% and overall survival (OS) rates of 98% using Intergroup Rhabdomyosarcoma Study Group protocol IV. However, the protocol prescribed 26.4 g/m^2 of cyclophosphamide, which causes infertility. JRS-I LRA0401 protocol objectives included reducing the cyclophosphamide dose to 9.6 g/m^2, which could keep fertility.

Methods

Subgroup A patients (lowest risk, with ERMS, stage 1 group I/IIA, stage 1 group III orbit, stage 2 group I) received 8 cycles (24 weeks) of vincristine, dactinomycin and 1.2 g/m^2/cycle cyclophosphamide (VAC1.2) therapy. Patients in group II/III received radiotherapy: 36 Gy for stage 1 group IIA patients and 45 Gy for group III orbit patients.

Results

Three-year PFS rates were 92% (95% CI, 76% to 100%) and 3-year OS rates were 100% for subgroup A patients (n = 12). Median follow-up was 5.6 years. Among five Group III patients, three patients achieved a best response of CR and two achieved a best response of PR. Adverse events included neutropenia (100%), anemia (67%), thrombocytopenia (58%), nausea (50%), stomatitis (25%), peripheral neuropathy (17%) and constipation (25%). Administration of vincristine and dactinomycin was reduced in two cases who developed veno-occlusive disease. Late effects of orbital primary tumor included cataracts in three cases and ptosis and eye movement disorder in two cases. Bladder wall thickening, vesicoureteral reflux and hydronephrosis were observed in one

case of paratesticular primary tumor. A cosmetic problem arose in the case of a head and neck primary tumor. No protocol-related mortality occurred.

Conclusions

No significant therapy-related toxicity occurred using 9.6 g/m^2 of cyclophosphamide. The survival rates were similar to those of the previous low-risk protocols of other study groups.

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Soft Tissue Sarcomas

A DOSIMETRIC COMPARISON OF PROTON RADIOTHERAPY AND IMRT IN PEDIATRIC RMS PATIENTS ENROLLED ON A PHASE II PROTON STUDY

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Objectives

With chemotherapy and radiation, pediatric rhabdomyosarcoma (RMS) is highly curable. However, cure may come with significant radiation related toxicities in exposed developing tissues. Proton therapy (PT) may spare excess dose to normal structures potentially reducing the incidence of adverse effects.

Methods

Between 2005 and 2012, 54 patients were enrolled on a prospective phase II trial of PT in pediatric RMS. Intensity modulated radiation therapy (IMRT) plans were generated for comparison to clinical PT plans. Clinical target and normal tissue volumes were held constant and IMRT plans optimized for target volume coverage and normal tissue sparing according to COG protocol guidelines.

Results

Target coverage was comparable between PT and IMRT plans with a mean CTV V_{95} of 100% for both modalities (p=0.82). However, integral dose was 1.8 times higher for IMRT (range 1.0-4.9). By site; integral dose for IMRT was 1.8 times higher for H&N pts (p<0.01), 2.0 times higher for GU (p=0.02) and trunk/extremity pts (p<0.01), and 3.5 times higher for orbital pts (p<0.01). Significant sparing was seen with PT in 32 of 40 critical structures assessed. Mean temporal lobe V_{20} and V_{30} were 2.0 and 1.7 times higher and mean hypothalamic dose 1.8 times higher for IMRT plans in H&N and orbital sites (p< 0.01 for all cases). Lens dose of >6 Gy was seen in 16 (21%) of PT patients and 35 (45%) of IMRT patients (p< 0.01). Mean testicular dose was 0.5 Gy for PT and 5 Gy for IMRT (p< 0.01). Mean ovarian dose was 2 Gy for PT and 10 Gy for IMRT (p=0.05). Pelvic growth plate V_{30} was 14% for PT and 68% for IMRT (p=0.02).

Conclusions

Proton radiation lowers integral dose and improves normal tissue sparing when compared to IMRT for pediatric RMS. Correlation with clinical outcomes is necessary.

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Soft Tissue Sarcomas

PROFILE AND OUTCOME OF CHILDREN WITH RHABDOMYOSARCOMA: 23-YEARS EXPERIENCE FROM PGIMER, CHANDIGARH, INDIA

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Objectives

The aim was retrospective evaluation of the clinico-investigational profile and outcome of children with Rhabdomyosarcoma (RMS) from a single center.

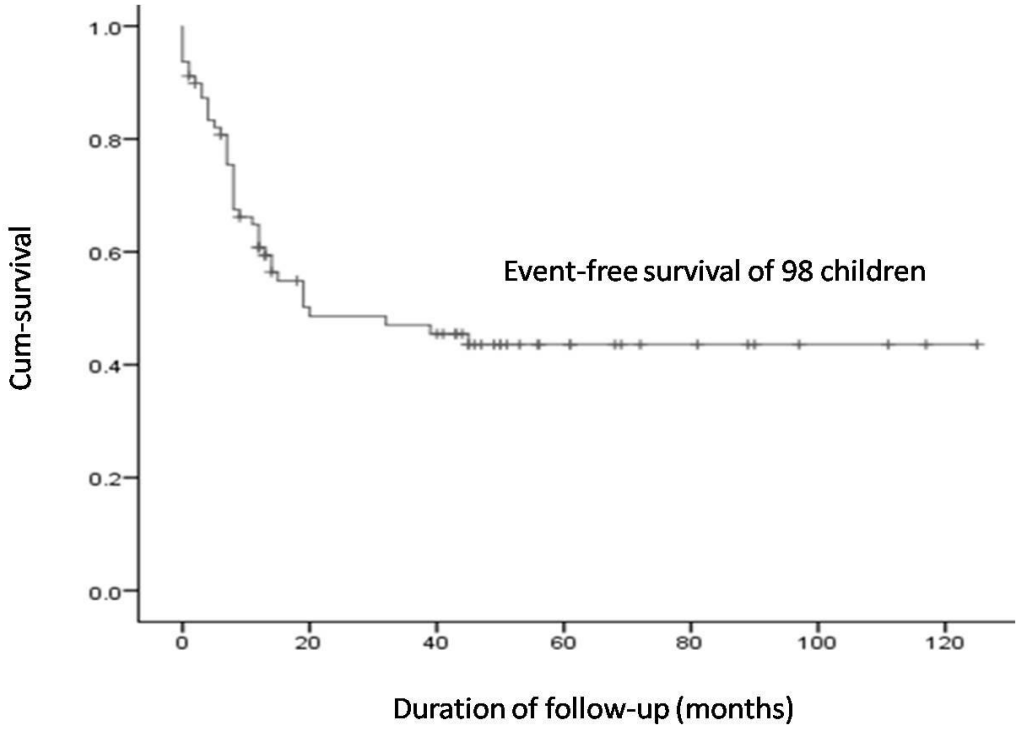
Methods

The case records of children with RMS from 1990-2012 were analyzed.

Results

Case records of 159 children were examined. Median age at presentation was 4 years (interquartile range (IQR): 2-7). The M:F ratio was 2.3:1. The mean symptom-diagnosis interval was 2 months (IQR: 1-5). There were 20 (13%) infants; 5 (3%) had congenital RMS. Frequent sites of involvement included head/neck (44%) and genitourinary (18%); 67% were at an unfavorable site. A majority (43%) of tumors were >5 cms. The most-common pathology was embryonal (61%); pathology was not-specified in 30%. Risk-categorization: 33% low-risk, 56% intermediate-risk and 11% high-risk. Treatment included neo-adjuvant chemotherapy and surgical excision, if feasible, followed by radiotherapy for residual disease and inoperable tumors, as well as chemotherapy. Low risk patients were given vincristine and actinomycin-D for 26 weeks, while intermediate and high risk groups received vincristine, actinomycin-D, cyclophosphamide, doxorubicin and etoposide for 40 weeks. Treatment refusal (18%) and abandonment (33%) were major concerns. Among the 129 patients who opted for treatment, surgery was performed in 63 (49%); 54 (42%) received radiotherapy. Of the evaluable 77 patients, 5 (6.5%) died of febrile neutropenia, 7 (9%) had progressive disease, while 29 (38%) relapsed. The mean time to relapse was 11 months (IQR 7-15). There are 36 (47%) survivors, free of disease, on follow for a mean duration of 4.4±2.6 years. The 5-year

event free survival was 43.6±6%.



Conclusions

In a large study on pediatric RMS from India, the 5-year event free survival was 43.6±6%. Treatment abandonment was a major concern, particularly in the early years. The unit has strengthened the management strategy by initiating several remedial measures.

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Soft Tissue Sarcomas

LONG TERM OUTCOME OF ORBITAL RHABDOMYOSARCOMA IN CHILDREN: EXPERIENCE OF THE INSTITUT CURIE

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Objectives

Localized rhabdomyosarcoma is associated with a good survival rate, and considered as a favorable site when primary concerns orbit (ORMS). Treatment is based on a poly-chemotherapy associated to the best local therapy, sometime surgery but more often radiation therapy, regarding to initial tumor features and tumor response.

Methods

A retrospective monocentric analyze was set up to better define long-term outcome of patients with localized ORMS, parameningeal or not, treated in the Institut Curie between 1975 and 2010, in order to better define patients that can avoid aggressive local treatment at diagnosis. **Results**

Ninety-five patients were analyzed. Median age at diagnosis was 6 years [Ranges: 8months -19 years], and median follow-up was 8.5 years [Ranges: 7 months -24 years]. Parameningeal extension was present for 25 patients. Irradiation therapy was part of primary therapy for 79 patients. At 5 years, event-free (EFS) and overall survivals (OS) were respectively 65.4 ± 5.2% and 85.6 ± 3.9 %. EFS was similar for parameningeal and non-parameningeal tumors (60.3 ± 10.4% vs. 62.7 ± 5.9%; P= 0.07) whereas OS was significantly better for non-parameningeal tumors (90 ± 3.9% vs. 72.7 ± 9.6%, P=0.0496).). In multivariate analysis, initial tumor size remains statistically significant after adjustment on radiation therapy treatment (P<0.015), whereas radiation therapy as first line was no longer a statistical prognosis factor for OS after adjustment on tumor and treatment characteristics (P>0.64).

Conclusions

Localized ORMS remains a location with favorable outcome despite the actual tendency to reduce the agressivity and the indications of local therapy source of ophthalmologic and structural late effects. Patients with favorable pattern of strict ORMS can be treated without radiation therapy in first line treatment. ORMS with parameningeal extension should receive additional radiotherapy.

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Soft Tissue Sarcomas

RETROSPECTIVE ANALYSIS OF OUTCOMES OF PATIENTS WITH RELAPSED, REFRACTORY AND METASTATIC SARCOMAS WHO HAVE RECEIVED METRONOMIC CHEMOTHERAPY

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Objectives

To study the efficacy and tolerability of metronomic therapy with tamoxifen, etoposide and cyclophosphamide in refractory, relapsed and metastatic soft tissue sarcoma (Ewing Sarcoma; Rhabdomyosarcoma; and other Soft Tissue Sarcomas).

Methods

This is retrospective, single institutional, observational study. We retrospectively reviewed data of patients with relapsed, refractory or metastatic soft tissue sarcoma (STS) [Ewing Sarcoma (ES);Rhabdomysarcoma (RMS) or STS] who were treated with the metronomic protocol of oral Tamoxifen, Etoposide and Cyclophosphamide (TEC) during the period April 1998 to September 2013.Approval was obtained from the Institutional Review Board and waiver of consent was granted. The patients included in the analysis were those who had relapsed after the primary protocols and then treated with metronomic TEC protocol; or those with primary refractory or metastatic disease (RMS, ES) and received metronomic TEC therapy.

Results

49 patients were enrolled. Among the 49 patients, 32 were diagnosed ES, 13 RMS and 4 other STS. For the whole cohort response rates (RR) were 59% and clinical benefit rate (CBR) was 79%. Patients in the study were grouped into the following subgroups. Systemic recurrent/relapsed disease (N=24), metastatic disease at presentation (N=15) and local disease (refractory/recurrent) (N=10). None of the patients required blood or platelet support or admission for supportive care. The median PFS and OS was 12.35 months and 26.184 months for patients respectively with systemic recurrence v/s 16.8 months and 22.08 months for respectively for patients with primary metastatic disease and was best at 126.68 months and 138.87 months respectively for patients with locally recurrent/residual disease.

Conclusions

This study provides a preliminary evidence efficacy and tolerability of metronomic chemotherapy in poor risk ES and RMS. It also demonstrates that with this low cost low risk treatment few patients could go into long term remissions despite high disease burden. Also When given as maintenance therapy it shows excellent long term outcomes.

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SYNOVIAL SARCOMA RELAPSES IN CHILDREN AND ADOLESCENTS: PROGNOSTIC FACTORS, TREATMENT AND OUTCOME

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Objectives

Twenty-five to 32% of patients with synovial sarcoma (SS) relapse after appropriate treatment, and experience a poor outcome. Patients who can be salvaged by second-line therapy need to be more clearly identified.

Methods

Data of patients treated in SFCE (*Société Française des Cancers de l'Enfant*) centers with an initial diagnosis of localized SS before the age of 18 years and treated from 1/1988 to 12/2008, and who experienced at least one relapse were retrieved. After descriptive analysis, statistical analysis was performed to determine prognostic factors.

Results

Thirty-seven patients were identified. First relapse occurred after a median interval of 24 months and was localized in 73.0% of cases and metastatic in 24.3% of cases. Treatment of relapse consisted of new surgery in 75.7% of cases, second-line chemotherapy in 73.0% of cases and radiotherapy in 48.6% of cases. Response rate to ifosfamide-based regimens was 36.4%. Overall, 70.3% patients achieved a second complete remission. Median 5-year-event-free survival was 32.8% and 5-year overall survival was 42.1%. Factors significantly correlated with better survival were primary tumor involving the limbs, age less than 12 years at diagnosis, absence of chemotherapy or radiotherapy as initial treatment and local relapse.

Conclusions

Despite its poor overall outcome, relapse of synovial sarcoma sometimes remains curable. Aggressive surgery, when possible, in combination with chemotherapy and radiotherapy is the recommended treatment. Ifosfamide-based regimens may remain effective in patients with relapsed SS. However, alternative therapies should be proposed in patients with poor prognostic factors.

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Soft Tissue Sarcomas

THE ROLE OF PROGNOSTIC FACTORS IN SOFT TISSUE SARCOMAS OF NEUROGENIC ORIGIN (MPNST) IN CHILDREN TREATED WITH CWS PROTOCOLS BETWEEN 1992 AND 2013

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Objectives

The aim of the study was to assess the role of particular clinical prognostic factors in childhood soft tissue sarcomas of neurogenic origin (MPNST).

Methods

The study included 50 children with MPNST (M/F: 26/24, age 2-214 months; M: 142 months) treated with CWS protocols in Polish centers of pediatric oncology between 1992 and 2013.

Results

Neurofibromatosis type 1 (NF1) was found in 32% of patients. Over 70% of children presented with extensive invasive tumors (T2b). In 82%, only a diagnostic biopsy of primary tumor or R2 surgery was made. CR and PR response rate after CHT was 58%. Delayed surgery was done in 34% (R0 in most). Radiotherapy (RTX) in the Ist line therapy was used in 28% of patients. Recurrences occurred in 54%, including as many as 7/8 children initially qualified as IRS I and II. 42% of patients died of PD, 44% are alive in CR (FU 17 months-14 years). Negative prognostic factors for 5-y-OS included: tumor located retroperitoneally and in internal organs, tumor size> 10 cm and the coexistence of NF1. Failure to carry out complete resection of the tumor at any stage of the disease significantly worsened EFS and OS. Response to CHT depended only on the presence of NF1 and affected the 5-y-EFS significantly.

Conclusions

1. High rate of local recurrences after R0 primary surgery suggests an underestimation of MPNST stages.
2. Patients after R1 primary resection require adjuvant local therapy (surgical and/or RTX).
3. Complete resection of the tumor at any stage of the disease should be aimed, as it significantly improves the prognosis (77% of survivors had primary or secondary R0 resection).
4. A sustained CR after CHT is unlikely, however, CHT may prevent the metastatic recurrence.
5. The coexistence of NF1 significantly worsens the prognosis in children with MPNST.

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PHASE 2 STUDY OF SUNITINIB, AN ORAL MULTI-TARGETED TYROSINE KINASE INHIBITOR IN SUBJECTS WITH NF1 PLEXIFORM NEUROFIBROMAS: AN UPDATE

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Purpose. Sunitinib malate is an orally bioavailable, competitive inhibitor of vascular endothelial growth factor (VEGFR), platelet-derived growth factor (PDGFR), proto-oncogene c-KIT, and Fms-like tyrosine kinase 3 (FLT-3). This phase 2 efficacy trial is evaluating two cohorts of subjects, adult and pediatric, with NF1 and clinically significant plexiform neurofibromas. The primary response indicator is tumor response by 2D and 3D MRI imaging. Secondary response indicators include volumetric MRI imaging, quality of life measure, biomarker evaluation of cytokines and endothelial progenitor cells, and pain-related outcomes.

To assess a secondary response indicator i.e. pain in subjects with at least 6 months of follow-up.

Methods

Frequency, severity of pain, and medication usage was documented at initial enrollment visit and at 6 month follow-up for subjects on Sunitinib. Data from patients treated with Imatinib was obtained from retrospective chart review.

Results

To date 21/40 subjects have been enrolled, with 19 evaluable, consisting of 4 adult and 15 pediatric patients. Two subjects have completed the study, one with stable disease, and another with progressive disease. Two subjects withdrew from the study prior to being evaluated. Patients with at least 6 months of follow-up report 62.5% less pain, and 50% have decreased pain medication utilization, and no patients complained of either increased pain or pain medication usage. No subjects reported an increase in pain or in use of pain medication. When compared to patients treated with imatinib, patients treated with Sunitinib report statistically less pain ($p<0.0001$) and less pain medication usage ($p=0.0011$).

Conclusions

Limited patient follow-up data is currently available for other response indicators, but pain response as a secondary indicator and major contributor to quality of life and daily functioning for subjects on trial is encouraging.

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Soft Tissue Sarcomas

KAPOSI'S SARCOMA IN CHILDREN: AN OPEN RANDOMISED TRIAL OF VINCRISTINE, ORAL ETOPOSIDE AND A COMBINATION OF VINCRISTINE AND BLEOMYCIN

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Objectives

Introduction

Kaposi's sarcoma (KS) is a common childhood cancer in places where HIV is endemic and access to antiretroviral therapy (ART) is delayed. Despite this there are no randomised trials to compare and assess chemotherapeutic regimens.

Methods

An open label, randomised trial comparing intravenous vincristine alone, vincristine and bleomycin, and oral etoposide, was carried out in children with Kaposi's sarcoma in the Queen Elizabeth Central Hospital, Blantyre, Malawi. HIV infected children were given ART after 2 to 3 courses of chemotherapy if they were not already on treatment. Neither HIV nor widespread KS are curable and treatment is aimed at disease reduction and improved quality of life. Tumour reduction was assessed by measuring the size of sentinel KS nodules and quality of life (QoL) by using the Lansky score. Follow up was until death or for one year.

Results

92 children were enrolled of whom 46% were naïve to ART; 10 (11%) were HIV negative. Survival was not influenced by age or gender but was better in the oral etoposide and the vincristine and bleomycin groups. P=0.0045. The group receiving oral etoposide had a better quality of life. Toxicity was not significant, and any drop in haemoglobin or white cell count could have been causally related to HIV infection rather than cytotoxic therapy.

Conclusions

Oral etoposide is a safe, effective treatment to contain KS and improve QoL which can be achieved without many visits to hospital and intravenous injections.

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Supportive Care/Palliative Care

HEALTH CARE UTILIZATION AND COSTS IN THE LAST YEAR OF LIFE FOR CHILDREN WITH MALIGNANCIES

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Objectives

Little is known about how children with malignancies utilize health care in the last year of life. Our objectives were: to describe the duration and costs of admissions in the last year of life for children with malignancies who died in one of 40 U.S. children's hospitals; and to examine hospital resource use in the terminal admission.

Methods

We studied 455 children with malignancies, ages 1-18 years, who died in 2012. Data were obtained from the Pediatric Health Information System database. Malignancies were identified using ICD-9 codes. We assessed hospital days (total and intensive care unit) and hospital costs, stratified by class of malignancy (solid vs. hematologic), in the last year of life. We also characterized hospital days and interventions received in the terminal admission.

Results

Median age at death was 9 years (IQR 4-15). 42% of children were non-Hispanic white; 68% had public insurance. In the last year of life, children with malignancies spent a median of 59 days in the hospital (IQR 22-113) and 6 days in the ICU (IQR 1-18). Compared to children with solid malignancies, children with hematologic malignancies (N=204) had higher median hospital days and costs [median 85.5 hospital days (IQR 33.5-138); median cost $420,203 (IQR $170,531-$782,062)].

In the terminal admission, 322 children (71%) had unplanned hospitalizations. Children spent a median of 14 days (IQR 4-36) admitted, with 2 median ICU days (IQR 0-11). 55% of children were mechanically ventilated by this time; 36% visited the operating room in the terminal admission itself.

Conclusions

Children with malignancies experience lengthy, costly hospitalizations in the last year of life and undergo invasive procedures in the terminal admission. Children with hematologic malignancies appear to have the highest costs. Further investigation may reveal whether palliative care intervention for these children might improve hospital utilization and quality of life.

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Supportive Care/Palliative Care

ASSESSMENT OF INVISIBLE FINANCIAL BURDEN FACED BY FAMILIES WITH CANCER CHILDREN IN A DEVELOPING COUNTRY

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Objectives

The diagnosis of cancer in a child is a family crisis. The costs of treatment are not only direct medical expenses but also non-medical expenses and loss of pay. Though, the existence of financial strain is well known, it is not studied systemically and under-researched in medical literature especially in developing countries like India.
The principle objectives of this study are to systemically review the financial burden including invisible expenses incurred by the families of children with cancer from a social perspective.

Methods

70 families with children undergoing treatment participated in the study. The parents/guardians were interviewed in a prepared questionnaire session. Study Period - Aug 2012 -Aug 2013.

Results

Of the 70 patients with hematological malignancies, with 69% boys and 31% girls, the mean age was 7.8 ± 2.2 years. 54% of the patients household annual income ranged between Rs.60,000-1,19,999. Non-medical expenses accounts for about 46% of their monthly household income of parents from rural areas and 22% of their household income from urban areas. Out-of-pocket expenses for food and travel have emerged as a major contributing factor for severe economic effect on the family. 63% of patients used public transport like trains or buses for travel for treatments and follow–up. Invisible expenses (loss of pay) are seen more often with working mothers than with fathers.Households with multiple children have restricted the need for other siblings to provide for the diseased child. 38% of families have borrowed money from money lenders with an average interest rate of about 12.5% which pushes them to a state of debt for the next few years.

Conclusions

By bringing the financial burden experienced by the families to limelight especially the invisible expenses, the issue can be taken into serious consideration during healthcare planning and policy making.

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APREPITANT AS AN ADD-ON THERAPY IN CHILDREN RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

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Objectives

Aprepitant, a neurokinin-1 receptor antagonist, in combination with 5 HT-3 antagonist and dexamethasone is recommended in adults receiving moderately and highly emetogenic chemotherapy to reduce chemotherapy-induced nausea and vomiting (CINV). Data for use of aprepitant in children are limited and are not included in guidelines for prevention of CINV.

Methods

A randomized double-blind placebo-controlled trial was conducted at a single center in chemotherapy naïve children (5-18 years) receiving highly emetogenic chemotherapy. All patients received intravenous ondanseteron (0·15 mg/kg) and dexamethasone (0·15 mg/kg) prior to chemotherapy. Patients randomly assigned to aprepitant arm received oral aprepitant (15-40kg: days 1-3 80mg; 41-65kg: day1: 125mg and days 2-3 80mg) one hour before chemotherapy. Primary outcome measure was incidence of acute moderate and severe vomiting. Control group received placebo as add-on therapy.

Results

Of 96 randomized patients, three were excluded from analysis; 93 patients were analyzed (50 in aprepitant arm and 43 in placebo arm). Acute moderate and severe vomiting was reported in 72·09% patients receiving placebo and 38% patients receiving aprepitant (p=0·001). During acute phase of assessment, oral intake including fluid and food was significantly decreased in control group when compared with aprepitant arm (72·09% vs 52%, p=0·047; 62·47% vs 38%, p=0·031 respectively). No major adverse effects were noted.

	Placebo	**Aprepitant**	**Difference (95%CI)**	**p**
Acute Nil-mild Moderate-severe	12 (27·91%) 31 (72·09%)	31 (62%) 19 (38%)	34 (15-53)%	0·001
Delayed Nil-mild Moderate-severe	19 (44·19%) 24 (55·81%)	29 (58%) 20 (42%)	14 (0-34)%	0·18
Overall Nil-mild Moderate-severe	7 (16·28%) 36 (83·72%)	22 (44%) 28 (56%)	28 (10-46)%	0·004

Conclusions

This is the first double blinded, randomized placebo controlled trial which unequivocally shows that aprepitant significantly decreases incidence of acute moderate and severe vomiting when used as an add-on drug with ondanseteron and dexamethasone in children receiving highly emetogenic chemotherapy.
(ClinicalTrials.gov Identifier: NCT01402024)

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Supportive Care/Palliative Care

CLINICAL PRACTICE GUIDELINE ON THE PROPHYLACTIC USE OF GRANULOCYTE COLONY-STIMULATING FACTOR ON NEUTROPENIA INDUCED BY CHEMOTHERAPY IN PEDIATRIC PATIENTS

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Objectives

Febrile neutropenia is a complication of treatment for cancer. This is prevented with the use of Granulocyte Colony-Stimulating Factor (GCSF). There are two preparations (conventional and pegylated) but there are inconsistent reports about their efficacy; for this reason a clinical practice guideline was made to compare which preparation is more effective and safe in the prophylactic use in pediatric patients and establish recommendations on its administration.

Methods

The search was done in MEDLINE, EMBASE, The Cochrane Library, Lilacs, until June of 2013 using this MeSH terms: *Granulocyte colony-stimulating factor, pegylated granulocyte colony-stimulating factor, neutropenia, lymphoma, or neoplasms, or leukemia, trials and children*. We analyzed the risk of bias of these studies by 2 reviewers with the "risk of bias" of the Cochrane tool. The results were divided according to type of cancer and meta-analysis was applied with random effects model; the recommendations were generated by Delphi panel.

Results

Of 1776 trials only 27 studies were included (3,661 patients). We observed that in patients with leukemia treated with the conventional form factor, the reduction of the risk and duration of febrile neutropenia (RR=0.747; 95% 0.46-1.20; p=0.014 and SMD -0.838; 95% CI-1.43 to - 0.24 respectively); was lower compared with the pegylated form (RR= 0.10; 95% 0.051 to 0.21; (p = 0.000) but with an increase not significant in the risk of developing bone pain (RR= 2.74; 95% 0.308 to 24.51); (p= 0.081).

Conclusions

Based in the evidence, the experts recommended the prophylactic use of pegylated factor to reduce the risk of febrile neutropenia because it was more effective compared with the conventional form, in pediatric patients who receive chemotherapy, despite the increased risk of bone pain. It is necessary to perform more clinical trials to strengthen evidence.

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Supportive Care/Palliative Care

ORAL VS INTRAVENOUS ANTIBIOTICS IN LOW RISK PAEDIATRIC FEBRILE NEUTROPENIA: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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Objectives

Sepsis is a major cause of morbidity and mortality in paediatric oncology patients, particularly during periods of neutropenia, which is a well-recognised complication of immunosuppressive therapy. Stratification of patients into low and high-risk categories has facilitated a new tailored approach to empiric therapy. The availability of oral antimicrobial drugs with broad-spectrum activity against common pathogens may provide an attractive alternative.

The aims were to determine whether, in low-risk febrile neutropenic paediatric populations, oral antibiotics are as effective as intravenous antibiotics in obtaining resolution of the febrile neutropenic episode.

Methods

A comprehensive literature search of MEDLINE, EMBASE and CENTRAL identified prospective, randomised controlled trials comparing oral antibiotics to intravenous antibiotics in the treatment of febrile neutropenic episodes in low-risk paediatric oncology patients. Outcomes assessed were mortality, rate of treatment failure, length of the febrile neutropenic episode and adverse events. The random effects model was used to calculate risk ratios (RR) for dichotomous data and mean difference with standard deviation for continuous data.

Results

Seven trials were included in the overall analysis, which included 934 episodes of febrile neutropenia in 676 patients aged between 9 months and 20 years. The overall treatment failure rates were not significantly different between oral and intravenous antibiotics (RR: 1.02, 95% CI 0.78 to 1.32, p=0.91).

Conclusions

In carefully selected low-risk febrile neutropenic children, empiric treatment with oral antibiotics is a safe and effective alternative to intravenous antibiotics, as they lower the cost of treatment, and psychosocial burden on these children and their families.

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Supportive Care/Palliative Care

BACTERIAL SPECTRUM AND ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF BLOOD STREAM INFECTIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA CHILDREN WITH FEBRILE NEUTROPENIA AT CHILDREN CANCER HOSPITAL

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Objectives

Bacterial infections are the major cause of morbidity and mortality in chemotherapy induced febrile neotropenic patients. Regular monitoring of bacterial epidemiology allows evaluation of antibacterial strategies. Purpose of this study is to identify the type of organisms and antibiotic resistance pattern. It is necessary to know the category of resistance organisms before starting the antibiotic.

Methods

Data was retrospectively collected from medical records at CCH. Patients who were diagnosed with ALL and had chemotherapy induced febrile neutropenia along with positive culture between January and December 2013 were analyzed.

Results

30 patients were studied over the period of one year, 20 males and 10 females with the median age of 7 years. 25 patients presented with febrile neutropenia during their induction phase, 3 patients while consolidation and the remaining 2 during re-intensification. The induction phase of treatment in acute leukemia is the major cause of FN in hematological malignancies at the children cancer hospital. According to preliminary analysis of the pathogens, 47% of the isolates were gram-negative organisms, 40% were gram-positive organisms, and 13% were fungi. The most populous gram-positive organism isolated was coagulase negative staphylococcus (30%), followed by vancomycin-resistant enterococcus (6.67%). For the gram negatives, Pseudomonas was isolated in majority (16.67%). Coagulase negative staphylococcus was resistant to oxacillin (32%), levofloxacin (37%) but not to vancomycin until now. Enteroccocus was resistant to vancomycin, levofloxacin and amikcin but only sensitive to linezolid (100%). Pseudomonas was mostly sensitive to most antimicrobials; Meronium, Tazocin, levofloxacin, Polymixin B and Amikcin.

Conclusions

Cougulase negative staph was mostly found in our study and that can be controlled with the help of effective infection control. Antibiotic cycling for neutropenic fever was implemented and followed over an extended time period. Gram-negative resistance remained stable. Further study is necessary to clarify the effect of cycling on antibiotic resistance, patient outcomes, and hospital cost.

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Supportive Care/Palliative Care

PRESERVATION OF VARICELLA SEROLOGY TITERS IN PEDIATRIC ONCOLOGY PATIENTS FOLLOWING CHEMOTHERAPY

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Objectives

For pediatric oncology patients, current practice includes administering Varicella-Zoster Immunoglobulin (VZIG) as post-exposure prophylaxis (PEP) against Varicella-Zoster Virus (VZV) and isolating patients for 8 to 21 days. Pediatric oncology patients immune to VZV prior to their cancer diagnosis represent a population likely to preserve immunity against the disease. For these patients population the need for VZIG and isolation is poorly validated and may be an undue health care cost and inconvenience to patients. Therefore, we assessed VZV serology post-chemotherapy as a marker for persistence of immunity against VZV while on chemotherapy.

Methods

Approval from the research ethics board at the Children's Hospital of Eastern Ontario (CHEO) was obtained prior to this study. Varicella antibody titers were collected from 500 pediatric oncology patients treated at CHEO. Patients included in this study had positive titers at the time of their malignancy diagnosis and VZV antibody titers were re-tested at 6-months or 1-year post-chemotherapy treatment.

Results

Of the eligible 190 patients with positive antibody titers to VZV at time of malignancy diagnosis, 139 (73%), 16 (8%), and 5 (2.3%) patients had positive, negative or equivocal post chemotherapy VZV antibody titers, respectively. Moreover, 19 (10%) had varicella breakthrough disease and 11 (5.7%) developed zoster during chemotherapy or post-chemotherapy but prior to re-testing for VZV antibody titers. There was no correlation between age or tumour type with preservation of VZV antibody titers.

Conclusions

The majority of pediatric oncology patients with prior VZV antibody titers preserve their VZV immunity post chemotherapy. Consequently for this population, VZIG PEP and isolation in hospital may not be necessary. In Japan and the United Kingdom, acyclovir is used as a cost-effective alternative. For patients VZV seropositive prior to malignancy, further studies to determine the risk factors predisposing these patients to breakthrough disease may identify a subgroup for whom VZIG PEP is necessary.

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Supportive Care/Palliative Care

ROLE OF PARVO VIRUS B19 INFECTION IN CAUSING UNEXPLAINED COMPLICATIONS DURING CANCER CHEMOTHERAPY IN CHILDREN – A COMMONLY UNRECOGNISED PROBLEM

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Objectives

In children with cancer, cytopenias and transaminitis inappropriate to the intensity of chemotherapy cause treatment delays and may raise the concern for relapse. The causes for these often remain undetected. We examined the role of parvo virus B19 (B19V) in causation of such unexplained complications.

Methods

Children on cancer chemotherapy with unexplained cytopenias and/or transamnitis were screened for Parvovirus B19 infection (by anti IgM and/or DNA PCR) from January to December 2013.The clinical course, laboratory parameters and response to IVIg (intravenous immunoglobulin)of those who tested positive is described.

Results

B19V infection was detected in 52 of 163 (31.9%) children screened (30 of 84 leukemias, 4 of 24 lymphomas and 15 of 55 solid tumors).Of the 52 positive patients, isolated anemia, neutropenia and thrombocytopenia were seen in 18,11and 5 patients respectively. Remaining 18 patients had anemia along with neutropenia and/or thrombocytopenia and/or transaminitis.

B19V positive children with haematological malignancies had significantly lower haemoglobin when compared to those with solid tumors (5.15±1.76 vs 9.07±1.99 gm/dl; $p<0.001$). Chemotherapy interruption (>7 days) was seen in a higher proportion of children with haematological malignancies (36%) as compared to solid tumors (18%). Of the B19V positive children IVIg was given to 19/20 with severe illness. Only one child, who had not been given IVIg, expired (B19V report was available post-mortem). The median duration of recovery of counts in children who received IVIg was 11.0 (range: 4-14) days, thus allowing an early resumption of chemotherapy.

Conclusions

B19V accounted for nearly one-third of the cases with unexplained complications during chemotherapy in our series. Illness was more severe in children with haematological malignancies. Clinical suspicion and early treatment with IVIg reduces disease severity and duration of chemotherapy interruption.

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Supportive Care/Palliative Care

FEASIBILITY OF A NEW SCREENING TOOL TO OPTIMISE THE MANAGEMENT OF PATIENTS WITH CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)

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Objectives

The Dublin CIPN screening tool was developed to enhance the quality of pre chemotherapy examinations in patients receiving Vincristine, thereby improving detection rates of CIPN, and facilitating appropriate onward referral.

Methods

A retrospective review, undertaken in 2010, highlighted limitations in the pre chemotherapy assessment of patients receiving Vincristine at a tertiary children's cancer centre. The Dublin CIPN screening tool was consequently developed. It was piloted throughout 2013, as part of pre chemotherapy assessment in patients receiving Vincristine. A prospective review evaluated quality of pre chemotherapy assessment, CIPN detection rates, and subsequent management of CIPN. Compliance with the screening tool and user satisfaction rates were also evaluated.

Results

Introduction of the Dublin CIPN screening tool at a tertiary children's cancer centre resulted in increased recognition of potential signs and symptoms of CIPN (65.96% versus 33.3%). It prompted more frequent modification of Vincristine doses (19.15% versus 8.33%). Close monitoring of CIPN changes allowed administration of higher cumulative doses of Vincristine before dose modification was necessary (10.33 mg/m^2 versus 7.26 mg/m^2). Staff compliance with utilisation of the Dublin CIPN screening tool was 83.03%. Satisfaction rates were very high, although difficulties in examination of children less than 5 years of age were highlighted.

Conclusions

Introduction of the Dublin CIPN screening tool resulted in increased detection rates of CIPN, more timely recognition of severe CIPN, and more frequent modification of Vincristine doses at a tertiary children's cancer centre. We recommend that the Dublin CIPN screening tool, with minor amendments, be adopted as routine standard of care at this centre.

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Supportive Care/Palliative Care

HEALTH-RELATED QUALITY OF LIFE (HRQL), FATIGUE AND SLEEP AMONG CHILDREN WITH CANCER

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Objectives

To investigate the relationship between health-related quality of life (HRQL), fatigue and sleep in pediatric patients receiving chemotherapy and/or radiation therapy (RT) for cancer.

Methods

Between 11/12/09 and 03/19/14, 59 pediatric oncology patients 8-18 years of age completed the study. Participants were receiving chemotherapy and/or RT for cancer and were evaluated over 7 days without hospitalizations. HRQL of the study participants was assessed using the PedsQL 4.0 and PedsQL 3.0 Cancer Module administered to the children with cancer and their parents. Sleep was assessed objectively by actigraphy as sleep time, wake after sleep onset (WASO), number of wake bouts and sleep efficiency. Sleep was assessed subjectively by sleep diaries completed by participants and their parents to determine sleep time, sleep quality and morning mood. Fatigue was assessed using the Fatigue Scale (Child, Adolescent and Parent).

Results

The study participants consisted of 59 pediatric patients receiving chemotherapy and/or RT for cancer (36 males, 23 females, mean age 12.2 years). The HRQL scores were significantly correlated to sleep quality ($p=0.03$) and fatigue scores ($p<0.0001$). Participants who reported significant fatigue also reported lower HRQL scores ($p=0.001$). Although the parent-reported fatigue correlated with parent-reported HRQL scores ($p<0.0001$), the HRQL reported by the patients was higher than their parent's assessment of their HRQL for every HRQL domain ($p<0.01$). Parents of teens rated their children's procedure and treatment anxiety higher than parents of younger children ($p<0.01$).

Conclusions

HRQL was significantly associated with sleep and fatigue. Although the proxy report by parents demonstrated correlations between HRQL and fatigue, the discrepancy between participant and parent reports warrant further investigation. Fatigue and sleep may be modifiable factors which may offer a mechanism to improve HRQL among children with cancer.

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Supportive Care/Palliative Care

FULFILLING THE VISION OF YOUTH-FRIENDLY CANCER CARE: HOW WELL ARE WE MEETING THE SUPPORTIVE CARE NEEDS OF ADOLESCENT AND YOUNG ADULT (AYA) PATIENTS?

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Objectives

Despite global interest in cancer service reform, evidence for best practice adolescent and young adult (AYA) care is scare. This study investigated on-treatment experiences of AYAs/parents to inform a program logic model of best-practice psychosocial supportive care.

Methods

Stage 1 involved qualitative telephone interviews with AYA(n=60) and parent/partner carers(n=60). Stage 2 involved surveys with a nationally representative sample of AYA(n=200) and parents(n=200). Surveys were a combination of pre-established questions from other needs surveys and psychometric measures, as well as new questions prompted by analysis of the interviews. Topics included psychological health, information needs, social support and practical needs. 17 treatment centres disseminated surveys (5 paediatric, 12 adult).

Results

Little published data reflects on-treatment experiences of AYA, even less the experiences of their carers. For both, this project describes social, emotional and financial impacts of cancer and treatment, perceptions about quality of interactions with healthcare staff, types of supportive care services accessed(and barriers). This presentation focuses on unmet supportive care and information needs during treatment and soon after treatment ends. These include areas such as mental health support, exercise therapy, educational and vocational support, genetic counseling, peer support, and access to cancer-related information specifically designed for this age group. We also illustrate the way these issues differ across different treatment settings.

Conclusions

Data indicate considerable room for improvement in many areas of AYA supportive care, with several themes not previously described in the literature. Results show the value of conceptualizing an ecological model of supportive care needs, which attends to AYA and carers as individuals, but also as part of an inter-related system. This data has informed articulation of a best practice model of AYA care. Implications of these findings for health care delivery and the importance of attending to both patient and carer supportive care needs will be addressed.

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Supportive Care/Palliative Care

PAIN EXPERIENCE OF ADOLESCENTS WITH CANCER: REPORT FROM A LONGITUDINAL ELECTRONIC MOMENTARY ASSESSMENT STUDY

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Objectives

Adolescents with cancer report pain as a distressing element of the disease and its treatment, which negatively impacts health-related quality of life. Regardless, little is known about the daily pain experience of these adolescents, especially in everyday settings (e.g., home, school). This study used a multidimensional smartphone pain assessment application to understand the within- and between-day self-reported pain experience of adolescents with cancer.

Methods

A longitudinal, descriptive study was used to collect momentary pain data twice daily for 14-days from 70 adolescents recruited at 4 pediatric tertiary care centers. Adolescents were aged 8-18 years with various cancer diagnoses and were undergoing outpatient cancer care. Each adolescent completed a 22-question multidimensional pain assessment on a smartphone each morning and evening. Intensity scores were rated on a 5-cm visual analogue scale (0-10 point ranking), pain location was captured using a body map and categorical data related to pain duration, pain management and affective pain descriptors were recorded.

Results

Pain was reported by 93% (n=65) of adolescents during the 2-week period. Eleven adolescents (16%) reported currently experiencing pain on every assessment. Current pain was rated as 3.7/10 (SD=2.1) and worst pain was rated as 5.5/10 (SD=2.4). Mean pain interference with daily activities was 3.7/10 (SD=2.4). Adolescents reported pain as occurring in the abdomen (57%), head (42%), and low back (33%). Most adolescents (91%) did not use a pharmacological intervention when in pain, but often used non-opioids if a pain medication was used. Adolescents also used rest (70%), distraction (44%), and deep breathing (40%) to manage pain. Pain was described as tiring (31%), sickening (29%) and cruel (23%).

Conclusions

Adolescents with cancer reported pain as a common symptom that interferes with daily living. Despite its occurrence, adolescents frequently do not manage pain in the home setting and may benefit from interventions that provide in-the-moment pain management support.

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Supportive Care/Palliative Care

POLYSOMNOGRAPHY AND MULTIPLE SLEEP LATENCY TEST FINDINGS IN CHILDREN WITH CRANIOPHARYNGIOMA PRIOR TO PROTON THERAPY

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Objectives

Sleep related problems, such as excessive daytime sleepiness (EDS) are common in pediatric brain tumor patients. Craniopharyngioma patients are especially at risk due to the hypothalamic-pituitary-adrenal axis tumor location and an aggressive therapy regimen. Hypothalamic obesity is a common result of tumor and treatment and may contribute to sleep disordered breathing. Daytime sleepiness and slepp-related breathing patterns have yet to be explored in this population at time of diagnosis.

Methods

Pediatric craniopharyngioma patients (n=37) underwent an overnight polysomnography and multiple sleep latency test (MSLT) prior to proton therapy to assess for sleep disorders and daytime sleepiness. Age ranged from 3 to 19 years (M=9.59), and the sample was primarily female (56.8%).

Results

On average, participants spent 514.62 ± 77.45 minutes in bed while only sleeping an average of 453.34 ± 83.01 minutes. Sleep efficiency scores ranged from 55.4 to 99.6 (M=89.04 ± 9.48). Mean AHI=1.03 ± 1.18 with PLM = 6.78 ± 10.60. Results from the MSLT indicate the sample to be in the troublesome range for EDS (M SOL = 9.68 ± 5.43) with n= 9 (24%) having 2 or more SOREM. 17 (46%) were diagnosed with clinically significant EDS. 3 (8%) were found to have sleep disordered breathing.

Conclusions

Craniopharyngioma survivors have high rates of clinically significant EDS. This work demonstrates that nearly half of the children with this tumor present with clinically significant EDS and provides evidence for tumor and surgery-related impairment of alertness. Longitudinal assessment is planned for this cohort to describe the trajectory of sleepiness after proton therapy and interventions in this population.

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Supportive Care/Palliative Care

NUTRITIONAL STATUS OF PAEDIATRIC CANCER PATIENTS IN THE UK: A PROSPECTIVE COHORT STUDY

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Objectives

To investigate the prevalence of malnutrition (undernutrition and overnutrition), patterns of change in nutritional status (NS) and, potential factors that may contribute to the development of malnutrition in paediatric oncology patients.

Methods

A multicentre prospective cohort-study was performed. NS was assessed between Aug 2010-Oct 2013 using anthropometry, body composition and dietary assessment. Childhood cancer was categorised into four groups: solid tumours, haematological malignancies, brain tumours and other associated cancers. The primary outcome was malnutrition defined as body mass index (BMI) according to UK growth chart centiles; underweight (<2.3rd), overweight (85-95th) and obese (>95th). NS was also assessed by arm anthropometry; mid-upper arm circumference (MUAC) and triceps skinfold (TSF), and body composition; muscle (FFM) and fat mass (FM). Frisancho's (1981) percentiles were used to establish NS by arm anthropometry. Correlations, independent t-test and multilevel analysis were performed.

Results

74 patients were studied. At diagnosis, the prevalence of undernutrition was 9.5%, overweight 5% and obesity 11%. TSF identified the highest prevalence of undernutrition 13.5% and the lowest of obesity 1%. BMI [p=0.03; 95% CI(-17 to -12)] and FM [p<0.05; 95% CI(677-1122)] significantly increased after 3 months and remained steady thereafter, whilst FFM [p<0.001; 95% CI (2992-3550)] significantly decreased during the first year. Only energy intake showed minor correlation with BMI (r=0.1; p=0.04) and TSF (r=0.2; p=0.03) at diagnosis. No significant differences were observed between diagnostic categories during the first year. However, haematological malignancies showed higher BMI at 12 [p<0.05; 95% CI (-34.9 to -0.2)], 18 [p=0.02; CI (-45.6 to –3.7)] and 24 months [p=0.03; 95% CI (-60.6 to -1.6)] post-diagnosis in comparison to solid tumours.

Conclusions

Undernutrition was particularly prevalent at diagnosis, yet overnutrition increased significantly during treatment, especially in children diagnosed with haematological malignancies. The body composition changes observed emphasises the need to implement targeted strategies to improve the NS of paediatric cancer patients.

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Supportive Care/Palliative Care

OLANZAPINE FOR TREATMENT AND PREVENTION OF ACUTE CHEMOTHERAPY-INDUCED VOMITING IN CHILDREN: A RETROSPECTIVE, MULTI-CENTRE REVIEW

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Objectives

The addition of olanzapine to standard antiemetic prophylaxis improves chemotherapy-induced nausea and vomiting (CINV) control in adults. Published experience in children with cancer is lacking. The purpose of this review was to describe the safety and efficacy of olanzapine use for chemotherapy-induced vomiting (CIV) control in children.

Methods

Children <18 years old who received olanzapine for acute CINV control from December 2010 to August 2013 at 4 institutions were identified. Patient characteristics, chemotherapy, antiemetic prophylaxis, olanzapine dosing, CIV control, liver function test results and adverse events were abstracted from the health record. Complete CIV control was defined as the absence of vomiting or retching throughout the acute phase. Toxicity was graded using CTCAEv4.03 and the likelihood that toxicity was attributable to olanzapine was assessed using the Naranjo Scale.

Results

Sixty children (median age 13.2 years; range: 3.10-17.96) received olanzapine during 158 chemotherapy blocks. Olanzapine was most often (59%) initiated due to a history of poorly controlled CINV. The mean initial olanzapine dose was 0.1mg/kg/dose (range: 0.026-0.256). Most children who received olanzapine beginning on the first day of the chemotherapy block experienced complete CIV control (83/128; 65%). There was no association between the olanzapine dose/kg and complete CIV control (OR 1.01; 95% CI: 0.999 to 1.020; p=0.091). Sedation was reported in 7% of chemotherapy blocks and was significantly associated with increasing olanzapine dose (OR: 1.17; 95% CI: 1.08 to 1.27; p=0.0001). Of the 25 chemotherapy blocks where ALT and/or AST were reported more than once, grade 1-3 elevations were observed in 5. The mean weight change in 31 children who received olanzapine during more than one chemotherapy block was 0% (range: -22 to +18).

Conclusions

Olanzapine may be an important option to improve CIV control in children. Prospective controlled evaluation of olanzapine for CINV prophylaxis in children is warranted.

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Supportive Care/Palliative Care

CENTRAL LINE PLACEMENT AT TIME OF DIAGNOSIS IN CHILDREN WITH ACUTE LEUKEMIA: DOES THE NEUTROPHIL COUNT MATTER?

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Objectives

There are conflicting data on the risk of infections associated with early insertion of central venous cathethers (CVL) in neutropenic patients. We reviewed our institutional practice of CVL placement in children with newly diagnosed leukemia for quality assurance purposes and to provide further evidence to the ongoing controversy.

Methods

We retrospectively reviewed consecutive children at our institution diagnosed with leukemia and requiring CVL placement. Neutrophil counts, febrile episodes, documented infections, mechanical complications, thrombosis and CVL removal within the first 60 days of treatment were recorded.

Results

Between 2008-2013, 80 patients(49M/31F; median age 4.46 years) diagnosed with leukemia(61 ALL, 18 AML and 1 CML) underwent CVL placement at a median time of 1 day after diagnosis. The type of CVLs placed were port-a-caths(46), Broviacs(23) and PICCs(11).

At time of CVL insertion, 39 (49%) patients had a neutrophil count < 500(median ANC =200).

In the group of patient neutropenic at CVL placement 25 episodes of febrile neutropenia were described in 20 patients. Among these, 5 had documented infections(3 bacteremia, 2 tunnel infections). Two port-a-caths were removed for documented infection both at 22 days post-insertion. In the group of patients non-neutropenic at line placement, 38 episodes of febrile neutropenia were described in 20 patients. Among them, 3 had documented infections(bacteremia). One PICC was removed for thrombosis at 10 days post-diagnosis.

There was no significant difference between the 2 groups in terms of number of lines removed(p=0.53), documented infections(p=0.42), or febrile neutropenic episodes(p=0.42).

Conclusions

Our data indicate that there was no difference in febrile neutropenic episodes or line complications between neutropenic and non-neutropenic patients who had CVL placed at the time of diagnosis. Therefore, delaying Broviac or port-a-cath insertion to avoid infections or other line complications may not appear indicated for this population. The number of infections (tunnel infections), indicate vigilance is required after CVL placement.

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Supportive Care/Palliative Care

SIGNIFICANT IMPACT OF TREATMENT SUBSIDY AND INTENSIFIED COUNSELLING STRATEGY ON THERAPY ABANDONMENT IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA – A PROSPECTIVE INTERVENTIONAL STUDY

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Objectives

Treatment abandonment is a significant impediment to improvement in survival outcome of childhood ALL in developing nations with paucity of studies assessing impact of interventions to reduce abandonment. The present study was designed to assess the impact of treatment subsidy and counselling on the previously high abandonment rates in ALL at our centre.

Methods

Case records of ALL patients from 2007-2013 were assessed. The interventions evaluated were (i) intensified counselling and (ii) treatment subsidy. Treatment subsidy included (a) free supportive care drugs/antimicrobials from 2010, (b) free chemotherapy/radiotherapy from 2011 and (c) free investigations from 2012. Since 2010, support of a social worker and data manager obtained through a research scheme, allowed improved post-abandonment tracking and counselling. Intensified structured multi-stage pre-therapy counselling by multidisciplinary team of physicians and allied health workers (for disclosure of diagnosis, introduction of supportive services and therapy plan) with participatory and supportive family centred approach and periodic group counselling sessions (including physicians, social workers, survivors and families with children undergoing treatment) were introduced from 2010.Early and late abandonment were defined as abandonment before and after completion of induction respectively.

Results

77/418 (18.2%) patients abandoned therapy. The rate of abandonment after 2010 (post intervention) (9.1%,24/263) declined significantly ($p<0.0001$) as compared to earlier (34.2%,53/155). Patients presenting before and after 2010 were comparable in their socio-economic and demographic characteristics. Most parents (72%) attending the group counselling sessions rated them as “very useful/a moral boost” to fight the disease. The post 2010 decline was significant in early (from 17.5% to 2.3%; $p<0.0001$) as well as the late abandonment (from 16.7% to 6.8%, $p=0.009$).

Conclusions

The present study is one of the first to prospectively demonstrate significant impact of subsidised treatment, intensified pre-therapy counselling as well as group counselling in reducing both early and late abandonment in ALL patients.

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Supportive Care/Palliative Care

TRENDS IN HOSPITAL UTILIZATION AMONG PATIENTS RECEIVING HOSPITAL-BASED PEDIATRIC PALLIATIVE CARE

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Objectives

In adults, palliative care contributes to less frequent readmission, fewer intensive care unit (ICU) or emergency department (ED) visits, and lower costs. Few studies explore similar outcomes in pediatric palliative care (PPC). We evaluate how hospital utilization and costs vary for patients following hospital-based PPC consultation.

Methods

This is a retrospective cohort study of patients $\geq$ 2 years of age who received an initial PPC consultation at Boston Children's Hospital in April 2009-September 2010 (N = 109). Data were obtained from the Pediatric Health Information System database. We assessed frequency of inpatient admissions and ED visits, lengths of stay, use of the ICU or operating room (OR), frequencies of mechanical ventilation or technology assistance, and total inpatient and ED costs. Paired analysis methods, specifically the Wilcoxon signed rank test for continuous variables and McNemar's test for categorical variables, were used to compare outcomes as a cohort and per patient in the two years prior to and following PPC consultation.

Results

Preliminary analyses indicate that inpatient admissions in the cohort decreased from 4.64 admissions/year prior to PPC consultation to 3.72/year following PPC consultation (p

Conclusions

Following PPC consultation, patients experience fewer inpatient admissions, ED and OR visits. ICU admissions increase, but costs remain stable. These findings suggest that PPC may influence hospital utilization in children. Future research, employing case-control methodology, may help explain these trends.

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Supportive Care/Palliative Care

FUNCTIONAL INTERLEUKIN-6 AND CANCER-RELATED FATIGUE IN CHILDREN AND ADOLESCENTS WITH CANCER: EARLY FINDINGS

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Objectives

Persistent cancer-related fatigue (CRF) is one of the most troubling and prevalent side-effects of cancer and its tratement. Evidence suggests that cytokines might play a role in the etiology and mechanisms of cancer-associated symptoms, including fatigue. The objective of this study was to evaluate the associations among chemotherapy, proinflammatory cytokines (IL-6, TNF-α) and fatigue in children and adolescents with cancer.

Methods

A questionnaire was used to provide social-demographc information and clinical information (phase of treatment, week of treatment, medications in use, levels of hematocrit and hemoglobin lately performed). The 18-item PedsQL Multidimensional Fatigue Scale was used to measure fatigue in pediatric patients and a blood sample were collected. Flow cytometry was used to evaluate interleukin IL-6 and TNF-α levels using BD™ *Cytometric* Bead Array (*CBA*) flex kits from BD Bioscience. The entire procedure was performed following the instructions indicated by the manufacturer.

Results

A total of 39 blood collections were performed and the results showed heterogeneity among the different cancer types presented by our population, their chemotherapy protocols, subject's clinical characteristics and fatigue endpoints. The mean levels of IL-6 was 238, 2 ± 375,1 (MD±SD), and regarding TNF-α levels were 215,2 ± 368,6 (MD±SD). Weak to moderate correlations were observed among IL-6, TNF-α levels, and different degrees of fatigue. Diverse types of chemotherapy treatments might lead to varying presentations and severities of cytokine-induced fatigue. A number of confounding factors was identified to interfere with the expression levels of cytokines: subjects' cancer types, age, gender and psycho cognitive characteristics such as sleep patterns.

Conclusions

Our results suggest a role for proinflammatory cytokines in cancer-related fatigue. However, due our sample size our conclusions are limited. Methodological recommendations are proposed to improve future studies of this issue.

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Supportive Care/Palliative Care

BRINGING CHEMOTHERAPY ADMINISTRATION IN TO THE DAYTIME TO IMPROVE EFFICIENCY AND PATIENT SAFETY: A QUALITY IMPROVEMENT INITIATIVE

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Objectives

The safety and efficiency of chemotherapy delivery is paramount to the of care of pediatric oncology patients. In 2011, in our large tertiary pediatric oncology center, 97% of all planned chemotherapy was initiated after 6pm on the day admission. Concerns were identified related to late in the day initiation of chemotherapy, including less availability healthcare professionals to address chemotherapy administration related questions and to respond to reactions as well as additional nursing handoffs. Two improvement processes were initiated to move the time of initiating chemotherapy to prior to 6pm.

Methods

The first initiative, a standardized pre-chemotherapy rapid hydration protocol, was implemented after a literature review and consensus building. The second initiative was developed following a value stream mapping process used to identify barriers to efficient admission and initiation of chemotherapy. A streamlined patient admission process was generated and then evaluated in five Plan-Study-Do-Act (PDSA) cycles.

Results

The pediatric oncology program at the Hospital for Sick Children has approximately 550 planned chemotherapy admissions/year. Baseline data found that 3% of children had their planned inpatient chemotherapy initiated before 6pm on the day of admission. The implementation of a rapid hydration protocol improved this to 26%. The five sequential PDSA cycles designed to evaluate and improve the admission and start of chemotherapy process demonstrated continuous improvement. With the 5th PDSA cycle, which included 109 admissions over 9 weeks, 79% of all patients had chemotherapy initiated before 6pm. An analysis of length of stay for similar chemotherapy pre and post implementation of rapid hydration and early admission strategies demonstrated an average a one day decrease per cycle.

Conclusions

Two QI initiatives were successful in improving the percentage of patients initiating their chemotherapy prior to 6pm from 3% to 79%. The success of the initiatives was dependent on engagement of front line staff in design and implementation of changes.

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Supportive Care/Palliative Care

PROSPECTIVE TRACKING OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA WHO ABANDONED THERAPY: PARENTAL PERSPECTIVES, CAUSES AND IMPLICATIONS OF THERAPY ABANDONMENT FROM A TERTIARY CANCER CARE CENTRE

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Objectives

Therapy abandonment is being increasingly recognised as a major contributor to inferior survival outcome in developing nations. Limited information is available on the reasons and outcome of treatment abandonment. The current study provides insights obtained by tracking families of patients with acute lymphoblastic leukemia (ALL) who abandoned therapy at a large tertiary care cancer center in India.

Methods

Case records of all children with ALL managed at King George's Medical University who abandoned therapy were retrieved after ethics approval. Families who abandoned therapy were subsequently tracked using predesigned and prestructured telephonic interviews.

Results

77/418 (18.4%) children registered from January 2007 to July 2013 abandoned treatment.17/77 (22.1%) refused treatment upfront. The rest abandoned during various phases of chemotherapy [induction 16(20.7%), consolidation 10(12.9%), interim-maintenance 11(14.2%), delayed-intensification 8(10.5%), or maintenance 15 (19.4%)]. Rate of illiteracy was significantly higher in mothers ($p=0.008$) and fathers ($p<0.0001$) of children who abandoned therapy.

39/77 (50.6%) families could be tracked telephonically. Of these, 18 had expired, 13 were reported to be well at home (50% had abandoned after maintenance, and all after consolidation) and 8 came back for retreatment (4 with relapse). Parents cited financial constraint as the most common reason for abandonment. Perception of incurability was more common in families abandoning before completion of induction. Those abandoning later thought their children to be already cured of ALL.

Survival outcome was better in 11/18 who completed induction therapy (median 180 days) before abandonment as compared to 7/18 who did not (70 days); $p=0.000$ (Log-rank test).

Conclusions

Abandonment rates were highest before completion of induction (42.8%) followed by maintenance therapy (19.4%). Survival was worse in children who abandoned therapy before completion of induction. Illiteracy, financial constraints and false perceptions about cure contributed to abandonment in majority.

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Supportive Care/Palliative Care

SHORT TERM EFFECTS ON PHYSICAL FITNESS OF A 12-WEEK EXERCISE AND PSYCHOSOCIAL TRAINING PROGRAM IN CHILDHOOD CANCER PATIENTS

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Objectives

Evidence for exercise training interventions in childhood cancer patients (CCP) is limited. This study investigated the short-term physical fitness effects of a 12-week combined physical exercise and psychosocial training program, compared to usual care, in CCP.

Methods

In a multicentre randomized controlled trial CCP, 8-18 years old, on or within the first year after treatment, were invited to participate. Stratification included age, sex, solid tumour/ haematological cancer and during/ after treatment. Physical fitness was determined by cardiopulmonary exercise testing (peak oxygen uptake) at baseline (T0) and shortly after the intervention period (T1).

Results

Fifty-five CCP, aged 12.8 ± 3.1SD years (54% male) were included in the analyses; N=34 were treated for a haematological malignancy. The median change scores in both treatment groups, corrected for baseline scores, on peak oxygen uptake (ml/kg/min) were not significantly different (P=0.78); intervention group (INT): 0.04 (IQR: -0.09 – 0.10); control group (CTRL) 0.06 (IQR: -0.01 – 0.21). At T0 66% (N=16) of the INT scored below -2 standard deviation (SD) of Dutch paediatric norm values peak oxygen uptake, and 33% within the low normal range (- 2 SD to 0); and for the CTRL this was 64% (N=20) below the normal range, and 32% in the low normal range, plus one (3%) with above mean scores. At T1 three children of the INT and nine of the CTRL progressed from below the normal range to the low normal range (INT change within groups: P=0.08; CTRL change within groups: P=0.001; change between groups: P=0.15).

Conclusions

Both treatment groups showed little increase on maximal cardiopulmonary capacity. In contrast to the expected, the Intervention did not lead to short-term improvements. Factor analyses will be performed to further assess the study results.

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PLASMA 25-HYDROXYCHOLECALCIFEROL BEFORE AND AFTER SUPPLEMENTATION IN PAEDIATRIC ONCOLOGY PATIENTS IN THE UK: A TIME-SERIES CROSS SECTIONAL STUDY

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Objectives

To assess the impact of micronutrient and macronutrient supplementation on plasma 25-hydroxycholecalciferol [25(OH)D] in Scottish paediatric oncology patients

M

ethods

A time series case-control cross-sectional study was performed. Plasma 25(OH)D was measured in healthy children (controls) and in paediatric oncology patients (cases). Children aged <18 years diagnosed and treated for cancer in SE Scotland were included. Childhood cancer was categorised into four groups: solid tumours, haematological malignancies, brain tumours and other associated-diagnoses. Macronutrient (enteral+/-parenteral nutrition) and micronutrient (vitamin D, multivitamins +/-macronutrient) supplementation was prescribed according to Subjective Global Assessment by the multidisciplinary team. 25(OH)D deficiency was classified according to Endocrine Society Clinical Practice Guidelines-2011; suboptimal (50-75nmol/L), insufficient (25-50nmol/L) and deficient (<25nmol/L). Plasma 25(OH)D was measured using the Automated Vitamin D Immunoassay in Glasgow Royal Infirmary Laboratory. Descriptive statistics and Wilcoxon test were performed.

Results

Plasma 25(OH)D levels did not statistically differ between the 35 healthy-controls (median(IQR) 31(15-56)nmol/L) and the 67 patients (median(IQR) 38(20-61)nmol/L) at diagnosis. Children diagnosed with solid tumours had the highest prevalence of 25(OH)D deficiency and insufficiency (26.4%) followed by haematological malignancies (19.4%). 40/67 patients had plasma 25(OH)D measured before and after supplementation. Median(IQR) time between diagnosis and supplementation was 2.9(0.9-6.3) months and between supplementation and the repeated 25(OH)D measurement was 2.7(1.6-6.7) months. At baseline, plasma 25(OH)D was suboptimal in 23% of patients and insufficient or deficient in 62.5%. 17.5% received macronutrient supplementation alone; of these 43% remained below suboptimal and median(IQR) 25(OH)D decreased from 77(42-81) to 54(19-89)nmol/L. Conversely, those additionally supplemented with micronutrients (82.5%) had a significant improvement in 25(OH)D with median (IQR) increasing from 26.5 (15-37) to 65.5(44-87)nmol/L ($p<0.001$; r-0.7); however, 20% remained below suboptimal levels.

Conclusions

25(OH)D deficiency was highly prevalent, only improving following micronutrient supplementation. To optimise the 25(OH)D status of this population, regular monitoring alongside appropriate supplementation should be incorporated into clinical practice.

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VINCRISTINE INDUCED CRANIAL NEUROPATHY DURING THERAPY FOR PEDIATRIC MALIGNANCIES

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Objectives

Vincristine is widely used to treat pediatric cancer. However, the incidence and severity of vincristine-induced cranial neuropathies (jaw pain, facial weakness, vocal cord dysfunction, dysphagia, dysphonia, optic neuropathy) have not been well described.

Methods

Retrospective chart review of patients with hematologic and solid malignancies exposed to vincristine protocol-based therapy from 2000-2010 for evidence of symptomatic cranial neuropathies (CT-CAE grade 3 or 4 toxicity). Patients with cranial neuropathy at diagnosis or those receiving cranial radiation were excluded.

Results

Twenty-six of 1706 eligible subjects (1.5%) experienced cranial neuropathy. Toxicity was more common among solid malignancies (15/214, 7%). Fifteen were male and 24 were Caucasian with a median age of 4.9 years (range 0.2-20.8y). Diagnoses included acute lymphoblastic leukemia (n=10), Ewing sarcoma (n=5), rhabdomyosarcoma (n=3), retinoblastoma (n=3), Wilms tumor (n=2), primitive neuroectodermal tumor (n=2) and T-cell lymphoblastic lymphoma (n=1). Dysphagia and jaw pain were most prevalent (9 each). Vocal cord (VC) dysfunction was noted in seven patients, and one of these required monitoring in the intensive care unit. Three of seven patients with swallowing dysfunction required intervention: dose reduction (n= 3), naso-gastric tube (n=1), honey-thickened liquids (n=1), and speech therapy (n=3). Ten patients experienced multiple episodes of toxicity with re-exposure to vincristine therapy. Doses of vincristine were reduced, delayed or omitted in 14 of 18 patients with cranial neuropathy other than jaw pain. All patients recovered from toxicity within a median of 13 days (range 1-112).

Conclusions

This review, limited to protocol documentation, summarizes the reported incidence and morbidity of vincristine induced cranial neuropathy in children with cancer. Identification of patients at risk and early assessment of symptomatic patients is essential for therapy modifications and/or clinical intervention to ameliorate ongoing toxicity.

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PREVENTION AND CONTROL STRATEGIES IMPLEMENTED AFTER A HEPATITIS B VIRUS OUTBREAK IN A PAEDIATRIC HAEMATOLOGY AND ONCOLOGY UNIT IN SOUTH AFRICA

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Objectives

Hepatitis B remains an important public health concern in South Africa, despite the introduction of hepatitis B vaccination in 1995. Horizontal transmission of hepatitis B plays an important role in developing countries, and occurs mainly through body fluids like saliva. A recent nosocomial hepatitis B virus (HBV) outbreak involving 38 patients occurred in the paediatric haematology and oncology unit of a large tertiary hospital in South Africa. Possible breaches in standard infection control precautions, contaminated multiple-dose vials and transmission through body fluids were implicated. We describe subsequent infection prevention and control strategies that were implemented.

Methods

A series of strategies to minimise nosocomial transmission of HBV was implemented. Universal infection control precautions were emphasized, including strict hand washing and use of gloves. Further policies included eliminating use of multi-dose vials, cleaning and disinfecting reusable equipment, and preventing sharing of personal utensils. Testing for HBV infection and immunity on first admission and vaccinating patients with low levels of anti-HBs antibodies were put into practise. A full vaccination schedule is initiated in patients with anti-HBs titres <10 mIU/ml, and a booster HBV vaccine given to those patients with anti-HBs titres <100 mIU/ml. All patients attending the unit are routinely monitored every 3 months for declining levels of anti-HBs antibodies, and vaccinated if titres fall below 100 mIU/ml.

Results

Preventive measures that were introduced reduced the incidence of HBV infection significantly. Only one new case of HBV infection, suspected to be unrelated to the outbreak, has occurred in 13 months following implementation of these measures.

Conclusions

This outbreak highlights the importance of adequate infection prevention and control strategies in the prevention of nosocomial transmission of HBV. Paediatric haematology and oncology units should implement policies of active on-going surveillance for HBV infections and formulate clear guidelines for prevention and control thereof.

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THE LAPAROSCOPIC ONCOLOGIC SURGICAL PATHOLOGY AND POSTOPERATIVE PAIN MANAGEMENT THROUGH INTRAPERITONEALLY LOCAL ANESTHETIC IN PEDIATRIC PATIENTS

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Objectives

Although pain after laparoscopic surgery is less intense than after open surgery, some patients still experience considerable discomfort in PICU. Postoperative pain after laparoscopic oncologic surgical pathology is an important limiting factor for a rapid return to normal activity. In our study we demonstrate the efficacy and safety of intraperitoneally administration of low doses of local anesthetics.

Methods

After IRB approval 46 patients ASA I-II, 9-14 years old, received in double-blinded fashion 40 ml of 0.9 normal saline solution (group S), ropivacaine 0.2% (group R), levobupivacaine 0.25% (group L). A standard general anesthesia was performed with propofol, cisatracurium, mixture of air/O_2/sevoflurane and remifentanil in continuous infusion. The anesthetic solutions were intraperitoneally administered at the end of laparoscopic procedure and repeated in PICU through an intraperitoneally catheter. Postoperative pain was assessed during the first 24h (T_0 end of surgery, T_1 2h, T_2 4h, T_3 8h, T_4 12h, T_5 24h) using visual analogic scale (VAS 0-10). Further anesthetic drug in postoperative time, if administered, were also recorded.

Results

Pain was less intense in the group L, particularly in T_0-T_4-T_5 and rescue analgesic drugs consumption was lower in this group respect ropivacaine and normal saline groups. Postoperative pain at deep inspiration was higher in ropivacaine group respect levobupivacaine and normal saline groups.

Conclusions

The efficacy and safety of of intraperitoneally administration of local anesthetics has been well demonstrated in many studies but there is a lack of consensus regarding dose and concentration in laparoscopic oncologic surgical procedures. In our study we showed that the use of lower concentrations of local anesthetics led to significantly lower pain scores particularly for what concerns levobupivacaine.

References

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VARICELLA ZOSTER VIRUS INFECTIONS AFTER HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN CHILDREN WITH MALIGNANCY

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Objectives

Varicella zoster virus (VZV) infection is a frequent complication of High-Dose Chemotherapy (HDC) followed by Autologous Stem Cell Transplantation (ASCT) in children but few and conflicting data are published. The aim was to determine frequency, consequences and risk factors of VZV infection after ASCT in a large cohort and to adapt our therapeutic management.

Methods

We analyzed prospectively collected data of children treated with HDC and ASCT in the Pediatric Oncology Department of Institut Gustave Roussy and compared patients who developed or not VZV infection after intensive treatment.

Results

Between January 1985 and July 2009, 1056 children received HDC and ASCT without any VZV prophylactic treatment. Two hundred and thirty-six patients (22.3%) developed 244 VZV events (23.1%) consisted of 29 varicella (11.9%) and 215 herpes zoster (88.1%) including 8 double events. The median time of the VZV infection onset was 119.5 days post ASCT. Most (90.2%) of cases occurred within the first year. Evolution was simple with aciclovir treatment in 88% of the patients. Complications all resolved with treatment and consisted mainly in post VZV neuralgia. Age at date of the first ASCT ($p=0.000003$), underlying disease ($p=0.056$) and administration of a sequential HDC ($p=0.0001$), were significant factors associated with VZV infection's occurrence in the whole population, defined by Fisher test. Logistic regression models after single course of HDC and ASCT showed both in univariate and multivariate analysis that age under 3 years at date of the first graft and Hodgkin lymphoma was associated with the occurrence of VZV infection.

Conclusions

This incidence of VZV infections compared to these found in literature and the favourable outcome with a curative treatment with aciclovir, confirm the absence of benefits of a prophylactic strategy in management of children who received HDC followed by ASCT.

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RISK FACTORS TO DEVELOP A SEVERE INFECTION IN PEDIATRIC ONCOLOGY PATIENTS WITH FEBRILE NEUTROPENIA

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Objectives

To evaluate risk factors of suffering a "life-threatening" infection in myelosuppressed patients with a febrile neutropenia (FN) episode. Episodes were classified as high-risk febrile neutropenia (HRFN) or as low-risk febrile neutropenia (LRFN) and different approach was taken accordingly.

Methods

A study including all children prospectively enrolled with FN admitted to the hospital from October 2010 to December 2013 was performed.

Patients were classified into two groups on admission:LRFN and HRFN, according to a previously implemented protocol based on physical examination, laboratory tests, medical and social background, bacterial or fungal cultures and a nasopharyngeal wash for 16 respiratory viruses (RV) using a multiple-PCR test.

Results

One hundred and thirty FN episodes were evaluated from 45 patients (56.2% female, median age 5.6 years[3.1-13.8]). Among them, 108 (83.1%) were classified and treated as HRFN and 22(16.9%) as LRFN.

LRFN episodes were associated to a higher number of RV infections (40.9% vs 25.7% in HRFN), and fewer episodes of Gram negative bacterial infections(0% vs 12%)(p=0.086).

Among all episodes evaluated, 44(33,8%) were finally diagnosed as moderate or severe infection and 86/130(66,2%) as mild ones.

Trimethoprim-Sulfamethoxazole prophylaxis was associated to a lower incidence of moderate or severe infections(31.1% vs 63.6% in patients not receiving prophylaxis)(p=0,029).

Moderate to severe infections were related to a higher value of PCR (PCR≥9 mg/dl at diagnosis or 48 h later; 54.5% vs 33.7% in mild infections)(p=0,022), higher incidence of arterial hypotension (15.9% vs 2.3%;p=0.004),higher value of procalcitonin(PCT≥2 mg/dl:83.3% moderate to severe infection vs 16,7% mild infection(p<0,0001). There was a higher incidence of moderate to severe infection in non-remission leukaemia and non-hodgkin lymphoma compared to other malignancies(p=0.003)

Conclusions

Respiratory viral infections are associated to LRFN episodes. A higher CRP(≥9mg/dl) and PCT(≥2mg/dl), hypotension and chills and the absence of TMP-SMX prophylaxis may predict a moderate to severe infection and, therefore, the need for a HRFN management.

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SEEKING FOR A SECOND OPINION IN PEDIATRIC ONCOLOGY

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Objectives

The number of second opinions consultations in pediatric oncology is increasing, yet the grounds on which families decide to seek a second opinion have been little studied. The goal of the study was to identify patients and families factors that appeared to contribute to a second opinion being sought.

Methods

150 parents (75 from jewish origin, 75 from arab origin) of children with cancer recently treated in the Hematology Oncology Pediatric Department were interviewed. The questionnaire included epidemiologic data, details about the disease, timing of the second opinion consultation, reasons for seeking a second opinion and the risk/benefit of the consultation.

Results

37 parents (25%) had sought a second opinion. There was a correlation between higher socio-economy status (p=0.003) and number of educational years to the decision to go second opinion (p=0.001). Most of the parents which went to second opinion also use the internet as a data source, but using the internet did not correlate with the decision (p=0.157). There was no correlation between the age of parents, age of the sick child, family status, living place (urban vs. rural), the disease group, the stage of disease or using CAM (Complementary, Alternative, or Integrative Health) on the decision to go to second opinion..Non-religious parents went more to second opinion (p=0.003). 26 of 75 Jewish parents go to second opinion, versus 11 of 75 Arab parents (p=0.031).

Conclusions

Second opinions are an established part of health care, caregivers should express their empathy and take the initiative to discuss with parents their unmet needs, but sometimes even where ther is a successful communication, caregivers have to recognize that scientific evidence is not all that counts in the life of parents of a child with cancer that have to deal with a lifethreatening disease.

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PSYCHOLOGICAL DISTRESS, CAUSATION BELIEFS AMONG CAREGIVERS OF CHILDREN WITH CANCERS IN A DEVELOPING COUNTRY: INFLUENCE ON PATHWAY TO CARE AND TREATMENT UPTAKE

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Objectives

The caregivers of children with cancers often play significant roles in making decisions about pathway to care and treatment related issues. The treatment related decisons may be influenced by caregivers' belief about cancer causation and their emotional wellbeing. This study aims to investigate psychological distress and belief about causation of cancers in a developing context.

Methods

The study participants were made up of one hundred caregivers of children with histological diagnoses of cancers attending a tertiary health facility in West Africa. Eligible participants, who gave informed consent were interviewed with designed questionnaire to elicit socio-demographic profile, treatment related variables as well as pathway to care; subsequently this was followed by administration of General Health Questionnaire (GHQ-12) to ascertain psycholoical distress based on cut-off score of 3. Data Analyses was done using SPSS-17.

Results

The mean age of the caregiver was 49.02±0.12, and female gender was predominant 83(83.0%). About 42(42.0%) caregivers had psychological distress based on GHQ-12 and upto 66(66.0%) reported positive belief about preternatural/spiritual causation of cancers. Similarly, 70(70.0%) had opted for one form of alternative care (spiritual deliverance, prayers, herbal preparation among others) before presenting in the hospital. Good treatment uptake correlated positively with level of education, being employed and good social support from family members ($p>0.05$). However, financial constraint and preternatural causation belief correlated negatively with good treatment uptake ($p>0.05$).

Conclusions

The care of children with cancer is significantly impacted by caregiers' related factors. Psychosocial support for caregivers, promotion of awareness campaign and targeted cancers education programs as well as cancer treatment issues are indicated.

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SHARED CARE IN PAEDIATRIC ONCOLOGY: A MANAGED AND NEGOTIATED PARTNERSHIP OF TERTIARY AND SATELLITE HEALTH CARE PROVIDERS

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Objectives

Vast geography and limited human health resources dictate a need for collaborative care in the management of paediatric cancer patients in Canada. There is a lack of conceptual and empirical research to inform best practice in establishing and enhancing interprofessional and inter-organizational collaboration (Gagliardi, 2011). In particular, the complexity of relationships within and between professions is poorly understood (D'Amour, 2005). This study sought to examine the nature of these relational dynamics in an established paediatric oncology shared care program.

Methods

The Paediatric Oncology Group of Ontario (POGO) administers a formal satellite care program in Ontario. We conducted In-depth interviews of purposively sampled tertiary and satellite health practitioners to examine knowledge, skills and attitudes required for a successful collaborative care program. Interviews were audio- recorded, transcribed and inductively analyzed to generate emerging themes related to perceptions of interprofessional and inter-organizational interactions. Witz's model of professional closure strategies (1992) was used to explore and contextualize perceived relational dynamics.

Results

This study was approved through the local REBs of each participating institution. Twenty-three interviews (10 nurses, 3 nurse practitioners, 10 physicians) were conducted at the largest tertiary centre (SickKids) and the 6 provincial satellite centres. Unanimous commitment to the program appeared to be pivotal to navigating a number of inherent tensions identified within the working arrangement: 1) the partnership between tertiary and satellite centres is both managed and negotiated, 2) established guidelines are both necessary and overly restrictive, 3) tertiary providers balance loss of control with an evolving job profile and increasing access to tertiary services, 4) satellite providers balance increased job satisfaction with competing responsibilities and conflicting organizational agendas.

Conclusions

Providers within the shared care program navigate complex professional and organizational relationships while both maintaining and redefining traditional professional boundaries. Ongoing management and negotiation of the partnership is vial to the success and longevity of the program.

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BREAST MILK FROM IMMUNE THROMBOCYTOPENIC MOTHERS CONTAINS ANTI PLATELET ANTIBODIES THAT ARE ASSOCIATED WITH PERSISTENT THROMBOCYTOPENIA IN NEONATES

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Objectives

Maternal immune thrombocytopenic purpura (ITP) accounts for 5% of all cases of pregnancy associated thrombocytopenia and is a common cause of neonatal thrombocytopenia. One of the common mechanism involves transfer of IgG autoantibodies against platelet receptors which are found in the blood samples of affected patients. The neonatal thrombocytopenia usually subsides within 2-3 months. The autoantibodies are often of the IgG type and therefore can cross the placenta and cause fetal and/or neonatal thrombocytopenia. Recently we observed persistence of neonatal ITP which rapidly disappeared following discontinuation of breast feeding. The aim of our current work was to discern whether breast milk of mothers with ITP contains anti-platelet antibodies and whether these antibodies may be the cause for persistent neonatal ITP.

Methods

Breast milk samples were collected from 14 women with ITP. Seven of them were thrombocytopenic during pregnancy and their neonates also had thrombocytopenia. The remaining 7 mothers had a history of ITP but not during the current pregnancy, and neither did their neonates. As controls, breast milk from 10 healthy women was also examinied. The presence of anti-platelet antibodies were evaluated by incubating washed platelets from healthy donors with breast milk or extracted milk – Ig. The type of immune globulin was defined by flow cytometry using fluorescence conjugated anti-human IgA, IgG or total Ig antibodies.

Results

In four women with active ITP with accompanying neonates with thrombocytopenia, high levels of anti-platelet IgA antibodies were observed. In the three remaining women with active ITP and 7 with a history of ITP, no or minimal concentraions of anti-platelet antibodies were detected. No anti-platlet antibodies were found in breast milk of healthy women.

Conclusions

This is the first evidence that transfer of anti-platelet antibodies from mothers with ITP to their infants via breastfeeding was associated with persistent thrombocytopenic neonates.

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THE ROLE OF PRIMARY CARE IN THE MANAGEMENT OF TEENAGERS AND YOUNG ADULTS (TYA) WITH CANCER: A PRELIMINARY STUDY

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Objectives

Cancer in TYA is rare and primary care professionals may be unfamiliar with patient needs. With improved survival, the majority of TYA will return to primary care after completion of treatment but limited involvement of family (general) practitioners (FP) with TYA pre-diagnosis and during treatment, and potential perceptions of diagnostic delay, may impact the relationship between FP and patient/family to create barriers for effective aftercare. The Bristol On Target programme showed >40% TYA specifically wanted information about what to expect from FP during and after treatment. We explored FP experiences of TYA with cancer to understand barriers and to inform strategies for their increased involvement.

Methods

FP of recently diagnosed 15-24 year old with cancer were invited to an in-depth interview. A topic guide was developed with TYA clinicians and interviews were audio-recorded and transcribed verbatim. Of 56 FP contacted, 11 participated before interviews achieved theme saturation. Data were analysed using the constant comparative method.

Results

Analysis showed that FP mostly contributed to initial referral, emotional support and on-going care for un-related/intercurrent medical problems. Lack of knowledge, prolonged periods of hospital treatment, incomplete/ineffective communication and FP fear of burdening patients with additional input, were common reasons offered for limited involvement, especially during treatment.

Conclusions

These results align with general findings from cancer survivorship research and confirm that transition from specialist cancer care to care by FP may be difficult for both patient and FP. Effective communication during/after treatment and information about TYA cancer for FP at diagnosis could help clarify expectations for both FP and patients, prevent disruption of the patient:primary care relationship, and assist FP to contribute to care in partnership with TYA cancer teams. A strategy to promote engagement between TYA and FP early after diagnosis is under development as part of the On Target programme.

P-330

Surgery (IPSO)

ANALYSIS OF MAJOR SURGICAL PROCEDURE IN ONCOLOGIC PEDIATRIC PATIENTS WITH COAGULATION DISORDERS.

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Objectives

Coagulation disorders are found in many patients with neoplasm. Risk factors to bleeding and/or thrombosis are augmented in patients who need a surgical procedure. The objective of these report is to analyze the frequency of these risk factors and preoperative management in patients with abdominal neoplasm who requires major surgical treatment.

Methods

Retrospective study in patients submitted to major surgical abdominal neoplasm resection in National Cancer Institution, in the period between 2011 and 2013, under 16 years old. The patients who had suspicion of coagulation disorders (bleeding previous history, laboratory coagulation disorders) were evaluated by Coagulation Committee. Non hematological patients were enrolled in this study.

Results

In this three years our pediatric oncology surgical service performed 1183 surgical procedures. 87 patients were evaluated by Coagulation Committe, 22 were submitted to major surgical treatment. The histopatological diagnosis were: neuroblastoma (4), Wilms tumor (7), germinative (3), Ewing neoplasm (2), PNET (2), desmoplastic tumor (1), paraganglioma (1), hepatoblastoma (1) , soft tissue sarcoma (1). The patients were followed by specialized coagulation team, before and after surgical procedures. The initial protocol of investigation by the Coagulation Committee was to evaluate lupus anticoagulant (LAC), protein C, antithrombin III, D-Dimer, V, VII, VIII, IX, X, XI factors. We followed the Institutional Protocol to prevent bleeding and/or thrombosis, specific for each patient. No major postoperative complications have occurred.

Conclusions

Its important the access to a specialized coagulation team for the patients with coagulation disorders, specially for pediatric oncology patients. With adequate management of these patients major complications can be reduced.

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Surgery (IPSO)

SCF EXPRESSION IS ASSOCIATED WITH UNFAVORABLE PROGNOSIS IN NEUROBLASTOMA

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Objectives

To determine the prevalence and the prognostic significance of SCF expression in neuroblastoma.

Methods

SCF expression was investigated by immunohistochemistry. Univariable and multivariable analysis(Cox regression) and outcome analysis(Kaplan Meier) was done for 2-year overall survival(OS) and 1-year event-free survival(EFS) in relation to the SCF expression. Death, recurrence, progression and non-response were considered as events.

Results

Of the 91 cases, there were 67(74%) ≥12 months of age, 62(68%) adrenal, 42(46%) stage-4. Histopathology upfront, was done in 54(59%), of which 39(72%) were unfavorable histology(UFH) tumors. SCF expression was observed in 21(23%) of the 91 tumors. SCF expression was more commonly observed in stage-4 as compared to non-stag-4(36% vs. 12%; p=0.012) and among high grade than low grade(36% vs.0%; p=0.011). No response or progressive disease was commoner in those with SCF expression(62% vs.28%; odds-ratio 4.19(95%CI; 1.5-11.7); p=0.008). Five of 21(24%) with SCF expression died and 17(80%) had events giving a poorer OS(29% vs. 85%; p=0.0046) and EFS(7% vs. 56%; p=0.0001) for those with SCF expression. Of 17(27%) patients with SCF expression in the adrenal location, 4(24%) died and 14(82%) had an event giving poorer OS(21% vs.80%; p=0.025) and EFS(45% vs.66%; p=0.0007) for those with SCF expression. Among 42 stage-4 patients, 15(36%) had SCF expression and among these 5(33%) died and all 15(100%) had an event giving poorer OS(17% vs.77%; p=0.02) and EFS(40% vs.43%; p=0.05) for those with SCF expression. Thirteen among the 39(33%) with UFH had SCF expression and among these 2(13%) died 11(85%) had an event. The EFS (38% vs.58%; p=0.04) was significantly worse for those UFH with SCF expression.

Conclusions

SCF is expressed in 23% of the neuroblastomas and its expression is an independent prognostic variable responsible for shorter event-free survival [hazard-ratio 2.48 (95%CI; 1.11-5.52); p=0.026]. This difference in outcome is especially marked in those with age ≥12, stage4, adrenal and unfavourable histology tumors.

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Surgery (IPSO)

CLINICAL APPLICATION OF MULTIPARAMETER FLOW CYTOMETRY TO DIAGNOSTIC SCREENING AND CLASSIFICATION OF PEDIATRIC SOLID TUMORS

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Objectives

Multiparameter flow cytometry (MFC) immunophenotyping has proven to be essential for rapid diagnosis, classification and monitoring of therapy in most hematological malignancies, including pediatric leukemias and lymphomas. Conversely, it remains a research tool for pediatric solid tumors. Here we evaluate a MFC panel of markers for the diagnostic screening and classification of those tumors. The proposed strategy aims at differential diagnosis between tumor *vs* reactive samples, hematological *vs* non-hematological malignancies, and the subclassification of pediatric solid tumors.

Methods

A total of 125 samples from 91 patients suspicious of pediatric cancer – 51 males (56%) and 40 females (44%) were analyzed by MFC panel following a gating strategy analysis for identification of suspicious tumor cells and further characterization into hematopoietic *vs* non-hematopoietic solid tumor. To establish the statistical significance of differences observed between groups, the Mann-Whitney U test was used (continuous variables; SPSS software program, version 18.0, SPSS Inc., Chicago, IL, USA).

Results

Seventy-two patients (79%) had cancer, 31 of whom (43%) showed metastatic disease; the remaining 19 children (21%) had inflammatory/reactive diseases. The overall concordance rate between MFC analysis and histopathological exam was of 92.2% (diagnostic samples), with 100% agreement for all reactive/inflammatory, with only 9 false negative cases diagnosed as Hodgkin lymphoma, Anaplastic Lymphoma and a metastatic nasopharyngeal carcinoma in lymph node. Moreover, clear discrimination between samples infiltrated by hematopoietic vs. non-hematopoietic tumor cells was systematically achieved. Distinct subtypes of solid tumors showed different protein expression profiles, allowing the differential diagnosis of neuroblastoma (CD56hi/GD2+/CD81hi), primitive neuroectodermal tumors (CD271hi/CD99+), Wilms tumors (over 1 cell population), rhabdomyosarcoma (nuMYOD1+/nuMyogenin+), carcinomas(CD45-/EpCAM+), germ cell tumors (CD56+/CD45-/NG2+/CD10+) and eventually hemangiopericytomas (CD45-/CD34+).

Conclusions

In summary, our results show that MFC provides fast and useful complementary data to routine histopathology for the diagnostic screening and classification of pediatric cancer.

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Surgery (IPSO)

ACUTE SURGICAL COMPLICATIONS OF ABDOMINAL LYMPHOMA : A STUDY AMONG EGYPTIAN CHILDREN OVER A PERIOD OF 20 YEARS

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Objectives

To report and study cases of abdominal lymphoma presented with acute surgical abdomen.

Methods

All children with abdominal lymphoma treated in the Pediatric Surgery & Pediatric Oncology Departments,University of Alexandria, Egypt over a period of 20 years were reported and sudied concerning their demographic data, clinical presentation, pathological varieties,staging and the management modalities. Type of surgery and survival were recorded.

Results

A total number of 121 cases of abdominal lymphoma were were reported over a period of 20 years with a median age 5.45 years. Non-Hodgikin's lymphoma was encountered in 103 cases (85%),with lymphoblastic lymphoma was the most common followed by Burkitt's lymphoma. Primary intestinal lymphoma was encountered in 32 cases. Twenty seven of these were presented with acute surgical abdomen as follows: intussusception (19 cases), volvulus (5 cases) and intestinal perforation (3 cases). These cases were treated by right ileocaecal resection in 23 cases and ileal resection in 4 cases. All cases were treated by chemotherapy as a definitive therapy. Two years survival of all cases were correlated to the stage as follows: stage I (70.5%),stage II (50%), stage III (16.2%),and stage IV (0%).

Conclusions

*Primary intestinal lymphoma in Egyptian children is a special entity of abdominal lymphoma.

*It is more liable to complicate and present with acute surgical abdomen.

*Surgey is indicated as an emergency for the acute surgical abdomen followed by chemotherapy as the definitive therapy.

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Surgery (IPSO)

ROLE OF PET- CT IN STAGING OF PEDIATRIC ROUND CELL TUMORS.CAN IT ELIMINATE THE NEED FOR BONE MARROW BIOPSY?

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Objectives

To evaluate the efficacy of PET-CT in detection of bone marrow metastases in pediatric round cell tumors (Neuroblastoma, Rhabdomyosarcoma) and to compare it with the gold standard method of bilateral bone marrow biopsy.

Also to compare the results of bilateral marrow biopsy with unilateral biopsy to determine whether unilateral biopsy is sufficient for detection of bone marrow metastases.

Methods

This is a prospective observational study and includes all treatment naive patients with histologically confirmed diagnoses of Neuroblastoma or Rhabdomyosarcoma, attending pediatric surgery outpatient department in our hospital.

All the patients underwent a routine staging workup along with PET-CT. For evaluating the results of unilateral versus bilateral biopsy, findings of right sided biopsy were taken as a baseline for comparison for each patient. In cases of focal marrow positivity (PET showing a positive marrow site other than iliac crest) or discordance in results of PET-CT and bone marrow biopsy, presence of marrow metastases was confirmed with MRI scan of that region.

Results

At the time of abstract submission, of the 21 patients evaluated, there were 12 cases of Rhabdomyosarcoma and 9 cases of Neuroblastoma. There was no evidence of bone marrow metastases in 18 patients on both PET scan and bone marrow biopsy. Thus the negative predictive value of PET-CT for bone marrow metastases was 100% in our study.

PET-CT detected marrow metastases in 3 patients, of these two patients also had positive bone marrow biopsy. MRI done for one patient with negative bone marrow biopsy confirmed the findings of PET scan.

Of the two patients with positive bone marrow biopsy, one patient had unilaterally positive bone marrow.

Conclusions

PET-CT can obviate the need for bone marrow biopsy and its associated morbidities. Also it has the potential to be a single investigation for the staging work up of this group of patients.

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Surgery (IPSO)

OUTCOME OF ICE CHEMOTHERAPY AND SURGICAL RESECTION FOR THE TREATMENT OF RECURRENT WILMS TUMORS.

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Objectives

To evaluate the effectiveness of ICE (Ifosphamide+Carboplatin+Etoposide) as a salvage therapy in recurrent Wilms tumor (RWT).

Methods

Prospectively maintained data of patients of recurrent Wilms tumor managed in the pediatric solid tumor clinic from August 1999 through December 2013 was analyzed. Efficacy of ICE as a salvage regime as compared to other regimen using statistical program STATA 9. Significant difference was taken as $p< 0.05$. Kaplan Meier survival estimates for 2-year overall survival (OS) was done. Initial staging was done as per NWTS-5 protocol and treatment was done as per the AIIMS-WT-99 protocol.

Results

Of the 241 new cases of WT treated during this period, 41(17%) recurred (40 favorable histology, 1 diffuse anaplasia). The recurrence was following treatment for stage 1WT in 3(initially treated with Dactinomycin+Vincristin), stage 3 in 20, stage 4 in 11 and stage 5 in 7(all other stages following 3 drugs [Dactinomycin + Vincristin+ Doxorubicin] + RT). The recurrence was bilateral in 3, local in 10 and metastatic in 28. While 11(27%) opted for no further treatment, 2 had only re-resection (both for local recurrence following treatment for bilateral disease) and 28 received alternate chemotherapy(21 ICE;7 other protocols). Overall 18 patients underwent surgical resection for the recurrence (either upfront[2] or following chemotherapy[16]). Of the 21 who received ICE, 7 were alive giving an OS of 36% (95CI 16-57) while among the non-ICE group 11 survived(OS 49%; 95CI 22-72). The odds of survival among the non-ICE group was greater(OR 2.44; 95CI 69-86). Seven of 21(33%) in the ICE group and 4 of 7(57%) who received other protocols achieved disease free status.

Conclusions

One-fourth patients opted for no further treatment. ICE salvage regime resulted in disease free status far less frequently then by the other protocols and achieved OS of 36% in these intensely pretreated patients.

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Surgery (IPSO)

LONG-TERM RECURRENCES IN WILMS TUMOR: SINGLE CENTER SERIES

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Objectives

Wilms tumor (WT) is the most common renal tumor in children with an excellent outcome. Relapses occurred generally before two years from diagnosis. The aim of the study is to evaluate the rate and characteristics of long-term recurrence (LTR) in a single institution experience.

Methods

The Institutional WT register was checked in order to identify patients who presented a relapse after 3 years from diagnosis from 1999 to march 2011. Kaplan-Meier method was used for estimating overall survival(OS) and progression free survival(PFS) curve. Patients were treated according to SIOP 93-01 and SIOP 2001 Protocols.

Results

76 patients were diagnosed during the study period. 5 years OS and PFS were 93% and 81%, respectively. Relapses occurred in 16 patients at a median time of 7,5 months from diagnosis(range 2-82 months), 56% before 12 months. In this series, a bilateral kidney involvement occurred in 16(22%) patients while a metastatic spread in 9(12%). Out of 16 recurrences, 3 occurred locally at 82, 76 and 51 months from the onset. Two LTRs occurred in patients with bilateral disease at onset. The later patient presented monolateral WT who underwent a nephron-sparing surgery at diagnosis because of dominant polycystic kidney disease. This patient presented a second locally recurrence at 97 months and a third metastatic spread at 122 months from diagnosis. Three LTRs are alive in complete remission at 174, 134 and 130 months from diagnosis.

Conclusions

LTRs are rare events observed in less than 4% of population but representing about 20% of relapses. These are mostly local and often associated with a bilateral tumor at onset. Notably, in this series we reported a bilateral occurrence in 22% of patients. Further analysis may confirm an increased risk of LTRs in bilateral disease as suggested by our experience. However, a prolonged follow up with ultrasonographic scans should be recommended in bilateral disease.

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Surgery (IPSO)

DIARRHEAL NEUROBLASTOMA: DIAGNOSIS AND TREATMENT

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Objectives

The neuroblastoma cases with diarrhea as the main symptom, namely diarrheal neuroblastoma, are quite rare. Consequently , the experience for diagnosis and treatment of this disease is limited. Hereby to report a series of 6 cases of diarrheal neuroblastoma in our institute.

Methods

Six cases of diarrheal neuroblastoma from January1996 to December 2006 were analysed retrospectively. Clinicopathological features were summarized. Pathology confirmed the diagnosis. Vasoactive intestinal peptide (VIP) were detected with immunohistochemistry in the tumor tissue.

Results

Patients aged 11 to 30 months. The period from diarrhea begining to diagnosis was four months up to 1 year. Stool was loose or watery, 3-8 times each day with routine faece tests normal. Diarrhea was the first symptom and lasted permanently in five cases, and abdominal tumors were found by ultrasound finally. Two cases underwent the preoperative chemotherapy, of whom diarrhea stopped after chemotherapy in one and after surgery in the other. Three cases accepted upfront surgery and the diarrhea ended postoperation. One patient with persistent diarrhea and refractory electrolyte imbalance and passed away in the end. For one patient, whose preoperative serum potassium was 2.8mmol / L, had not been cured to normal level, cardiac arrest happened during the operation, at the exact time potassium was 1.8mmol/L.

The immunohistochemical staining of VIP showed positive in the tumor tissue of 6 patients.

Conclusions

Persistent and unreasonable diarrhea may predict neuroblastoma. The metabolic disorder of the diarrheal neuroblastoma were chronic dehydration, intractable hypokalemia, chronic malnutrition and growth stagnation. Even if the preoperative serum potassium had been corrected normal, hypokalemia would still occur in the operation, which could be lethal.

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Surgery (IPSO)

ROLE OF SURGERY IN PEDIATRIC NEUTROPENIC CANCER PATIENTS PRESENTING WITH GASTROINTESTINAL OBSTRUCTION OR PERFORATION

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Objectives

Was to evaluate the causes, and impact of surgical intervention on the outcome of gastrointestinal obstruction or perforation in pediatric neutropenic cancer patients post chemotherapy

Methods

This is a retrospective study that included all neutropenic pediatric patients following chemotherapy who were referred to surgery between Jan. 2008 to Dec. 2013 because of intestinal obstruction or perforation unrelated to the primary malignancy. Clinical, radiological, intraoperative findings and outcome were evaluated

Results

Exploration was done in nine cases (eight leukemia &one Retinoblastoma), because of obstruction (seven cases) and perforation (two cases). Pathologically proven mucormycosis was found in five patients (55%), three of them with intestinal obstruction and two patients with stomach perforation. On exploration the three obstructed cases had patches of gangrenous loops adherent together and resection anastomosis was done. On the cases with gastric perforation the edges were non-viable, trimming of the edge and primary repair augmented with omental patch was done in one case and partial gastrectomy on the other case.

In the remaining four cases, the cause of obstruction was due to fibrous band in two patients, intussusception in one patient, and non-specific inflammation in the last one. There was no specific clinical or radiologic presentation for mucormycosis. Two out of five cases died from progressive infection and inflammation and the other three patients recovered on postoperative maintenance antifungal therapy

Conclusions

Early and prompt surgical intervention in neutropenic pediatric oncologic patients with gastrointestinal obstruction or perforation may be life saving, although the patients' general condition may render it risky. Mucormycosis is not uncommon diagnosis in pediatric neutopenic patients have gastrointestinal obstruction or perforation, thus it should be kept in mind and appropriate antifungal agent should start as early as possible to prevent further complications.

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Surgery (IPSO)

LAPAROSCOPIC RESECTION OF THE PANCREAS IN CHILDREN WITH SOLID PSEUDOPAPILLARY TUMORS

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Objectives

Development rational surgery for solid pseudopapillary tumor (SPT) of the pancreas and implementation of Endosurgery.

Methods

5 children with SPT were operated since 2011 to 2013. We analyzed clinical data, operation options and results of treatment.

Results

All patients were girls age from 9 to 15 years (median 12y.o.). Course of the disease asymptomatic, however, was observed in 1 child pain in the epigastric region. Localization tumors in pancreas: in the tail. The size: 5,5 – 7,4 sm (M 6,5 sm). 5 children underwent laparoscopic distal pancreatectomy with splenic preservation. Time of operations: 90 – 190 min. Bleeding: 100ml. Complications occurred in 2 patients: pancreatitis with pancreatic fistula. The observation period of the patients was from 6 month to 2 years. All patients are alive without evidence of disease recurrence.

Conclusions

SPT of the pancreas is a rare disease in children, which usually occurs in girls puberty. The main method of treatment is surgery, the use of endosurgery possible, but very strictly necessary to define the indications for this type of treatment and the risk of postoperative complications.

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Surgery (IPSO)

MANAGEMENT AND LONGTERM OUTCOMES OF GIANT MEDIASTINAL GERM CELL TUMORS IN CHILDREN

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Objectives

To evaluate the outcome of children with giant mediastinal germ cell tumors.

Methods

All children up to 12 years of age, with mediastinal germ cell tumors (GCTs) treated at our hospital from 2008 through 2014 were evaluated for their tumor size, malignancy,chemotherapy, surgery, complications and outcome.

Results

Twelve mediastinal GCTs were included. The age ranged from 7-144 months with 5 (42%) being $\leq$ 1 year, 3 (25%) 1-10 years and 4 (33%) > 10 years of age. All except one were males(92%).The average size of the tumor was 9cm x 6 cm. Four were occupying nearly the entire hemithorax, displacing the diaphragm inferiorly. Nine of these 12 (75%) were benign (normal αFP) while 3(25%) were malignant (with elevated αFP). While all 12 benign GCTs were resected upfront, the 3 malignant ones received 2 courses of PEB (Cisplatin+Etoposide+Bleomycin).On neoadjuvant chemotherapy, though there was no significant reduction in size noticed, the αFP levels decreased in all the three. All patients underwent complete resection of the tumor, 8 (67%) through postero-lateral thoracotomy (5-left, 3-right) and the 4 (33%) through median sternotomy. One, a dumbell shaped thoraco-abdominal tumor through a Bochdelek hernia, required laparotomy as well as diaphragmatic repair. There were no post-operative complications and the malignant ones completed a total of 4 courses of PEB. The follow-up ranged from 6 to 72 months (mean 39.5) and all are alive and disease free.

Conclusions

In this study group, mediastinal GCT had a bimodal age distribution and male predominance.The tumors in older children were of giant size, occupying the whole of the hemi-thorax.Neoadjuvant chemotherapy in those with elevated αFP did not decrease the size of the tumors even though the αFP normalized. A complete excision led to minimal post-operative complications and ensured long term disease free survival.

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Surgery (IPSO)

RHABDOID TUMOR OF KIDNEY: DISMAL OUTCOMES AT A TERTIARY CARE CENTER IN A DEVELOPING COUNTRY

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Objectives

To evaluate the outcome of children with rhabdoid tumor of kidney (RTK).

Methods

Retrospective review from the records of children with RTK enrolled from 1988 through2013 for their presentation, chemotherapy, surgeryand outcome. Before 1999 the chemotherapy was DD4A(Vincristin+Dactinomycin+Adriamycin) while since 1999 it was RTK regime (Carboplatin+Etoposide+Cyclophosphamide).

Results

Among the 480 renal tumors treated in this period, 9(2%) wereRTK.Age ranged from 4 to 24 months(median12) and the male:female ratio was 1.3:1. All presented with an abdominal mass, 2(22%) also had hypertension and one (11%) hadgross hematuria. The tumor size ranged from 11-9 centimeters(mean 10.5). Seven (78%) children had stage IIIand 2 (22%) had stage IV disease with metastasis to bilateral lungs in one(11%) and bilateral lungs and liver in another.Four(44%) received neoadjuvantchemotherapy(3 DD4A and 1RTK regimen) and of these 2 could be resected(gross complete resection) while 2 died pre-operatively of progressive disease.Overall 7(78%) patients underwent surgery(5 upfront and 2 following neoadjuvant chemotherapy) of whom 5 had gross complete resection, 2 had gross residue. Five of 7(71%) resected had tumor spill (all upfront resection). Two died soon after resection while the remaining 5 (56%) patients received adjuvant chemotherapy and only 2(22%) received radiotherapy. All 5 (56%) patients who underwent complete excision had early local recurrence ranging from 15 days to 4 months (median 1 month) post-excision. The other 4 (44%) had progressive disease (2 following incomplete resection and 2 without resection). All 9 patients died with period of survival ranging from 2-6 months from diagnosis (median 2 months).

Conclusions

RTK is a rare pediatric renal tumorof very young children. They had very high incidence of tumor spill during upfront resection. They demonstrated very early recurrence or rapid progression and death within median of 2 months of diagnosis despite aggressive chemotherapy and complete surgical resection.

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Surgery (IPSO)

PAEDIATRIC TESTICULAR TUMOURS: A SINGLE-INSTITUITION EXPERIENCE

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Objectives

To describe a single-institution's series of paediatric testicular tumours and our experience with testis-sparing surgery(TSS).

Methods

Following IRB approval, a retrospective clinical chart review was conducted for patients with primary testicular tumours diagnosed between January 2001 and July 2012. Data on clinical presentation, demographics, pre-operative investigations and surgical procedures were collated and analysed using conventional statistics.

Results

Nineteen tumours were analysed and 89%(17) were of germ cell origin. Median age at diagnosis was 20 months(1-197). The most common presentation was a painless scrotal swelling(15,79%). All patients underwent testicular exploration via inguinal approach. Orchidectomy was performed with high ligation of the cord. In select cases of benign pathology, TSS was done. Nine patients had benign tumours(7 teratomas, 2 epidermoid cysts) and 10 lesions were malignant(5 yolk sac tumours(YST), 3 mixed malignant germ cell tumours(GCT), 1 follicular lymphoma, 1 rhabdomyosarcoma). In GCT, pre-operative Alphafetoprotein was elevated in all malignant subtypes when corrected for age. All except one malignant GCT were stage 1 at diagnosis and orchidectomy alone was curative(100% event-free survival at 88 months). The last patient had stage 4 YST and received adjuvant chemotherapy according to BEP protocol. He has remained disease-free for 9 years. TSS was performed for 6 of the 9 benign GCT. Of these, all had post-operative ultrasound demonstrating viable remaining testicular tissue. At least 1 child had undergone puberty and demonstrated growth of the remaining testicular tissue. None of the patients with benign GCT had tumour recurrence at median follow-up of 60 months(18-135).

Conclusions

Majority of paediatric testicular tumours are of germ cell origin. These tumours have an excellent prognosis even in advanced disease or delayed diagnosis. TSS is therefore a feasible option and completion orchidectomy can be employed in cases of recurrence. With close imaging surveillance, TSS can perhaps also be offered to selected patients with malignant GCT.

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Surgery (IPSO)

PERIOPERATIVE TUMOR RUPTURE CONFERS POOR SURVIVAL IN WILMS TUMOR

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Objectives

Wilms tumor (WT) is the most common tumor of kidney in childhood. In the present study, we focused on preoperative and perioperative ruptures of tumors and their impact on survival.

Methods

From 7/1988 to 5/2009 239 patients with WT were treated at our institution. Event free survival (EFS) and overall survival (OS) was analyzed using Stat View statistical program.

Results

Patients were treated according to protocols: SIOP 9 (94 patients), SIOP 93 (80) and SIOP 2001 (65). Median follow-up is 12.5 years (3-21). 120 patients of 239 (50%) were treated with neoadjuvant CHT, 119 patients (50%) underwent primary nephrectomy. EFS and OS patients treated with neoadjuvant CHT or primary nephrectomy did not differ (EFS 76.6% versus (vs.) 79.8%, P>0.05; OS 85.8% vs. 86.5%, P>0.05). 29 patients out of 239 (12%) suffered from tumor rupture, EFS and OS did not differ in comparison to non-ruptured cases (EFS 76.6% vs. 78.8%, P>0.05; OS 83.3% vs. 86.5%, P>0.05). Preoperative tumor spillage was diagnosed in 21 cases; all the patients underwent primary nephrectomy. Perioperative tumor spillage occurred in 8 cases, 7 patients suffered from tumor spillage during primary nephrectomy (7 out of 98, 7%), only 1 patient suffered from tumor spillage when nephrectomy was performed after neoadjuvant CHT (1 out of 120, 0.8%, P=0.02). Four patients (50%) with perioperative tumor rupture had metastatic disease at diagnosis in comparison to 2 patients with spontaneous tumor spillage (10.5%, P=0.03). EFS of 21 patients with spontaneous tumor rupture is 90% in comparison to 37% with perioperative tumor rupture, P=0.001, OS is 100% vs. 37% P

Conclusions

Patients suffering from perioperative tumor spillage had more likely metastatic disease and poor prognosis at our institution. Our findings should be confirmed in a multicenter study.

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Surgery (IPSO)

DOES THE ADDITION OF TOPICAL VANCOMYCIN DECREASE THE INCIDENCE OF SURGICAL SITE INFECTION IN BONE TUMORS?

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Objectives

A retrospective audit compared a consecutive group of patients operated for bone tumors who received only perioperative antibiotics (Group A) against a similar group that had additional topical vancomycin sprinkled in the wound prior to closure (Group B), to determine if addition of topical vancomycin decreases the incidence of surgical site infection (SSI).

Methods

221 patients operated between Jan 2011 and Dec 2011 (Group A) and 183 patients operated between April 2012 and Dec 2012 (Group B) were analysed. Any patient needing operative intervention for wound discharge was considered infected. All patients had a one year follow up to determine incidence of SSI.

Results

The overall rate of SSI was 7% (29 of 404 patients). 17 (8 %) of Group A and 12 (7 %) of Group B patients had SSI – p = .669. In a subgroup analysis of patients with endoprosthetic reconstruction, 9 of 97 (9 %) of Group A patients and 7 of 74 (9 %) Group B patients had SSI. Similarly 3 of 76 (4 %) Group A patients and 2 of 64 (3 %) Group B patients with internal fixation implants (plates / IM nails), had SSI.

Conclusions

Addition of topical vancomycin prior to wound closure in patients operated for bone tumors does not decreases the incidence of surgical site infection (SSI). A longer follow up may determine its efficacy in reducing the incidence of late infections.

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Surgery (IPSO)

EARLY SURGICAL INTERVENTION IMPROVES CHANCE OF SURVIVAL IN NEUTROPENIC PATIENTS WITH CLOSTRIDIUM SEPTICUM SEPSIS

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Purpose

Due to our identification of high mortality rates in neutropenic patients with *Clostridium septicum* sepsis, we sought to identify prognostic and/or interventional measures that could be associated with improved outcome.

Method

Retrospective review of patients diagnosed with *C. septicum* infection from 1/2003 to 3/2014 with collection of prognostic and interventional measures that might be associated with outcome.

Results

Six patients were identified, 5 were female. Median age at infection was 13.5 years (range 3.5-21.2 years). Three had Acute Lymphoblastic leukemia, 2 Acute Myeloid leukemia and one Rhabdoid brain tumor. All were receiving myelosuppressive chemotherapy All patients were severely neurtopenic and 5 were not yet in remission. *C. septicum* were isolated by culture from all patients with 5 from blood and 1 from biopsy tissue. All patients presented with septic shock, 4 had clinical features of severe enterocolitis, one with abdominal wall and perirectal necrotizing fasciitis (); and another with erector spinae myonecrosis. All patients were treated with broad spectrum antibiotics and hospitalized in intensive care. Surgery was performed in 4 patients, 3 patients underwent surgical resection/debridement, and one had decompression exploratory laparotomy for compartment syndrome. Two patients survived, one with extensive erector spinae myonecrosis following extensive debridement surgery, and the other resection of perforated terminal ileum. The remaining four patients died within 4 hours to 6.5 days of first positive *C. septicum* culture.

Conclusion

In immuncompromised pediatric oncology patients, *C. septicum* infection is rapidly and highly fatal. High index of suspicion, particularly in patients with severe abdominal pain, septic shock, together with prompt therapeutic intervention by instituting anti-anaerobic antimicrobial coverage and early surgical intervention are critical in improving the chance for survival.

Document not received

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Psychosocial

TOWARDS A DYADIC UNDERSTANDING OF PARENTAL COULES' MARITAL SATISFACTION IN THE PEDIATRIC CANCER CONTEXT

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Objectives

In the context of pediatric cancer, parents have various caregiving and support roles in the child's rehabilitation (Hutchinson et al, 2009; Long & Marsland, 2011), thus their well-being (including their conjugal well-being) is of vital importance. This research provides a dyadic understanding of the martial satisfaction of mothers and fathers of acute lymphoblastic leukemia (ALL) patients through predictors including individual mood and perceived family well-being.

Methods

Couples completed the Family Well-Being Assessment (family well-being) and the Profile of Mood States-Bipolar Form (mood states) at diagnosis and three months later, as well as the Locke-Wallace Marital Adjustment Scale (marital satisfaction) at 1-year (n = 72) and 2-years post diagnosis (*n* = 61). Specifically, this data comes from a cohort of parents of children treated for ALL at the CHU Sainte-Justine.

Results

Analyses based on the Actor-Partner Interdependence Model (APIM; Kenny et al., 2006) demonstrated that there are different marital satisfaction predictors for mothers and fathers of pediatric cancer patients. Mothers' marital satisfaction at 1 and 2-years post diagnosis was predicted by her family well-being variables at diagnosis and 3-months (actor effects); whereas fathers' marital satisfaction was predicted by his mood (actor effects) and his partners' role conflict and fatigue at diagnosis and 3-months (partner effects).

Conclusions

These research findings indicate that predictors of marital satisfaction for mothers and fathers of children with leukemia differ. This suggests the importance of using dyadic models to examine the relational adjustment of the parental couple and account for potential partner effects and gender effects. Thus, clinical interventions designed to help these couples should be tailored to address their specific needs and continued support should be provided throughout the cancer trajectory.

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Psychosocial

INTEGRATED ASSESSMENT MAP (I AM) – A DOMAIN BASED HOLISTIC FRAMEWORK

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Objectives

Peer Review standards require that all patients are offered a holistic assessment of their needs. Within the Teenage and Yound Adult (TYA) population this is seen as a priority given the range and complexity of needs. The South West TYA service operates an online Multidisciplinary Advisory Team (MDAT) and so a framework to capture the holistic needs of TYA's and for meeting guidance was required.

Methods

A collaborative approach was used to develop the Integrated Assessment Map (IAM) and a multi-domain model was created to provide a structure to ensure that all TYA's were offered an assessment that incorporated the impact of diagnosis of cancer additional to treatment within a bio-psycho-social-educational-vocational framework. The domains used in the IAM model are; Physical impact, Emotional impact, Beliefs &Spirituality, My support network, Intimate relationships & fertility, My lifestyle-health , Education Training & Work, Accommodation & finance, My lifestyle-Activities/Interests. A scoring system was developed with a score assigned to each domain

· Level 1 – Universal: No additional input
· Level 2 – Targeted: Some additional input
· Level 3 – Specialist: significant input

The IAM is completed at stages throughout the pathway to allow for individual tracking by professionals and patients, and as a tool to guide service development.

Results

Internal service evaluation has been completed.The IAM is used consistently when discussing the needs of TYA's via the online Multi-Disciplinary advisory Team (MDaT) meeting and provisional data has been examined for service development purposes. A review and 'next steps' phase has begun, considering validation and publication.

Conclusions

The IAM provides the TYA service with a quantifiable measure of the TYA's support needs at various points in their pathway. It ensures the young person is at the centre of their care planning and that all areas of support are discussed at the appropriate time.

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Psychosocial

HISTORY OF RELAPSED DISEASE IN PEDIATRIC BRAIN TUMOR SURVIVORS: PSYCHOSOCIAL OUTCOMES AND QUALITY OF LIFE

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Objectives

Advancement in medical treatment has allowed for improved survival rates for pediatric brain tumor patients, even after relapse. Although pediatric brain tumors survivors are at-risk for psychosocial challenges, little is known about how relapse history affects psychological outcomes and quality of life. This study examined the associations between disease relapse, psychological functioning, and quality of life in adolescent and young adult (AYA) survivors of pediatric brain tumors.

Methods

Participants were 84 adolescents (age 12-18) who completed the Beck Youth Inventory-II and 79 young adults (age 19-30) who completed the Brief Symptom Inventory-18 and the SF-12. Parents completed the Child, and Adolescent Behavior Checklists for respective age groups. Clinicians rated participants on the Global Assessment of Functioning (GAF) following semi-structured clinical interviews. Previously established cut-off scores were used to identify cases of clinically significant distress. Disease and treatment variables were taken from the medical record.

Results

14% (23/162) of participants experienced relapse and 48% (11/23) of relapsed participants had a low grade glioma. Clinically significant anxiety was significantly more common in survivors with relapse history than in those with no history of relapse (33.3% vs. 10.5%, p=.005). There were no significant relationships between relapse history and patient-reported depression or QOL, parent-reported behavior problems or clinician GAF ratings. Anxiety was not significantly related to time since diagnosis (p>.05).

Conclusions

Relapse can be considered a risk factor for clinically elevated anxiety in AYA brain tumor survivors. Anxiety symptoms were present regardless of length of time since diagnosis. Results point to the importance of using self-report anxiety measures to capture this distress. Early identification of at-risk survivors could allow for implementation of empirically validated treatment for anxiety, particularly for low grade glioma patients, who may experience multiple relapses.

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Psychosocial

ETHNIC DIFFERENCES IN COPING, SOCIAL SUPPORT AND QUALITY OF LIFE AMONG PARENTS OF CHILDREN WITH CANCER

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Objectives

Pediatric cancer is widely accepted to drastically impact the parents' quality of life. Adaptive coping skills and social support are seen as important protective factors (e.g., Greening & Stoppelbein, 2007). Despite our multicultural society, pediatric cancer research on ethnic differences in parents' coping and social support is scarce. The current study investigated (a)mean level differences in coping strategy, social support and quality of life between Caucasians and immigrants and (b)whether the impact of coping and social support on quality of life was moderated by ethnicity.

Methods

Validated questionnaires on coping, social support and quality of life were administered from two matched samples of parents (23 Caucasians, 21 north Africans).

Results

Mean-level differences were uncovered through MANOVA analyses. As for coping, immigrants were found to score higher on positive reappraisal ($p<0.10$) and on putting into perspective ($p<0.01$). In terms of social support, immigrants generally reported receiving equal or more social support than Caucasians ($p<0.10$). At the same time, they also reported a lower satisfaction with social support as well ($p<0.01$). Also, immigrants seemed to have a lower quality of life due to a higher incidence of physical complaints (pain ($p<0.05$) and sleep ($p<0.01$)) and depression symptoms ($p<0.05$). Linear regression analyses were performed to investigate the impact of coping and social support on quality of life. The degree of experienced social support was no significant predictor; yet, satisfaction with social support was found to be an important predictor of quality of life ($p<0.01$). None of these associations were moderated by ethnicity.

Conclusions

In conclusion, the current childhood cancer investigation uncovered several important ethnic differences in parents' coping and especially in (satisfaction with) social support. More profound investigation with larger groups of parents is warranted in order to guarantee support tailored to the needs of each person regardless of their ethnic origin.

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Psychosocial

Attention Bias Modification Therapy (ABMT) as a modern technique for pain management in children with cancer

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Introduction:

The purpose of Attention Bias Modification Therapy (ABMT) is to implicitly shape anxiety related biases in attention orienting. Continuing pain problems in children with cancer are often assumed to be excessively attentive for their symptoms, and this is referred to as hyper-vigilance. This model assumes that fearful children become increasingly vigilant for signs of bodily threat, which in turn leads to avoidance behavior, increased disability and maladjustment to cancer treatments.

Methods:

ABMT uses the dot-probe task as a therapeutic tool by computer program. Potential applications of attention bias modification (ABMT) for acute (injection pain) in the children were investigated. In this study 98 children with cancer who were under daily injection were recruited and randomized to receive 8 session of ABMT or placebo. Children were followed up 3 months later.

Results:

Participants who were randomized to receive ABMT reported better coping to injection pain ($P = 0.043$) and adherence of self management program for control pain ($P = 0.003$) and show better communication for nurses who did the injection ($P = 0.01$) than those who received placebo.

Conclusion:

The results of these studies show that there is potential in the application of ABMT to pain conditions, and a positive effect of ABMT on clinical outcomes suggests that this technique is worthy of future study as an intervention for pain patients.

Document not received

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Psychosocial

PSYCHOSOCIAL PROFILE OF PEDIATRIC BRAIN TUMOR SURVIVORS WITH NEUROCOGNITIVE COMPLAINTS

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Objectives

With more children surviving a brain tumor, neurocognitive consequences of the tumor and/or its treatment become apparent. We studied the psychosocial functioning of this growing group of pediatric brain tumor survivors (PBTS).

Methods

Psychosocial functioning of PBTS (8-18 years) with neurocognitive complaints was compared to normative data on the following domains: Health Related Quality of Life (HRQOL), self-esteem, social-emotional functioning, executive functioning, (one-sample t-tests) and fatigue (sibling control group, independent samples t-test). We included self-, parent-, and teacher-report questionnaires where appropriate.

Results

82 PBTS (mean age=13.4 years, SD=3.2, 49% boys) and 43 healthy siblings (mean age=14.3, SD=2.4, 40% boys) were included. PBTS reported decreased physical, psychological and generic HRQOL (*d*s 0.39 to 0.62, *Psd*=0.57, *Pd*=0.81, *Pd*s 0.35 to 0.43, *Psd*=0.69, P

Conclusions

PBTS show increased psychosocial problems, as reported by themselves, parents and teachers, with small to large effect sizes. Better understanding of psychosocial functioning in the growing group of PBTS with neurocognitive complaints, will help to provide tailored support to this group of vulnerable children.

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Psychosocial

LIFE GOALS IN PATIENTS WITH CANCER: A SYSTEMATIC REVIEW WITH IMPLICATIONS FOR ADOLESCENT AND YOUNG ADULT PATIENTS

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Objectives

One characteristic of adolescent/young adult (AYA) development is the identification and pursuit of life goals; unknown is how cancer affects life goals during this developmental stage. A critical examination of existing research is needed to establish what is currently known, and to inform subsequent study design. Purposes of this systematic review were to: 1) identify theoretical models used to examine cancer patient life goals, 2) identify life goal constructs being examined and their assessment, and 3) summarize what is known about the impact of cancer on life goals.

Methods

Our systematic review examined research on life goals in patients with cancer published between 1993 and 2013. Inclusion criteria were: 1) cancer population, 2) original research article, and 3) assessed life goals. Based on these criteria, 156 articles were screened and 32 included in the final review. Theoretical models, goal constructs, assessment methods, and findings were summarized and informed discussions centered on AYA life goals.

Results

Self-regulation was the most commonly applied theoretical model (28%), and nearly half (44%) used theories not replicated in other studies. Goal constructs included self-identified life goals, change in life goals, goal disturbance/hindrance, and goal adjustment. Goal assessment methods included validated questionnaires (47%), author-developed questionnaires (31%), and semi-structured interviews (22%). Review study findings suggest: 1) cancer hinders ability to achieve pre-diagnosis goals and changes life priorities (i.e., greater focus on social and health-related goals), and 2) goal adjustment is related to better psychosocial/physical health outcomes.

Conclusions

Review findings offer theoretical frameworks and validated questionnaires for inclusion in subsequent research. Cancer negatively impacts patient goal achievement, and interventions targeting goal adjustment may improve patient outcomes. However, representation of AYA in the reviewed study samples was low, and research specific to AYA life goals is needed to elucidate the impact of the cancer experience on patients during this unique developmental stage.

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Psychosocial

ON THE CHILD'S OWN INITIATIVE - PARENTS COMMUNICATE WITH THEIR DYING CHILD ABOUT DEATH

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Objectives

Open and honest communication has been identified as an important factor in providing good palliative care. Parents having lost a child to cancer in some cases regret not having talked to their child about death. Still, there is no easy solution to if, when and how parents and a dying child should communicate about death. This study reports on how parents communicated about death with their dying child.

Methods

Nation-wide questionnaire with bereaved parents having lost a child to a malignancy during a six-year period in Sweden. Parents were asked how they communicated with their child about death and if they used fairy-tales, drawings, films, music or other activities as facilitators of the communication. In addition, parents were asked to elaborate on their answer with written comments. Both quantitative and qualitative content analyses have been used.

Results

449/561 (80%) parents returned the questionnaire. Using fairy tales was the most commonly reported mean of communication, regardless of the age of the dying child. Parents with children younger than four, used music and drawings to communicate, less often than parents with older children. 67 parents provided free-hand comments revealing that often it was the child who initiated communication about death. Analysis revealed four categories as to how communication about death occurred, 1) *communicating about death by using narratives*, 2) *talking about friends and family that had died, or about death itself*, 3) *talking about life after death,* and 4) *preparing for death through practical preparations.*

Conclusions

There are many ways in which a parent can communicate about death with his or her dying child. In our study many used fairy-tales or other means to facilitate the communication about a difficult subject. Providing appropriate literature and/or movies at the pediatric wards may help parents and children in their communication at minimal risk of causing harm.

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Psychosocial

STABILITY OF TWO SHORT DISTRESS MEASURES AS APPLIED TO PARENTS OF SURVIVORS OF CHILDHOOD BRAIN AND OTHER SOLID TUMOURS

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Objectives

To estimate the stability of the Distress Thermometer-Parents (DT-P) and the Anxiety and Depression Scales of the Edmonton Symptom Assessment System-Revised (ESAS-R -A, -D) with parents of survivors of childhood brain tumours and other solid tumours.

Methods

Fifty-six parents completed distress questionnaires immediately after a usual follow-up appointment of their child (M0) and a month later (M1). Parents rated children's HRQoL and life events on separate scales.

Results

The DT-P and the ESAS-R -A and -D demontrated high test-retest reliability in a stable clinical situation (*r*s > .65). Changes in children's HRQoL and life events were associated with changes on distress measures. DT-P and ESAS-R -A and -D scores were associated with scores of other validated distress measures (*r*s > .60).

Conclusions

The DT-P and the ESAS-R -A and -D may be stable measures of parental distress. The results support the use of these instruments in caregivers. It is important to study test-retest correlations in single-item distress measures since it is the only way to ascertain the reliability of these measures.

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Psychosocial

A MULTI-SITE EVALUATION OF SUMMER CAMPS FOR CHILDREN WITH CANCER AND THEIR FAMILIES

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Objectives

More children are surviving childhood cancer. Children with cancer and their families often attend specialized summer camps (therapeutic recreation) through their cancer treatment journey. Evaluations of these programs are emerging over the recent decade. Previous evaluations have infrequently used standardized measures, and typically enrol small sample sizes drawn from one summer camp. To address these gaps, this study sought to use standardized outcome measures, and to enrol a large sample size from multiple centres to enable stratification of outcomes by sub-groups.

Methods

A cross-sectional study in 2012 at 19 camps in North America was used to evaluate summer camps for children with cancer and their siblings. Outcomes were measured using the 29-item Pediatric Camp Outcomes Scale (PCOS) which uses a Likert Scaling to score. This study had approval by the Stanford Ethics Review Board and participants signed consent forms.

Results

A total of 2,286 campers (N=1215 females) were enrolled in this study. Of these campers, 1,332 were patients and 951 were siblings. Participants (patient or sibling): “on” treatment were 444 (20%), relapsed 294 (14%) and 1st year at camp 535 (24%). The mean score on the PCOS emotional subscale was 29.8 (SD=4.5); social subscale was 39.8 (SD=5.3); physical subscale was 20.6 (SD=3.2) and self-esteem was 22.3 (SD=2.8). The PCOS total mean score was 112 (SD=12.6).

Conclusions

This study uses the standardized PCOS tool to measure outcomes for children attending camp. This allows for comparison of data across camps and across specialty camp types (eg cancer, diabetes etc). The findings demonstrate that camp helps campers feel improved emotional, social, and physical functioning, and helps children improve their self-esteem. Strongest scores were observed for the emotional and social functioning subscales. Ultimately it is hoped that these increased skills gained at camp will help build coping and resiliency for children who have been diagnosed with cancer.

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Psychosocial

TWO OVERLOOKED CONTRIBUTORS TO ABANDONMENT OF CHILDHOOD CANCER TREATMENT IN KENYA: PARENTS' SOCIAL NETWORK AND EXPERIENCES WITH HOSPITAL RETENTION POLICIES

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Objectives

Principal reason for childhood cancer treatment failure in low-income countries is treatment abandonment. Two often neglected factors may contribute to abandonment: 1) Lack of information and guidance by doctors, along with beliefs of those surrounding parents, can increase misconceptions regarding cancer and its treatment, 2) National policy in public hospitals by which patients are retained after doctor's discharge until medical bills are settled. This study explored parents' social network and experiences with hospital retention policies in a Kenyan academic hospital.

Methods

Home-visits were conducted to interview parents of childhood cancer patients who had been diagnosed between 2007-2009 and abandoned treatment.

Results

Retrospective chart review revealed 98 childhood cancer patients had abandoned treatment. During 2011-2012, 53 families (54%) could be reached and 46 (87%) interviewed. Community members surrounding parents (grandparents, relatives, friends, villagers, church-members) believed that the child was bewitched (61%), advised parents to seek alternative treatment (74%), and stop medical treatment (54%). Parents discussed with other parents of cancer patients that child's life is in God's hands (87%), trauma of forced hospital stays (84%), importance of completing treatment (81%), financial burden of treatment (77%), and incurability of cancer (74%). These discussions influenced their perceptions of cancer treatment and its usefulness (65%). Thirty-six families (78%) had no health-insurance and nineteen of these parents (53%) could not pay their medical bills and were not allowed to take their child home. Parents felt desperation (95%), powerlessness (95%), sadness (84%), and that their child was imprisoned (80%) during the retention period. Most parents (87%) felt hospital retention must cease.

Conclusions

The beliefs of those surrounding parents may influence their perceptions of cancer treatment and contribute to abandonment. Hospital retention policies are highly distressing for parents and may contribute to both treatment delays and treatment abandonment. These factors jeopardize treatment outcomes for children and require attention and modification.

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Psychosocial

EXAMINING THE EFFECTS OF CHILDHOOD CANCER ON THE PARENTAL SUBSYSTEM

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Objectives

This study investigated the effects of childhood cancer on the parents' relationship. Some past studies report that childhood cancer can have a negative effect on the relationship and others that it can even strengthen it. Though it may not ever be known whether or not the relationship suffers or strengthens, what is little understood is *how* the cancer experience affects the relationship between the parents and what might health care professionals do to support the relationship.

Methods

23 unstructured interviews were conducted to a total of 29 participants. Data were analyzed using hermeneutic phenomenology methods of interpretation. The participants included parents of children who were 1) treated and cured and live with little or no side effects; 2) treated but live with long term effects; 3) did not survive.

Results

The state of the relationship prior to cancer had, in many situations, important implications on how the relationship fared during and after the cancer experience. This cannot be the only predictor however, as some challenged relationships thrived and repaired as a result of the experience. The strongest finding in this study is that the relationship can be affected in intense ways, even to the surprise of the couples and they offered advice to other couples facing this experience. The participants also had advice to offer health care professionals about things that are helpful and not helpful to say and do regarding supporting them as a couple.

Conclusions

The relationship between the parents has profound effects on the health and well being of the child and any support that can be offered in this area is preventative healthcare.

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Psychosocial

DETAILED PSYCHOAFFECTIVE STATUS IN A LONG TERM PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) SURVIVORS COHORT: DESCRIPTION AND PREDICTION

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Objectives

Survivors of pediatric ALL are at increased risk of mental health difficulties. Previous research suggests that emotional patterns could be specific in this population. Although rates for broad psychiatric conditions have been studied, no description of individual emotional symptoms has been offered. Describing psychoaffective symptoms is essential to orient further treatment. The objective of this study is to present a detailed description of psychoaffective status in a sub-group of a large pediatric ALL survivors cohort. We describe positive and negative emotions, depression and anxiety symptoms (including concerns), mental quality of life and fatigue.

Methods

The present sample consists of 70 survivors from an ongoing cohort follow-up (Sainte-Justine UHC, Montreal). Mean age is 21yrs (range=14-34 yrs). Self-reported questionnaires include the Distress Thermometer, Depression and Anxiety modules of the Beck Youth Inventory, the Brief Symptom Inventory-18, the Assessment of Survivor Concern, the PedsQL Generic Scale and the PedsQL Fatigue Scale. We describe this statistically and use effect sizes to compare the sample with external norms.

Results

A minority of survivors reported significant distress (26%). Anxiety (29%) was more frequently reported than depression (9%). Anxiety affects were more frequently reported (jittery, nervous, anxious, upset, scared). Fatigue was particularly high in the sample. ALL survivors reported fewer concerns about there health, cancer relapse and death, than other survivors samples. Exploratory results suggest that risk status and treatment history were associated with symptoms of anxiety and patterns of fatigue.

Conclusions

These results suggest that the symptomatic pattern of this population could be marked by a relatively high number of anxiety and fatigue symptoms but fewer depression symptoms.

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IDENTIFYING CAUSES OF MISSING APPOINTMENTS AND IMPLEMENTING INTERVENTIONS IN REAL TIME INCREASES TREATMENT COMPLIANCE AND REDUCES ABANDONMENT RATES FOR CHILDHOOD CANCER IN EL SALVADOR

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Objectives

In El Salvador, about 200 new cases of pediatric cancer are diagnosed each year and survival rates are approaching 70%. Although treatment is available at no cost, abandonment of therapy has been high (13%) during the last decade. The reasons for abandonment are not clear. In 2011, a procedure designed to detect missing appointments, register their root causes, and intervene in a timely fashion was implemented.

Methods

Absences to medical appointments in any of the areas of the pediatric oncology unit were informed to the medical team daily. Patient demographics and reasons for the absences were determined and registered. Cases of lymphoblastic leukemia (ALL) in induction therapy were contacted within 24 hours from the notification. All other cases were contacted within 48 hours and patients who had completed treatment within a week. Reasons for absences were obtained through telephone or in person interviews. If a patient failed to show up after initial contact, local health clinics and municipalities were contacted to conduct a search of the patient. Law enforcement was used as a last resort in patients in first line treatment with good prognosis.

Results

Absences were efficiently registered and families reasons behind absences were detected and proper interventions conducted. Categories for reasons of absences were established with cultural and social context considered. Abandonment rates dropped from 13% to 3%. Institutional costs were reduced.

Conclusions

The relationship between adherence and abandonment of treatment needs to be addressed; information of the first might shed light on abandonment showing possible similarities as well as differeneces between the two. Analysis of the impact of absenteeism on survival needs to be further explored. Abandonment of therapy is not necessarily a result of non-adherence in this study.

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FAMILY PSYCHOSOCIAL FUNCTIONING AFTER RECENT DIAGNOSIS WITH CHILDHOOD CANCER

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Objectives

Being diagnosed with childhood cancer is a stressful event for the entire family, which puts them at risk for developing psychosocial problems. We aimed to determine psychosocial functioning in parents (of patients 0-18 years), patients (8-16 years), and siblings (8-16 years) after a very recent diagnosis of childhood cancer and to compare this with scores from the healthy population.

Methods

Psychosocial functioning was assessed online one month post-diagnosis in n=116 families (response rate 60%). The Hospital Anxiety and Depression Scale (HADS) was used for parents. The parent-report of the Strengths and Difficulties Questionnaire (SDQ) was used for patients (N= 54) and siblings (N=30). HADS and SDQ scores were compared with Dutch reference groups by t-tests for means and χ^2-tests for percentages in the clinical range.

Results

Parents of children with cancer scored significantly higher than the reference group (p<.0001) on anxiety and depression. The percentages of parents in the moderate to severe range were higher than in the reference group (p<.0001); anxiety 14.2% vs 7.7%; depression 16.3% vs 3.6%. No significant differences were found for the mean SDQ-scores of patients and siblings compared with the norm. One fifth of the patients (20.4%) and siblings (20.0%) scored in the borderline to clinical range of the SDQ.

Conclusions

Parents reported high levels of anxiety and depression. Even though on average patients and siblings (8-16 years) psychosocial functioning is comparable to the norm, a considerable proportion of children seems to struggle. Structural and early attention for family problems at diagnosis is necessary, such that early (preventive) intervention is possible.

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PSYCHOSOCIAL AND ALLIED HEALTH WORKFORCE: QUANTIFYING WORKFORCE RATIOS FOR PAEDIATRIC ONCOLOGY SERVICES. HOW DO WE PLAN FOR OUR FUTURE?

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Objectives

Management of paediatric oncology requires extensive multidisciplinary staffing. A recent audit of activity in Victorian primary treating centres, for the period 2006-07 to 2009-10, revealed significant increases in usage for inpatient activity (^26%), chemotherapy (^38%) and radiation therapy (^50%). Within the context of this increasing service usage, together with increasing birth rates, treatment complexity and survival, a project was undertaken to estimate patient to staff ratios for psychosocial and allied health workforce for Victorian paediatric oncology primary treating centres.

Methods

Workforce ratios were estimated for nine psychosocial and allied health groups. Where available, ratios were informed by industrial awards, guidelines and/or models of care. Professional disciplines identified tasks required for newly diagnosed children at key pathway points. Time was allocated to each task, for each level of care, using a risk adaptive approach (low, moderate and high risk/need).

Results

The methodology used in this project allowed for the calculation of ratios of newly diagnosed children per annum to 1 full-time equivalent (FTE). Ratios were calculated for art, music and play therapy, educational play therapy, dietetics, mental health, neuropsychology, occupational therapy, pharmacy, physiotherapy and social work. For example, a ratio of 83 newly diagnosed children to 1 FTE Neuropsychologist is recommended. For Mental Health clinicians, a ratio of 67 newly diagnosed children to 1FTE is recommended.

Conclusions

Limited national and international models are available to estimate paediatric oncology psychosocial and allied health workforce ratios. These ratios will assist the primary treating centres to plan to meet the future workforce needs for Victorian children and adolescents with cancer. In addition, the methodology used may assist other states in Australia, as well as overseas health services, to plan for oncology psychosocial and allied health workforce in the future.

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COMMUNICATING RESULTS OF MEDICAL IMAGING TESTS IN PAEDIATRIC ONCOLOGY: OPINIONS AND NEEDS OF RADIOLOGISTS: A SURVEY

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Objectives

Discovering a malignancy, or progression or recurrence of a malignancy during an imaging test is a stressful event for a radiologist. Radiologists often have no previous relationship with patients and only have limited time to build rapport which hampers communication of such results. Moreover, skills for breaking bad news may be limited as communication training is not mandatory in the radiology curriculum. We conducted a survey investigating opinions, attitudes and needs regarding discussing imaging results with parents of children with cancer.

Methods

A questionnaire was presented to all members of the European Society of Paediatric Radiology. Radiologists who have children with cancer among their patients were asked to anonymously answer 42 questions about their background, practice, opinions and needs regarding communicating results to parents of children with cancer.

Results

From the 121 radiologists with an interest in oncology, 74, representing 22 countries, responded. Seventy percent of respondents reported that parents of pediatric cancer patients frequently ask for results. Sixty-six percent of respondents agreed they have a role in discussing results directly with parents. Thirty-four percent reported not feeling comfortable discussing worrisome results. Fifty-three percent of respondents indicated they had never received training in communication skills. Seventy-two percent would sign up if training in communication skills was available to them. Seventy-five percent reported being unaware of a policy or guidance on disclosing results within their department or institution.

Conclusions

Parents of children with cancer frequently ask radiologists to discuss results of imaging tests with them and many radiologists agree they have a role in doing this. A substantial percentage of radiologists does not feel comfortable discussing bad news and reports there is a lack of guidelines. Our findings suggest there is room and need for guidelines and training regarding communication between radiologists and patients.

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FEASIBILITY TESTING HELP: AN ONLINE INFORMATION INTERVENTION FOR PARENTS SHARING INFORMATION ABOUT ACUTE LYMPHOBLASTIC LEUKAEMIA WITH THEIR CHILD

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Objectives

Our previous research identified that parents of children with Acute Lymphoblastic Leukaemia (ALL) felt that they received minimal support to facilitate the acquisition of knowledge about the disease, especially the period close to diagnosis. We developed an online intervention named HELP (Harmonising Education about Leukaemia for Parents) to facilitate easy access to information about leukaemia. This resource is aimed at parents. At SIOP 2011, we presented an early description of what an intervention might look like. At SIOP 2012, we presented the basis for HELP and explained its initial development. This paper will focus on how we have feasibility tested and validated the intervention with families and health professionals prior to its evaluation in the second phase of the study.

Methods

After the development stage, feasibility testing and validation took place in five sequential steps. Firstly, our family advisory group provided comments on the content, look and feel of the website. Next, a group of clinicians and parents at one hospital were invited to use HELP and provide comments. Thirdly, health professionals at each of the other four sites reviewed the intervention, provided comments and advise on any hospital specific changes. The intervention was revised to reflect these comments. Finally, a health professional reviewed the intervention to validate all the information.

Results

Feasibility testing and validation of the intervention was a lengthy but important step in the development of HELP. Trials and tribulations in the recruitment of families on treatment and busy health professionals to take part in research will be discussed. The final version of HELP will be presented.

Conclusions

In the second phase of the study, HELP will be tested in a prospective two group non-randomised study. We anticipate HELP will increase parents' knowledge, confidence and competence, decrease stress and make communication with professionals easier.

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EXPLORING CANCER WORRY PREDICTORS IN ADOLESCENT AND YOUNG ADULT SURVIVORS OF CHILDHOOD CANCERS

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Objectives

The experience of cancer in childhood can influence the psychosocial wellbeing of AYA (adolescent and young adult) survivors, who report having cancer-related worries years beyond the completion of their treatment. Cancer worry has been shown to be an important barrier/facilitator in transition to long-term followup care and also impacts psychosocial adjustment in survivors. Despite its importance, there is a lack of research on cancer worry in this population. The aim of this study was to investigate the relationship between patient, cancer, and treatment-related factors and cancer worry in AYA childhood cancer survivors.

Methods

Between July 2011 and January 2012, AYA survivors aged 15 to 26 were recruited either in person or through mail from three Canadian pediatric hospitals. 250 participants (75.5% response rate) completed a questionnaire booklet that included a newly developed psychometrically sound 6-item Cancer Worry Scale (CWS). Selection of predictors for cancer worry were based upon review of literature and guided by expert opinion. Univariate analysis was used to identify predictors significantly related with CWS scores, which were then included in a multivariable regression model.

Results

In the multivariate analysis, females AYA survivors reported significantly greater cancer worries than males, scoring on average 9.4 points lower on the CWS (β= -9.4; P<0.001*; 95% CI: -14.4 to -4.5). Level of treatment intensity was also significant, as survivors who received the most intense therapy were significantly more worried than patients who received the least intensive therapy (β= -18.5; P<0.012*; 95% CI: -31.16 to -5.89). These predictors contributed to a good fit in the multivariable regression model ($F_{12,221}$=2.696, p<0.002*).

Conclusions

Our study identified two important factors associated with increased cancer worry in the AYA population. These results can help identify survivors who are most likely to worry and further direct appropriate programs to mitigate the burden of cancer worry on their transition process and overall wellbeing.