

O-001

High Risk Neuroblastoma

RESULTS OF AN INTENSIVE INDUCTION PROTOCOL FOR HIGH-RISK NEUROBLASTOMA IN MOROCCO (HR-NBL-MA-10)

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Objectives

The Survival for high-risk neuroblastoma in Morocco has been <10%, despite recent improvements in high-income countries to 50%. In 2012, we activated the first multi-center treatment protocol for high-risk neuroblastoma in Morocco, and report here the early results of our first aim, to test the feasibility, toxicity and response to an intensive induction therapy.

Methods

Eligible patients with newly diagnosed high-risk neuroblastoma from Rabat (n=23), Casablanca (n=15), Fez (n=9), and Marrakech (n=10) were treated with five cycles of rotating pairs of combination chemotherapy without G-CSF (*Pediatr Blood Cancer* 2012; 59:902-7). Disease evaluations were performed at diagnosis and end of induction.

Results

Fifty seven patients were entered on study, including 53 with stage 4 disease and 4 with stage 3. The median age was 2.5 years. Initial evaluation showed metastases in bone (52%), bone marrow (75%), liver (14%) and 74% had adrenal primary. MIBG scans were performed in 17 patients, and MYCN copy number was determined in only 1 patient. As of February 1, 2014, 37 patients completed 5 cycles of induction, 9 progressed during induction and are off study, and 11 are still on induction therapy. The regimen was tolerable, without any toxic deaths. There were 17 hospitalizations for complications, consisting of 13 fever/neutropenia and 3 sepsis. At completion of induction therapy, 37 evaluable patients had 10 complete responses, 6 partial responses, 3 stable disease, 2 progressive disease. Surgery on the primary tumor was performed on 14 patients, with 9 complete resections.

Conclusions

An intensive induction therapy for high-risk neuroblastoma in a multi-center setting is feasible in Morocco without unusual toxicity and with response in 43%, which would allow proceeding with myeloablative therapy and ASCT, with improved chance of survival. Future efforts are underway to improve access to MYCN testing, MIBG scans, PBSC harvest and to ASCT.

O-002

High Risk Neuroblastoma

LATE RECURRENCES, MORTALITY AND SECOND CANCERS IN FIVE-YEAR SURVIVORS OF HIGH RISK NEUROBLASTOMA

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Objectives

To investigate late outcomes in 5-year survivors of high-risk neuroblastoma (HR-NB) treated between 2001 and 2009.

Methods

We identified a cohort of 708 HR-NB patients enrolled on the COG Neuroblastoma Biology Study ANBL00B1 who survived at least five years from diagnosis. The 5-year timepoint was chosen to be comparable to other survivor cohorts. Clinical, demographic and biologic features of this group were examined, including cause of death (COD) in those who subsequently died after 5 years. Event-free survival (EFS) and overall survival (OS) (\pm standard error) were calculated using the Kaplan-Meier method. Cumulative incidence of secondary malignant neoplasm (SMN) was calculated, and second tumors are described.

Results

Median follow-up time from diagnosis for the 5-year survivor cohort was 7.7 years (range: 5 to 12.1 years). Eleven SMNs were reported after 5 years from diagnosis: osteosarcoma (5), soft-tissue sarcoma (2), meningioma (1), thyroid cancer (1), AML (1), unknown (1). Cumulative incidence of SMN at 10 years from diagnosis was $3\% \pm 1\%$. 459 patients reached the 5-year timepoint without an event; for these survivors the 10-year EFS was $87\% \pm 6\%$. Seventy-nine patients died after the five-year time-point. COD included progressive disease ($n=73$), treatment related toxicity ($n=3$), SMN ($n=1$) and other ($n=2$). The OS at 10 years from diagnosis was $81\% \pm 3\%$ ($n=708$).

Conclusions

Within HR-NB patients who survive at least 5-years from original diagnosis, progressive NB remains a major cause of mortality; however, patients without a relapse before 5 years appear to have a favorable outcome. Further investigation of this newly established cohort will probe the incidence and impact of treatment-related illness and identify genetic factors associated with late toxicities including second cancer.

O-003

High Risk Neuroblastoma

**RELAPSES AFTER HDC AND ASCT IN HIGH RISK NEUROBLASTOMA
PATIENTS: CLINICAL PRESENTATION, TREATMENT AND PROGNOSIS
FACTORS**

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Objectives

This study aimed analysing high-risk neuroblastoma recurrence after high dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT). To this purpose, we focused on clinical presentation, treatments performed, and prognosis factors

Methods

Between 2000 and 2010, at Gustave Roussy Cancerology Institut, 67 out of 134 children affected with high-risk neuroblastoma, who had received HDC and ASCT, presented tumour recurrence.

Results

Out of 67 patients, 40 had a progression and 27 a relapse. There were 35 males and 32 females. Median age at diagnosis was 39.5 mos (3% <1 year; 74.6% between 1-5 years; 15 >5 years). 65 patients had a stage 4 neuroblastoma and 2 had a stage 3 with *MYCN* amplification. 17 patients (26%) presented *MYCN* amplification. HDC consisted of busulfan and melphalan in 62 patients (92%). Median time from transplantation to first relapse was 13 months (1-48). Median survival after recurrence was 9 months (0-28 months).

All patients died but 3 (5.5%) who are alive (11 months+, 14 months+ and 50 months+). Patients (N=35) treated with temozolomide alone or in combination with topotecan had the longest time to progression, median 122 days (4-632+). Oral etoposide (40 patients), even if administered late, increased survival with a good quality of life, median 65 days (9-393). Prognosis factors, influencing life expectancy after recurrence, were: age at diagnosis <18 months, *MYCN* amplification, and time <1 year between diagnosis or transplantation and recurrence.

Conclusions

Outcome after recurrence post HDC and ASCT is poor. However, factors involved in life expectancy duration can be identified. These factors should be taken into account in trials evaluating new treatment strategies as well as stratification criteria in randomized studies to avoid bias and wrong conclusions.

O-004

High Risk Neuroblastoma

VIROTHERAPY DELIVERED BY AUTOLOGOUS MESENCHYMAL STEM CELLS FOR CHILDREN WITH METASTATIC AND REFRACTORY NEUROBLASTOMA: RESULTS OF A TRIAL OF COMPASSIONATE USE

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Objectives

We have developed a new strategy for the systemic delivery of oncolytic viruses: Celyvir. Celyvir consists of autologous marrow-derived mesenchymal stem cells (MSCs) carrying an oncolytic adenovirus. We previously reported a pilot study on the use of Celyvir in 4 children with metastatic neuroblastoma (NB) (Cancer Gene Therapy, 2010, 17: 476) and now present the extended clinical experience of this program of compassionate use of Celyvir in 14 new patients.

Methods

The Spanish Medicine Agency and the hospital internal review board approved the trial. All patients had failed to at least 3 lines of therapy, and presented a metastatic disease. The children received multidosis of Celyvir in a weekly basis (minimum 4, maximum 70, total 218) with no concomitant treatments. Total cells (min. 70×10^6 , max. 2640×10^6) and viral particles (min. $1,8 \times 10^{12}$, max. $5,28 \times 10^{13}$) varied among patients. Hematological and biochemical test were done in blood samples at the time of each infusion. Clinical outcome was evaluated after 8 doses.

Results

The tolerance was excellent, with very mild and autolimited viral-related toxicities. Peripheral blood lymphocytes raised and the profile of tumor infiltrating lymphocytes (whenever a biopsy was available) changed after Celyvir therapy. Clinical outcomes were progression (10), stable disease (1), partial remission (3) and complete remission (1). The patient with a complete response relapsed after 6 months and received a second round of Celyvir, achieving a partial remission. MSC cultures presented differences in the expression levels of adhesion molecules and immune-related molecules, suggesting interpatient differences in the homing and immune modulation capacities of the therapy administered.

Conclusions

Celyvir has an excellent safety profile in children with metastatic NB. Further uses of this strategy are needed in order to find out factors related with efficacy.

O-005

Epidemiology 1

A STATEWIDE ASSESSMENT OF CHILDHOOD CENTRAL NERVOUS SYSTEM TUMORS AND TRAFFIC-RELATED AIR POLLUTION

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Objectives

Few risk factors have been identified for childhood central nervous system (CNS) tumors. Due to increasing concerns regarding air pollution and childhood cancer risk, we conducted a population-based assessment evaluating the association between selected traffic-related air pollutants (benzene, 1,3-butadiene, or diesel particulate matter [DPM]) and the incidence of childhood CNS tumors.

Methods

All CNS tumors diagnosed at <15 years of age in Texas for the period of 2001-2009 (n=2,014) were identified from the Texas Cancer Registry. Information on the corresponding at-risk population was obtained from the 2000 United States' (US) Census. Annual census tract-level pollutant concentrations, estimated by the US Environmental Protection Agency's 2005 National-Scale Air Toxics Assessment, were categorized (low, medium, medium-high, and high) using cutpoints based on quartiles of the statewide distribution of each pollutant. Poisson regression was used to estimate relative risk (RR) and 95% confidence intervals (CI) adjusted for age at diagnosis, sex, race/ethnicity, and area-level poverty. Tumor phenotypes were independently evaluated and included astrocytomas (n=386), medulloblastomas (n=243), ependymomas (n=145), and primitive neuroectodermal tumors (PNET) (n=49). The affiliated institutions' Institutional Review Boards approved this study and waived informed consent.

Results

Medium DPM levels were associated with increased incidence of all CNS tumors (RR=1.20, 95% CI: 1.06-1.37) and astrocytomas (RR=1.42, 95% CI: 1.05-1.94) compared to low DPM levels. Medium and medium-high 1,3-butadiene levels were associated with increased incidence of astrocytomas (RR=1.46, 95% CI: 1.05-2.01 and RR=1.69, 95% CI: 1.22-2.33, respectively) and were suggestive of an increased incidence of PNET (RR=2.60, 95% CI: 0.94-7.24 and RR=2.76, 95% CI: 0.98-7.72, respectively) compared to low levels. No statistically significant associations were found with medulloblastoma or ependymoma incidence.

Conclusions

This large population-based assessment indicates a positive association between traffic-related air pollution and childhood CNS tumors, particularly among astrocytomas. Additionally, our results suggest a strong positive association with PNET, although, not statistically significant.

O-006

Epidemiology 1

TEMPORAL CLUSTERING OF NEUROBLASTOMA IN CHILDREN AND YOUNG PEOPLE FROM NORTHERN ENGLAND

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Objectives

The aetiology of neuroblastoma (NB) is unclear. Hereditary NB with germline mutations accounts for < 1% of all NB with single nucleotide polymorphisms predisposing to NB in other cases. Environmental factors have also been implicated with the possibility that an infectious agent may be involved. 'Temporal clustering' occurs if cases display an irregular temporal distribution and may provide evidence for the aetiological involvement of an agent that exhibits epidemicity. We tested for the presence and nature of temporal clustering of date of diagnosis.

Methods

We extracted all cases of NB diagnosed in children and young people aged 0-24 years during 1968-2003 from the Northern Region Young Persons' Malignant Disease Registry. This population-based registry includes all cases of cancer in children and young people who were resident in northern England at the time of diagnosis. Tests for temporal clustering were applied using a modified version of the Potthoff-Whittinghill method. Estimates of extra-Poisson variation (beta), together with standard errors (SEs), were obtained.

Results

There were 193 cases of NB diagnosed during the study period. All the analyses between fortnights and between months found significant extra-Poisson variation, with estimates of beta of 0.440 (SE 0.179, $P = 0.009$) for the analysis between months within quarters, and 0.609 (SE 0.334, $P = 0.036$) for the analysis between fortnights within months. Restricting the analyses to the 49 cases diagnosed at age < 1 year did not show significant evidence of extra-Poisson variation, although there was borderline evidence from the analysis between fortnights within months (estimated beta = 2.006, SE 1.155, $P = 0.057$).

Conclusions

This study suggests that transient environmental agents may be involved in NB aetiology in children and young people. In particular, our findings indicate that the initiating factor might be an agent such as an infection that occurs in 'mini-epidemics'.

O-007

Epidemiology 1

CONSTITUTIVE MISMATCH REPAIR DEFICIENCY SYNDROME: CLINICAL DESCRIPTION IN A FRENCH COHORT

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Objectives

Constitutive mismatch repair deficiency syndrome (CMMR-D) is a recently described childhood cancer predisposition syndrome involving biallelic mutation of MMR genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). More than 140 cases have been previously reported but only as case reports. We present here the first series of unselected patients.

Methods

We performed a retrospective review of all 28 cases of CMMR-D diagnosed in French genetics laboratories in order to describe clinical characteristics, treatment and outcome of malignancies, and biological diagnosis data of an unselected series of patients.

Results

Overall, 60 tumors were diagnosed in these 28 patients, 17 (28%) hematologic malignancies, 19 (32%) brain tumors, 21 (35%) Lynch syndrome-associated malignancies, and 3 (5%) other tumors. Median age of onset of first tumor was 6.98 years [1.23-22]. 21 (75%) patients had NF1-unrelated CALMs or hypopigmented macules and 4 (14%) had brain malformative features. Overall, 18 patients died, 7 (39%) due to the primary tumor. Median survival after diagnosis of the primary tumor was 23.3 months [0.26-213.2]. Among the patients who survived after their first malignancy, 19 (68%) developed a second malignancy. No obvious excess of toxicity to treatment was reported. A familial history of LS-associated cancer was found in only 5 families, and consanguinity in 35% of cases. *PMS2* mutations (15 patients) were more frequent than mutations of *MLH1* (4 pts), *MSH2* (3 pts) and *MSH6* (6 pts).

Conclusions

CMMR-D is a severe condition associated with multiple malignancies in childhood. Its rarity warrants international collaboration to define diagnosis criteria and guidelines for surveillance and prevention in order to decrease tumor-related mortality.

O-008

Epidemiology 1

MOLECULAR CHANGES IN SAUDI PATIENTS WITH FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Objectives

Familial Hemophagocytic lymphohistiocytosis (FHL) in different ethnicities has been described in the literature, but this is the first report from Saudi Arabia. Here we describe the mutations present in FHL genes in Saudi patients diagnosed with FHL

Methods

DNA from 87 patients diagnosed with FHL were used for mutation detection in various FHL-causing genes by PCR-sequencing method

Results

In a total of 15 patients with STX11 gene, a novel mutation (c.173 C>T) were identified in 14 patients of the same tribe. Another one (Q140Pfs*46) was identified in one patient. Among 7 patients with PRF1 gene mutations one patient was found to have a nonsense novel mutation (W374*). For 12 patients with UNC13D gene, Y673 STOP, E1017R, V495G and A1018D; C>A were identified in one, five, one and two patients respectively. The previously reported mutation (c.766 C>T; R256X) were identified in 3 patients. Although, STXBP2 was found to be the most common defective gene of FHL in Saudis, only one novel mutation (W288R) was found in one patient, the remaining 24 patients were found to have the previously reported P477L mutation. Four patients were found to have 3 novel mutations (Splice site c.9044+1G>T EX39, Splice site c.7503+1G>C EX43 and A1546V) in LYST gene. Another two novel mutation (I397Nfs*405 and K134Q) were identified in one and two patients with XIAP and Rab27A respectively. All patients with STX11 mutations were from one tribe and majority of patients with STXBP2 mutations were from another tribe. No molecular defects were identified in the remaining 21 (24%) patients

Conclusions

Almost half of the mutations in our FHL cohort were novel. This data shows the high consanguinity rate in Saudi population. There are still more genetic aberrations to be discovered in this subset of patients as no molecular defects were identified in a quarter of our patients

No conflict of interest

O-009

Supportive Care

**ANALYSIS OF PALONOSETRON VS ONDANSETRON IN PREVENTING
CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV) IN PEDIATRIC
PATIENTS RECEIVING MODERATELY OR HIGHLY EMETOGENIC
CHEMOTHERAPY (MEC/HEC)**

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Objectives

Evaluate efficacy/safety of two palonosetron (PALO) dose-levels, compared with ondansetron (standard comparator) in preventing CINV in pediatric patients receiving MEC or HEC in a multicenter, multinational, randomized, double-blind, non-inferiority study.

Methods

Patients with malignant disease scheduled for treatment with MEC or HEC were randomized to receive PALO 10 mcg/kg, PALO 20 mcg/kg, or ondansetron (three 150 mcg/kg doses) and stratified by emetogenicity (HEC/MEC, day 1) and age (

Results

A total of 502 patients were randomized and 493 included in the full analysis set (166 PALO 10 mcg/kg, 165 PALO 20 mcg/kg, 162 ondansetron). Patients ranged in age from 64 days to 16.9 years. The majority were male (53.1%) and white (95.1%). The CR rate across the age groups ranged from 53.3%–59.3% for ondansetron, 41.3%–70.4% for PALO 10 mcg/kg and 50.0%–74.1% for 20 mcg/kg. For patients treated with HEC, the CR rate was higher for PALO 10 mcg/kg and 20 mcg/kg (42.6% and 51.0%, respectively) compared with ondansetron (41.2%). For MEC, the PALO 20 mcg/kg CR rate was higher (62.9%), than 10 mcg/kg (59.8%) and comparable to ondansetron (66.7%). The percentage of treatment-emergent adverse events (including prolonged electrocardiogram QT) and serious adverse events, according to age strata and emetogenicity, were similar. All study withdrawals/deaths were unrelated to study drug.

Conclusions

High-dose PALO (20 mcg/kg), given as a single dose, was more effective in preventing CINV in pediatric patients receiving MEC/HEC compared with ondansetron. The results indicate higher-dosage PALO does not require dose adjustment according to patient age. The safety profiles raised no concerns.

O-010

Supportive Care

SIX PRESENTING CLINICAL VARIABLES ROBUSTLY PREDICT THE RISK OF MICROBIOLOGICALLY DEFINED INFECTION IN FEBRILE NEUTROPENIC EPISODES

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Objectives

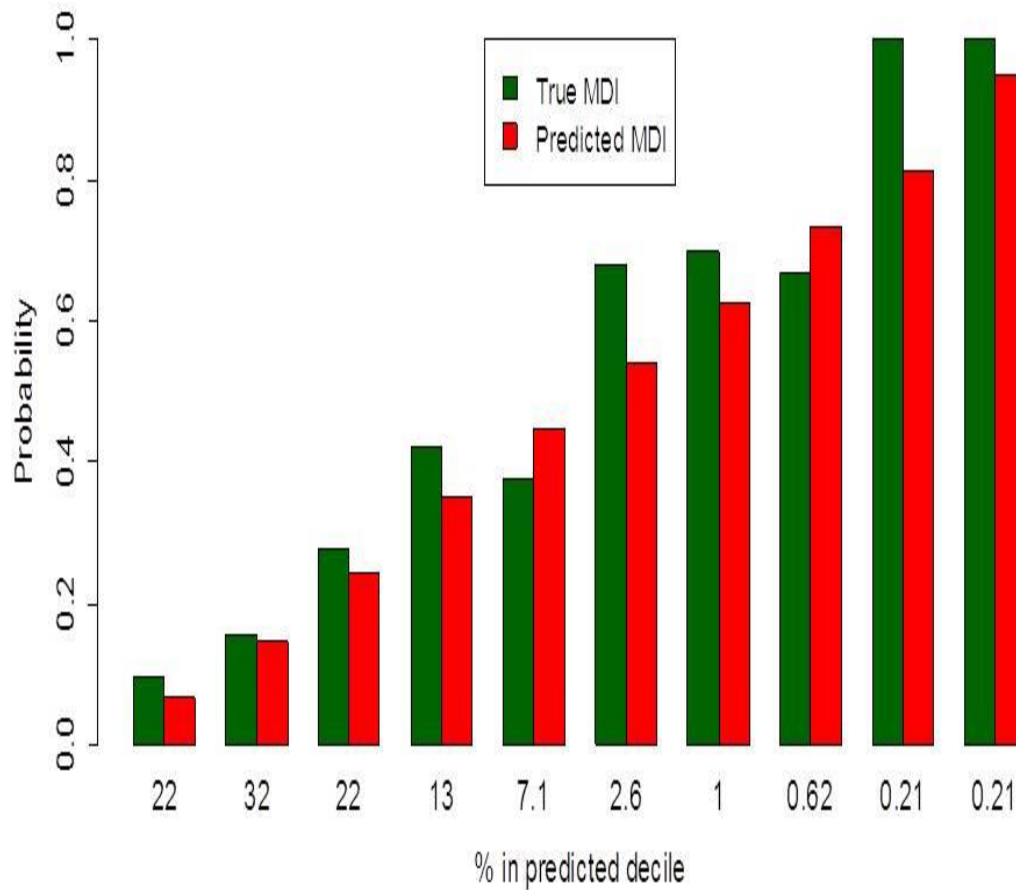
Risk stratified management of febrile neutropenia (FN), also known as “fever with neutropenia”, allows intensive management of high-risk cases and early discharge of low-risk cases. No single, internationally validated, prediction rule exists for children and young people. An individual participant data (IPD) pooled analysis was undertaken to devise one.

Methods

The “Predicting Infectious ComplicationNs In Children with Cancer” (PICNICC) collaboration was formed by engaging international clinical and methodological experts, authors of studies identified in the systematic reviews, parent representatives and healthcare researchers. The PICNICC collaboration consists of 22 different study groups from 15 countries.

Results

IPD information from 5,127 episodes of FN in 3,504 patients was provided for meta-analysis, with 1,070 episodes in 616 patients from 7 studies in higher-income countries suitable for multivariate analysis. Univariate analyses showed anticipated associations between microbiologically defined infection (MDI) and higher temperature, lower white cell counts and a diagnosis of acute myeloid leukaemia. There was no clear relationship demonstrated between age and risk of MDI. Episodes in osteosarcoma/Ewings sarcoma patients and patients with more severe mucositis were associated with a decreased risk of MDI. The multivariable risk prediction model derived from the IPD had six components: Tumour type, temperature, clinically “severely unwell”, haemoglobin, white cell count and absolute monocyte count. This model showed moderate discrimination (AUC ROC 0.736) and good calibration (calibration slope 0.95, figure) and was robust to bootstrap and cross-validation sensitivity analyses.



Conclusions

This new risk prediction model for microbiologically defined infection is robust to internal validation techniques but requires prospective validation and studies of implementation. A basic implementation of the model has been made 'live' on: <http://tinyurl.com/PICNICC1>. When validated this could be adapted to work off a web page or smartphone 'app' to assist clinicians in individualised decision making regarding location and intensity of therapy.

O-011

Supportive Care

REDUCTION OF CATHETER ASSOCIATED BLOODSTREAM INFECTIONS IN PAEDIATRIC ONCOLOGY PATIENTS USING ETHANOL LOCKS; A RANDOMIZED CONTROLLED TRIAL

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Objectives

The prevention of central venous catheter- (CVC-) associated bloodstream infection (CABSI) in pediatric oncology patients is essential. Ethanol locks can eliminate biofilm embedded pathogens and have no known microbial resistance. Up to date no randomized controlled trial in pediatric oncology has been performed on the efficacy of ethanol locks to reduce CABSI.

Objective; To determine whether 70% ethanol locks can cause a 50% reduction in CABSI in pediatric oncology patients.

Methods

We conducted a randomized, double blind, multicenter trial in pediatric oncology patients (1-18 years) with newly inserted CVCs. Patients were randomly assigned to receive two hour ethanol locks (3 ml 70%) or heparin locks (3 ml 100 IU/ml), maximum frequency once weekly. Primary outcomes were CABSI, CVC removal or death due to CABSI.

Results

We included 307 patients, 153 were allocated to ethanol and 154 to heparin locks. In the ethanol group 16/153 (10%) patients were diagnosed with CABSI versus 29/154 (19%) in the heparin group; incidence was 0.77/1000 and 1.46/1000 catheter days respectively ($p=0.04$), resulting in a number-needed-to-treat of 12 patients.

Particularly Gram-positive CABSIs (ethanol, $N=8$; heparin, $N=21$; $p=0.01$) were reduced. Less CVCs were removed because of CABSI in the ethanol group (ethanol, $N=5$; heparin, $N=12$; $p=0.08$). No patients died because of CABSI. During ethanol locks patients experienced significantly more transient symptoms compared to heparin locks (maximum grade 2) (nausea, $p=0.03$; taste alteration, $p<0.001$; dizziness, $p=0.001$; blushing, $p<0.001$), no suspected unexpected serious adverse reactions (SUSAR) occurred.

Conclusions

This is the first RCT to show that ethanol locks can prevent CABSI in pediatric oncology patients, in particular CABSI caused by Gram-positive bacteria.

Implementation of ethanol locks in daily practice should be considered.

O-012

Supportive Care

A RANDOMIZED OPEN LABELED PARALLEL GROUP PHASE III STUDY OF ANTIBIOTICS ALONE VS. ANTIBIOTICS PLUS G-CSF IN PEDIATRIC CANCER PATIENTS WITH FEBRILE NEUTROPENIA IN A LOW-INCOME SETTING

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Objectives

Granulocyte colony-stimulating factor (G-CSF) use in children with febrile neutropenia (FN) in high-income countries has been shown to decrease the duration of FN, hospital admission, and antibiotics usage with no reduction in infection related complications and mortality. FN in low-income countries (LIC) is associated with higher degree of morbidity and mortality due to limitations in supportive care, limited manpower and host comorbidities such as malnutrition. Hence, reduction in duration of FN by G-CSF in LIC setting may have much more impact on morbidity and mortality and would be potentially more cost-effective.

Methods

In this prospective randomized study, 200 pediatric patients with FN were randomized to receive antibiotics with G-CSF (filgrastim; 5 microgram/kg/d subcutaneously) or antibiotics alone. Children were stratified for their diagnosis and focus of infection. G-CSF was started within 24 hr of antibiotics. The study protocol required a resolution of fever and a neutrophil count $\geq 0.2 \times 10^9/L$ for hospital discharge.

Results

Patients randomized to G-CSF had a shorter duration of neutropenia (median, 5 v 10 days; $P = 0.001$), shorter duration of grade IV neutropenia (median, 2 v 5 days; $P = 0.001$), shorter febrile neutropenia (median, 5 v 6 days; $P = 0.02$), fewer days of total antibiotic use (median, 6 v 8.5 days; $P = 0.01$), and less severe neutrophil nadir (mean, 0.32 vs 0.14; $P = .006$) but there was no difference in ICU admissions, shock or infection related mortality. The reduction in duration of FN did not significantly reduce the cost per patient admission.

Conclusions

G-CSF used with antibiotics at the onset of FN in children with cancer in LIC accelerated neutrophil recovery and shortened the duration of febrile neutropenia as well as antibiotic usage but did not reduce hospital admission, cost of therapy and mortality.

O-013

Leukemia/MDS and Bone Marrow Transplantation Biology

EARLY T-CELL PRECURSOR (ETP) ACUTE LYMPHOBLASTIC LEUKEMIA IS CHARACTERIZED BY ABERRANT ACTIVATION OF THE JAK/STAT PATHWAY AND PROFOUND RESPONSES TO RUXOLITINIB IN XENOGRAFT MODELS

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Objectives

Novel therapies are urgently needed for early T-cell precursor (ETP) acute lymphoblastic leukemia (ALL), a recently described subtype of T-ALL with a poor prognosis. Defined by a unique immunophenotype, ETP-ALL expresses myeloid/early progenitor markers in addition to T-lineage markers. While ETP-ALL does not harbor a unifying genetic lesion, a fraction have mutations in genes involved in JAK/STAT signaling. This study sought to determine the dependence of ETP-ALL on JAK/STAT signaling and the activity of JAK-targeted therapy.

Methods

JAK/STAT signaling in 6 primary ETP-ALL samples from pediatric patients was evaluated by phosphoflow cytometry and immunoblot, and xenografts of these samples were established in NOD/SCID/yc null (NSG) mice, under approval of the Institutional Animal Care and Use Committee. Disease burden was monitored by flow cytometry of peripheral blood for human cytoplasmic CD3 (cCD3). Xenografts were randomized to the JAK1/2 inhibitor ruxolitinib or vehicle after they developed >1% peripheral blasts.

Results

We identified aberrant hyperactivation of the JAK/STAT pathway in 6/6 ETP-ALL samples with heterogeneous mutations. ETP-ALL cases had markedly increased levels of pSTAT3 and pSTAT5 compared to non-ETP T-ALL by immunoblot and phosphoflow cytometry. Moreover, ETP-ALL showed hyperactivation of STAT5 in response to IL7, an effect that was abrogated by ruxolitinib. *In vivo*, ruxolitinib displayed activity in 6/6 xenograft models of ETP-ALL, with profound single-agent efficacy in 5/6. Ruxolitinib treatment decreased peripheral blast counts relative to pre-treatment levels and yielded significantly lower peripheral blast counts compared to control ($P<0.05$) in 5/6 ETP-ALL samples and 75-99% reduction in mean splenic blast counts ($P<0.01$) in 6/6. Both JAK/STAT pathway activation and ruxolitinib efficacy were independent of the presence of known JAK/STAT pathway mutations.

Conclusions

These results strongly suggest that ETP-ALL blasts are dependent on JAK/STAT signaling and establish ruxolitinib as a potential novel therapeutic option, which should be translated to clinical trials rapidly.

Conflict of interest

O-014

Leukemia/MDS and Bone Marrow Transplantation Biology
LOSS OF IKZF1 FUNCTION MEDIATES RESISTANCE TOWARDS
GLUCOCORTICOID-INDUCED APOPTOSIS IN BCP-ALL

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Objectives

Glucocorticoids (GCs) are critical components in the treatment of ALL and the initial response to prednisolone is a major prognostic factor. At relapse, resistance to GCs is common and represents an important determinant in treatment failure. Recent studies performed by us and others have identified *IKZF1* gene deletions and mutations as an independent prognostic factor in children with B cell precursor ALL (BCP-ALL). However, it has not been established whether loss of IKZF1 function directly impacts the response to glucocorticoids.

Methods

We examined whether haplodeficiency for *Ikzf1* gene expression in mouse lymphocytes affects glucocorticoid-induced apoptosis. To assess the effect of IKZF1 overexpression on glucocorticoid receptor (GR)-dependent transcription, luciferase reporter assay were used. Lentiviral-mediated *IKZF1*-shRNA expression in Nalm6 cell line was established to investigate loss of IKZF1 function in a human leukemia cell line. Furthermore, MTT assays were performed on 187 primary leukemia samples after treatment with individual chemotherapeutic agents, comparing *IKZF1*-deleted patient samples with wild-type controls.

Results

B-lymphocytes haplodeficient for IKZF1 showed a significantly enhanced survival after treatment with GCs compared to wild type cells, as measured in an MTS assay and by AnnexinV staining. In case of prednisolone, the inhibitory concentration (IC₅₀) was about ~200-fold higher in the *Ikzf1*^{+/-} splenocytes as compared to the wild-type cells. Gene expression analysis revealed that *Ikzf1*^{+/-} splenocytes displayed lower expression levels as well as diminished transcriptional activation of several GR-induced target genes (i.e. *Sgk1*, *Irs2*, *Zfp36L2*). Furthermore, luciferase reporter assay revealed that IKZF1 overexpression enhances GR-mediated transcriptional activation in response to prednisolone. Lentiviral-mediated *IKZF1*-shRNA expression in Nalm6 cell line inhibits prednisolone and dexamethasone-induced apoptosis. Finally, MTT assays on patients samples revealed a significant (30-fold) GC ($P<0.001$).

Conclusions

Our data provide evidence that loss of IKZF1 function mediates resistance to glucocorticoid-induced apoptosis, which may contribute to the poor outcome of *IKZF1*-deleted BCP-ALL.

O-015

Leukemia/MDS and Bone Marrow Transplantation Biology
IKZF1 DELETIONS IN PEDIATRIC ACUTE MYELOID LEUKEMIA

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Objectives

IKAROS family zinc finger 1 (IKZF1) is a zinc finger transcription factor important in lymphoid differentiation that acts as tumor suppressor in acute lymphoid leukemia. Recent studies suggest that IKZF1 is also involved in myeloid differentiation.

Methods

To investigate whether *IKZF1* deletions play a role in pediatric acute myeloid leukemia (AML) we screened a panel of 258 newly diagnosed pediatric AML samples obtained from the DCOG (The Hague,the Netherlands), the AML–Berliner-Frankfurt-Münster Study Group (Germany,Czech Republic), the Saint-Louis Hospital (Paris,France) and the Royal Hospital for Sick Children (Glasgow,United Kingdom) for deletions of the *IKZF1* locus on chromosome 7p12.2 using multiplex ligation-dependent probe amplification (MLPA).

Results

Median age of the patients was 9.5 years(range 0.1-18.5 years), median white blood cell count was $46.7 \times 10^9/L$ (range $1.2-483 \times 10^9/L$). All major cytogenetic subgroups were included and patients were treated with intensive cytarabine-anthracycline based pediatric AML protocols. Of 11 patients with an *IKZF1* deletion, 8 cases showed a monosomy 7, and 3 cases showed a focal deletion of *IKZF1*. These deletions included the complete *IKZF1* gene(n=2) or exons 1-4(n=1), leading to a loss of IKZF1 function. The focal deleted cases were an 1.5 year old boy diagnosed with fusion of *MNX1/ETV6* who relapsed and died, an 11.3 year old girl diagnosed with acute monocytic leukemia who relapsed, and a 2.3 year old boy diagnosed with acute myelomonocytic leukemia with a disease-free survival. Genes differentially expressed in monosomy 7 cases significantly correlated with gene expression changes in focal *IKZF1* deleted cases when comparing significant differences to non-deleted samples(n=247). This suggests that loss of *IKZF1* may be an important determinant in pediatric AML with monosomy 7. Genes increased in expression in *IKZF1* deleted samples included genes involved in myeloid cell cycle and self-renewal.

Conclusions

Our findings suggest evidence for a driving role of *IKZF1* haploinsufficiency in pediatric myeloid leukemias.

O-016

Leukemia/MDS and Bone Marrow Transplantation Biology
GATA2 DEFICIENCY IN CHILDREN AND ADOLESCENTS WITH
MYELODYSPLASTIC SYNDROME

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Objectives

The etiology of childhood myelodysplastic syndromes (MDS) remains largely unknown. Recently, germline loss-of-function GATA2 mutations were identified in hematopoietic stem cell disorders with variable phenotypes unified by the predisposition for myeloid malignancy. In this study we aimed to define the frequency and clinical characteristics of GATA2 deficiency within primary MDS in children and adolescents.

Methods

We investigated a cohort of 508 consecutive patients with MDS (426 primary and 82 secondary) diagnosed in Germany between 01.01.1998 and 30.06.2013 and enrolled in the studies of the European Working Group of MDS in Childhood (EWOG-MDS) 98 and 2006.

Results

GATA2 mutations were identified in 7% (28/424) of patients with primary MDS and in none of the secondary MDS cases. Interestingly, 20/28 children with mutations had a karyotype either indicating monosomy 7, t1;7, or trisomy 8.

We next identified additional 42 cases with GATA2 deficiency (35 EWOG-enrolled and 8 referred for diagnostics), bringing to 71, the total number of GATA2-deficient patients diagnosed at our institution. Intriguingly, of a total cohort of 100 children with monosomy 7, 37 patients (37%) had underlying GATA2 deficiency. While age at diagnosis of MDS was significantly higher in mutated patients (median age at diagnosis 12.5 vs. 4.2 years, $p < 0.01$), the 5-yr overall survival and event-free survival after HSCT was comparable in patients with monosomy 7 with or without underlying GATA2-deficiency. Investigations of unaffected parents or siblings did not reveal silent exonic mutation carriers.

Conclusions

In summary, GATA2 deficiency accounts for 7% of all primary childhood MDS and a third of all primary MDS cases with monosomy 7. Family investigations imply a full penetrance of MDS for exonic GATA2 mutations and might help guide clinical decision making in terms of an early transplantation. Further investigations will be critical to better define the clinical penetrance and prognosis of this novel MDS predisposition syndrome.

O-017

Leukemia/MDS and Bone Marrow Transplantation Biology
JUVENILE MYELOMONOCYTIC LEUKEMIA AFFECTS THE FUNCTION AND GENE-EXPRESSION OF MESENCHYMAL STROMAL CELLS

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Objectives

Aberrant mesenchymal stromal cell (MSC) function was linked to disease and contributed to the pathophysiology of malignant disorders in murine models. Juvenile Myelo-Monocytic Leukemia (JMML) is an aggressive disease affecting young infants and is characterized by presence of a high percentage of blasts. In this study we present the impact of JMML on MSC.

Methods

Bone-marrow samples of children with JMML were collected at diagnosis (n=9) and after HSCT (n=7; from 4 patients) for the expansion of MSC. Bone-marrow of 10 healthy pediatric controls was collected at time of stem cell donation. MSC were characterized by phenotyping, differentiation, gene-expression (DeepSAGE) analysis and functional studies assessing immunomodulation and hematopoietic support.

Results

The gene expression profile in JMML-MSC differed significantly from controls (Figure 1). Differential expression was observed a.o. for genes encoding proteins of the IL-1 superfamily and the leptin pathway, and adhesion molecules. Chimerism analysis confirmed the patient origin of MSC expanded from post-HSCT samples. Gene expression of e.g. DKK1, IL-6, CXCL12 and CXCR7 in MSC expanded from bone-marrow of JMML patients after HSCT was comparable to control MSC, but significantly altered compared to MSC of these patients collected at diagnosis. Whereas hematopoietic support and suppression of PBMC and NK-cell activation was not affected, suppression of differentiation of monocytes towards dendritic cells was significantly stronger by JMML derived MSC compared to healthy controls as depicted in Figure by decreased CD1a expression.

Figure 1

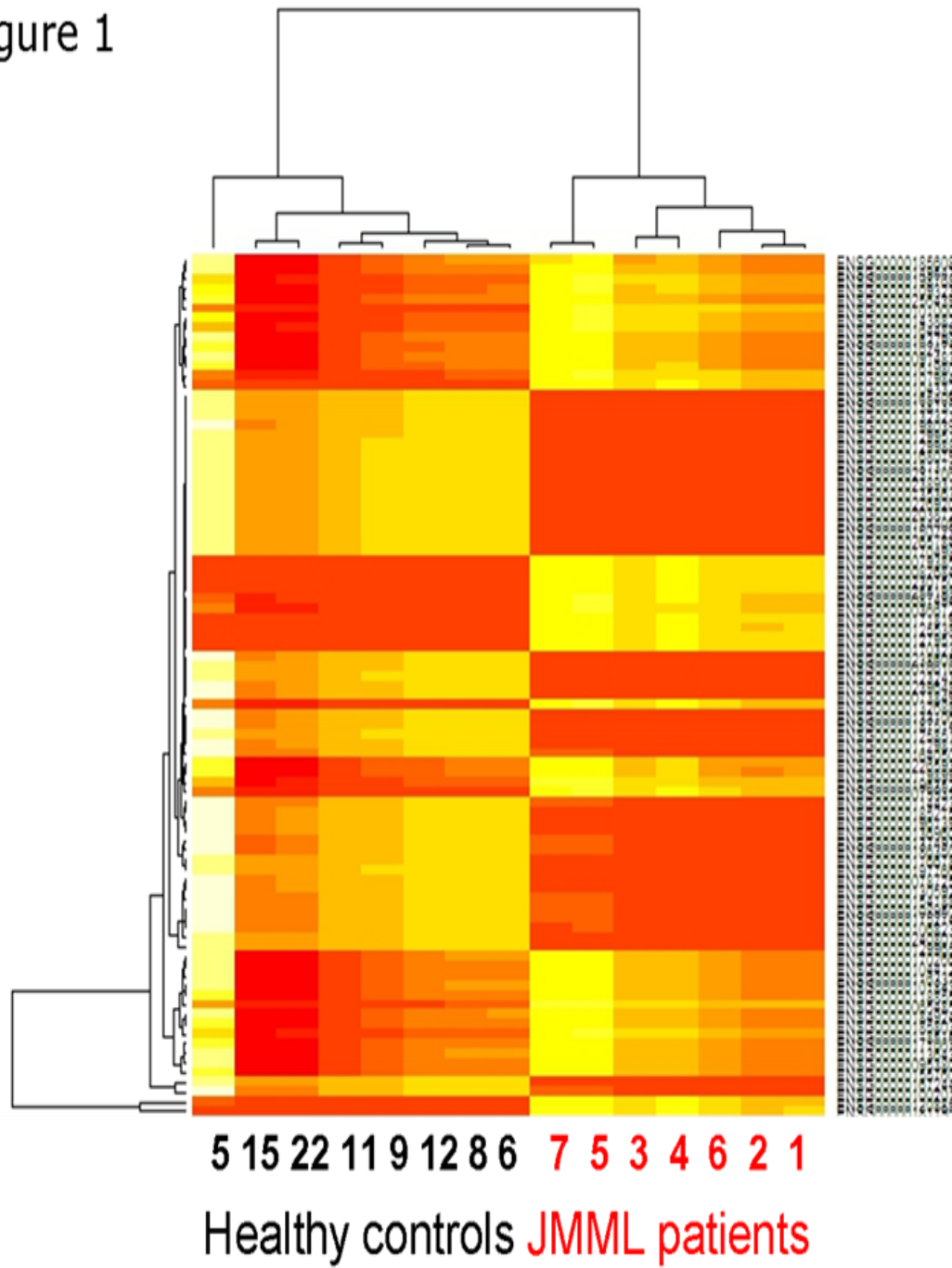
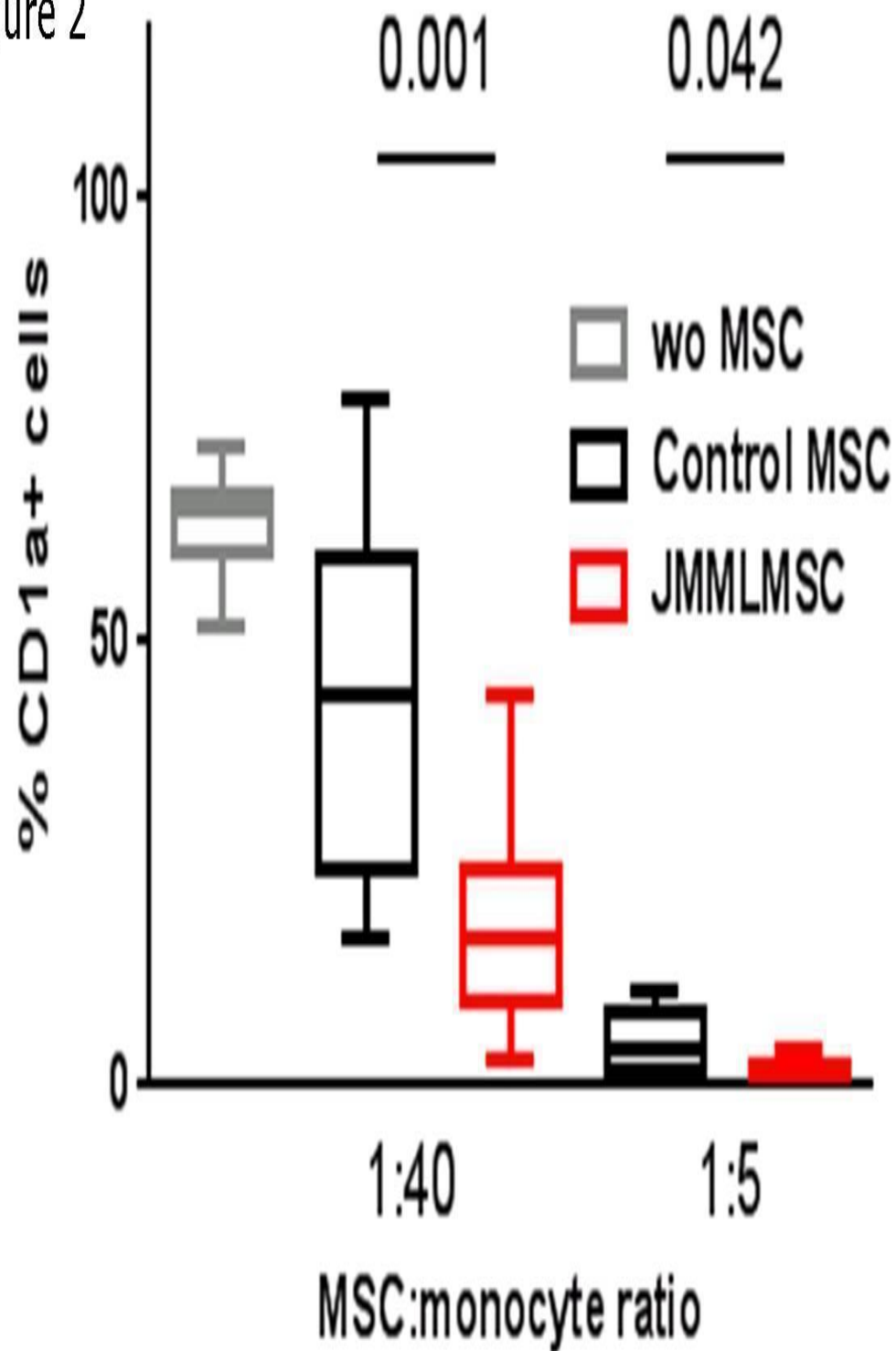


Figure 2



Conclusions

This is the first study to show the impact of leukemic cells on the microenvironment in man. Using MSC from children with JMML at diagnosis and after HSCT treatment, we

have shown that these alterations can be partially reversible. Our data shed a new light on the changes occurring in the microenvironment of children with leukemia.
No conflict of interest

O-018

Leukemia/MDS and Bone Marrow Transplantation Biology
NATURAL KILLER CELL RECEPTOR GENETIC PROFILING AND THE
OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Objectives

Allogeneic hematopoietic cell transplantation HCT is a curative therapy for hematologic malignancies as well as for numerous life-threatening disorders of hematolymphopoiesis. The most common indication for HCT is acute myeloblastic leukemia (33% of all HCT), followed by lymphoblastic leukemia, chronic myeloblastic leukemia refractory to tyrosine-kinase inhibitors, and lymphoid malignancies. In spite of high resolution HLA matching and optimal care, complications of HCT, including graft versus host disease (GVHD), relapse of the underlying disease and reactivation of otherwise latent viral infections are substantial. Recently, the natural killer (NK) cell genetic system, regulated by the activating and inhibitory Killer Immunoglobulin-like Receptors (KIR) has garnered substantial research interest as a modifier of HCT outcomes. Here we set out to determine the influence of KIR gene repertoires of HCT pairs on HCT complications including GVHD, relapse, posttransplant lymphoproliferative disorder (PTLD) and cytomegalovirus (CMV) reactivation.

Methods

KIR typing was obtained for 100 paediatric and 200 adult HLA- matched allo-HCT pairs in addition to 50 healthy individuals by a Luminex-based rSSO method. Effect of KIR genotypes on HCT outcomes was analysed using binomial regression and Kaplan-Meier tests. Peripheral blood mononuclear cells (PBMNCs) from healthy volunteers were stimulated against different targets to enumerate KIR dependent target specific NK cell responses.

Results

Donor-recipient pairs matched for the KIR-AA and B/x genotypes were significantly protected from GVHD (HR=2.224; p=0.01) without any effect on disease relapse (HR=1.098; p=0.934). Incidence of PTLD was strongly correlated by donor KIR cen-B linkage group (p=0.01), whereas higher activating donor-KIR protected against CMV reactivation (p=0.02). Unique target-induced functional response with higher number of herpes-virus induced functional NK cells in individuals lacking KIR cen-B was observed.

Conclusions

NK cell responsiveness, a function of KIR gene repertoire modified the risk of GVHD, PTLD and CMV reactivation indicating relevance of KIR gene profiling for predicting HCT outcomes.

No conflict of interest

O-019

Medulloblastoma – Clinical

METASTATIC MEDULLOBLASTOMA - UK RESULTS WITH INDUCTION AND HIGH DOSE CHEMOTHERAPY WITH HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (THE MILAN STRATEGY)

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Objectives

Historically, the 5-year overall survival (OS) for metastatic medulloblastoma (MB) is less than 40%. The Milan Strategy of post-operative induction chemotherapy followed

by hyperfractionated accelerated radiotherapy (HART) and response directed myeloablative high dose chemotherapy (HDC) or maintenance chemotherapy was reported in a study of 33 patients with metastatic MB to improve 3-year OS to 77% (95% CI 61, 93) and 5-year OS to 73% (59, 87). We report the UK outcomes of this strategy.

Methods

Questionnaires were sent to all 20 UK paediatric oncology centres to collect retrospective data on treatment delivered, toxicity and survival with the Milan strategy.

Results

Between February 2009 and October 2011, 34 patients who fulfilled the entry criteria of the original study, were treated de novo for metastatic MB in 14 centres. The median age at presentation was 7 years (range 3 - 15). Median interval from surgery to HART was 109 versus 85 days in the Milan series. Induction and HDC were toxic with 83-100% incidence of grade 3 toxicities: febrile neutropaenia, blood and platelet transfusion. Response was highly correlated with survival: 16/17 patients who achieved CR by the end of therapy remain alive and in remission but only 3/17 with lesser responses are still alive ($p < 0.0001$). With follow up from induction chemotherapy (as in the Milan study) of 30-60 months, we estimate 3-year overall survival of 55% (95% CI 38, 71). This result is outside the 95% CI of the Milan results and encompasses the historical result of 40%. We did not observe major late neurotoxicity in this cohort, although some children had residual cerebellar signs and changes on follow up MRI.

Conclusions

We did not replicate the improved results reported by the Milan group. The reasons could include differences in patient sub-groups and protocol compliance in these small cohorts.

O-020

Medulloblastoma – Clinical

TANDEM HIGH-DOSE CHEMOTHERAPY WITH STEM CELL RESCUE FOLLOWED BY RISK-ADAPTED RADIATION IN CHILDREN WITH HIGH-RISK CEREBRAL PRIMITIVE NEUROECTODERMAL TUMOR: RESULTS OF THE SFCE-TRIAL PNET HR+5.

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Objectives

To assess the 3-year progression-free survival (PFS) rate of patients with newly diagnosed high-risk medulloblastoma (MB) or supratentorial primitive neuroectodermal tumor (sPNET) between 5-20 years treated according to the prospective multicenter trial PNET HR+5.

Methods

Children received as postoperative induction chemotherapy two cycles of etoposide (500mg/m²) - carboplatine (800mg/m²), followed by two courses of thiotepa (600mg/m² per course) with autologous stem cell rescue. Risk-adapted conventional radiotherapy (RT) was delivered around day 45 after second transplantation. Craniospinal RT dose was 36 Gy for patients with metastatic disease or with unfavourable histology (anaplastic MB, large cell MB, MB with *myc* amplification) followed by a tumor bed boost of 18 Gy. Patients with localized sPNET received focal RT at the dose of 54 Gy. Maintenance treatment with 6 cycles of temozolomide was planned to start between 1-3 months after the end of RT.

Results

From January 2009 to February 2012, 64 patients (MB=51; sPNET=13) between 5 and 19 years (median age, 9 years) were enrolled. Five patients didn't received RT due to progressive disease. Maintenance treatment was administered in 42 patients. The median follow-up was 32 months (range, 16-54 months). The 3-year PFS and overall survival (OS) were 80% (95% CI: 68-88%) and 85% (95% CI: 74-92%), respectively. The 3-year PFS was 79% (95% CI: 65-88%) for children with MB and 85% (95% CI: 58-96%) for those with sPNET. No major unexpected toxicities and no treatment-related deaths were reported.

Conclusions

This treatment based on high-dose chemotherapy and conventional RT resulted in a high overall survival rate in children and adolescent with newly diagnosed high-risk cerebral PNET.

O-021

Medulloblastoma – Clinical

**CLINICAL OUTCOMES OF CHILDREN WITH STANDARD RISK
MEDULLOBLASTOMA TREATED WITH PROTON AND PHOTON
RADIOTHERAPY**

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Objectives

To compare long-term recurrence-free survival (RFS) and overall survival (OS) between children treated with proton and photon radiotherapy (RT) for standard risk medulloblastoma. **Methods**

This multi-institution cohort study includes 105 children treated with chemotherapy and proton (n=45) or photon (n=60) RT between 1991 and 2009. OS and RFS were estimated by the Kaplan-Meier method and compared with the long-rank test. The effect of RT type and other covariates on each outcome was assessed through multivariable analysis using logistic regression and backward selection method with an alpha level of removal of 0.1.

Results

Median (range) age at diagnosis was 6 yrs (3-21) for proton patients vs. 8 yrs (3-19) for photon patients (p=0.002). Cohorts were similar with respect to gender, histology, extent of surgical resection, craniospinal and total RT dose, and whether the RT boost was delivered to the posterior fossa or tumor bed. The median CSI dose was 23.4 Gy (18-37.2) and the median total dose was 54 Gy (50.4-60). Median follow-up time is 5.7 years (0.6–9.9) for proton patients vs. 8 years (1.3–19.7) for photon patients (p<0.001). There was no significant difference in OS or RFS between patients treated with proton vs. photon RT: 5 yr OS 82.0% (CI 0.65-0.91) vs. 89.4% (CI 0.78-0.95), and 5 yr RFS 82.2% (CI 0.68-0.91) vs. 79.7% (CI 0.67-0.88). On multivariable analysis, female gender (p=0.038) and higher CSI dose (p=0.041) were associated with a better RFS. There was a marginally significant relationship between better OS and older age at diagnosis (p=0.054), classic histology (p=0.062), and female gender (p=0.072). A second primary malignancy occurred in four (6.7%) photon patients, at a median time of 12.7 years (3.7-13.0), vs. no (0%) proton patients (p=0.133).

Conclusions

Disease control with proton and photon radiotherapy appears equivalent for standard risk medulloblastoma.

O-022

Medulloblastoma – Clinical

THERAPEUTIC IMPLICATIONS OF MEDULLOBLASTOMA SUBGROUPS IN NON-INFANTS: A SINGLE CENTRE POPULATION BASED EXPERIENCE

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Objectives

The advent of integrated genomics has fundamentally changed our understanding of medulloblastoma. Although survival differences have been shown to exist between the four principle subgroups, treatment related differences have yet to be elucidated. We sought to delineate these differences at a large referral centre.

Methods

All patients older than three years of age treated with surgery, craniospinal irradiation, and adjuvant chemotherapy were identified at the Hospital for Sick Children in Toronto from 1998-2012.

Results

Ninety-four patients met our inclusion criteria. Two periods were identified, those patients treated prior to 2006 as per the open protocols of the Children's Oncology Group (CCG9961, POG9631), and patients treated after 2006 treated as per the SJMB03 protocol. Five-year progression free survival over the entire cohort was 78%. When stratified by treatment, 5-year survival pre and post 2006 were identical (76.8% pre-2006 and 79.3% post-2006). When re-analysed in a subgroup specific manner, we find no significant differences in progression-free survival pre and post 2006. Strikingly, we found that Group 3 and 4 patients have excellent survivals compared to those previously reported, with 5 year progression-free survival in average risk Group 4 patients of over 90% and over 75% in average risk Group 3 patients regardless of treatment protocol. Survival of SHH patients was relatively poor across both treatment protocols with 5 year progression free survival of 60% likely owing to a higher proportion of *TP53* mutated patients at our center.

Conclusions

In a cohort of homogenously treated non-infant patients, progression free survival appears to be improved compared to initial reports based on retrospective cohorts. The impact of subgroup affiliation in children over age 3 needs to be assessed in large prospectively treated cooperative protocols to determine the prognostic and predictive implications of subgroup affiliation.

O-023

Medulloblastoma – Clinical

EXPERIENCE WITH A METRONOMIC ANTIANGIOGENIC THERAPY IN CHILDREN WITH RECURRENT MEDULLOBLASTOMA, ATRT, AND VARIOUS OTHER MALIGNANT CNS TUMORS

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Objectives

Patients with recurrent malignant CNS tumors have a poor prognosis irrespective of salvage therapy used. We report on an updated and extended series of patients with recurrent medulloblastomas, ATRTs, and various other malignant CNS tumors partly included in a previous publication and treated with an alternative approach consisting of an antiangiogenic combination therapy (1).

Methods

From 11/2006 to 9/2013, 43 patients with various recurrent brain tumors started treatment with an antiangiogenic multidrug-regime consisting of bevacizumab, thalidomide, celecoxib, fenofibrate, and etoposide alternating with cyclophosphamide, with or without intraventricular therapy (etoposide and liposomal cytarabine).

Diagnoses were medulloblastoma (n=9), ATRT (n=5), ependymoma (n=4), CNS PNET (n=3), ETANTR (n=3), pineoblastoma (n=2), HGG (n=2), DIPG (n=3), NGGCT (n=2), MPNST (n=2) and choroid plexus carcinoma, astroblastoma, paraganglioma, meningioma, oncocytoma, epithelioid sarcoma, endolymphatic sac tumor and neuroblastoma in one each.

Results

As of 3/2014, 5/9 patients with medulloblastoma are alive for 67, 63, 63, 37 and 35 months and 3/5 patients with ATRT are alive for 71, 39, and 31 months after their last recurrence, all of them off therapy. Patients with CNS PNET, ETANTR, HGG, DIPG, oncocytoma and neuroblastoma did not appear to respond to this strategy. The two patients with pineoblastoma survived for 38 and 27 months, respectively, despite extensive leptomeningeal disease. The two patients with NGGCT showed a dramatic drop of their Alpha-Fetoprotein levels.

Conclusions

The proposed antiangiogenic regimen that is currently being evaluated for medulloblastomas in an international phase II protocol (MEMMAT; ClinicalTrials.gov Identifier: NCT01356290) seems to be also efficacious in recurrent ATRTs. In a number of other tumor entities time to progression could be prolonged while maintaining good quality of life.

1. Peyrl et al. (2012). *Pediatr Blood Cancer*, 59(3):511-7.

O-024

Medulloblastoma – Clinical

LONG TERM NEUROPSYCHOLOGICAL FOLLOW UP OF YOUNG CHILDREN WITH MEDULLOBLASTOMA TREATED ACCORDING TO THE CCG 99703 REGIMEN

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Objectives

High dose chemotherapy (HDC) strategies were developed in infant brain tumor protocols to prevent neuropsychological (NP) impairments associated with radiation. However comprehensive NP evaluations of young children treated with such strategies remain scant. Our aim was to examine long term NP outcomes in young children with medulloblastoma treated with sequential HDC according to protocol CCG 99703.

Methods

This retrospective study included young children diagnosed with medulloblastoma from 1998-2011 at 6 North American institutions. Neurocognitive data were extracted from institutional NP reports on children old enough to be tested.

Results

The initial cohort included 47 patients. Twenty of the 37 survivors (42%) had at least one NP assessment. This sample was 55% male (n=11) and mean age at diagnosis was 29.2 months (SD=14.3). Posterior fossa syndrome (PFs) was reported in five patients (26%). Eight (40%) received radiotherapy (4 Focal, 4 CSI), 2 received IT chemotherapy and 2 received HD MTX during induction. On average, children were assessed 3.2 years (SD=1.6) post-diagnosis, at 5.7 years of age (SD=1.7). FSIQ ranged from 67-119 (mean=94; SD=16.1).

The majority of children had low average to average NP functioning (78%). Four children (3 received RT) accounted for the majority (56%) of the impaired scores (<10th percentile). While sample size limited power, patients treated with radiotherapy had lower working memory scores (WMI; mean=88 vs. 100; p=.08); patients with PFs had lower perceptual reasoning scores (PRI; mean=85 vs. 100; p=.09); and patients with hearing support had lower verbal comprehension scores (VCI; mean=85 vs. 100; p=.09). NP outcomes did not statistically differ by age at diagnosis, gender, extent of resection, metastasis, or histology.

Conclusions

NP data obtained from this sample of survivors of infant medulloblastoma treated according to the 99703 regimen are encouraging and indicate average neurocognitive functioning.

O-025

Renal Tumor - Clinical

**UNILATERAL WILMS TUMOR TREATED BY PARTIAL NEPHRECTOMY
ENROLLED ON THE CHILDREN'S ONCOLOGY GROUP (COG) RENAL TUMOR
BIOLOGY AND CLASSIFICATION STUDY AREN03B2.**

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Objectives

The long term renal failure rate in children with unilateral Wilms tumor (WT) is less than 1%. The standard recommended surgical treatment for unilateral WT is a nephroureterectomy with lymph node sampling. Despite this recommendation, some patients with unilateral renal tumors undergo partial nephrectomy. Little is known about the technical considerations and outcomes of these patients. The purpose of this study is to increase that understanding, through report of the operative outcomes, event free survival (EFS) and overall survival (OS) of patients enrolled on AREN03B2 with unilateral WT who have undergone partial nephrectomy.

Methods

Eligible patients enrolled on AREN03B2 from 2/27/2006 to 9/30/2013 with a unilateral surgical review form that indicated partial nephrectomy as the surgical procedure were considered in this analysis. Further eligibility criteria included 1) no enrollment on AREN0534 (bilateral study) and 2) confirmation of histologic diagnosis of WT by central pathology review. Surgical outcomes, EFS and OS were assessed.

Results

39/4,021 (1.0%) unilateral WT patients (38 FHWT, 1 anaplastic WT) on AREN03B2 underwent a partial nephrectomy. Median tumor weight was 701.1gm (range 133-1870). Local stage distribution was Stage I (15), II (11) and III (11). 13/39 (33%) patients did not have their lymph nodes sampled. Among the patients with stage III disease, 8 had intraoperative tumor spill and 9 had microscopic residual tumor. 9/11 were upstaged. The 5-year EFS and OS estimates were 89.4 ± 13.0% and 95.7 ± 8.9%.

Conclusions

Patients with unilateral WT undergoing partial nephrectomy had greater than expected occurrence of microscopic residual disease and intraoperative tumor spill, which resulted in local upstaging and consequent increased therapy. The potential long-term renal benefit of nephron-sparing surgery must be weighed against the potential risks of additional chemotherapy and abdominal radiation in patients who had incomplete surgical resections.

O-026

Renal Tumor - Clinical

TREATMENT OF STAGE II-IV DIFFUSE ANAPLASTIC WILMS TUMOR: RESULTS FROM THE CHILDREN'S ONCOLOGY GROUP AREN0321 STUDY

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Objectives

In National Wilms Tumor Study-5 (NWT5-5), 4-year relapse-free survival for patients with stages II-IV diffuse anaplastic Wilms tumor (DAWT) treated with vincristine, doxorubicin, cyclophosphamide, and etoposide, plus radiotherapy (XRT) (Regimen I) was 55%. AREN0321 evaluated whether a more intensive regimen containing carboplatin in addition to agents used in Regimen I (Regimen UH-1) improves EFS for these patients.

Methods

Patients with stages II-IV DAWT without measurable disease received Regimen UH-1. Patients with stage IV measurable disease had the option to receive vincristine in combination with irinotecan (VI) in an upfront window; those with partial response (PR) had VI incorporated into Regimen UH-1 (Regimen UH-2). Dosages of doxorubicin, cyclophosphamide and etoposide were reduced mid-study (revised UH-1/UH-2) due to excessive non-hematologic toxicity. The study was designed to detect improvement in EFS compared to historical controls treated with regimen I.

The study was approved by the Central Institutional Review Board.

Results

Sixty-six eligible patients were treated: 22 with UH-1, 14 with VI window followed by UH-1/UH-2, and 30 with revised UH-1/UH-2. Nineteen patients had stage IV with measurable disease, 14 of whom participated in VI window; 11/14 (79%) had PR. Three-year EFS for all patients was 69% (95% CI, 56-80%). Nineteen events were observed versus 29 expected based on NWT5-5 data ($p=0.028$). Four-year EFS was 85% (95% CI, 51-96%) for stage II, 74% (95% CI, 45-89%) for stage III, and 46% (95% CI, 25-65%) for stage IV. For patients with stage IV DAWT, 4-year EFS was 57% (95% CI, 28-78%) for the 14 patients treated with VI window and 33% (95% CI, 8-62%) for the 10 patients treated with UH-1 upfront. Three patients (4.5%) died of toxicity: cardiomyopathy ($n=1$), pulmonary hypertension ($n=1$), and pulmonary edema ($n=1$).

Conclusions

Regimen UH-1/UH-2 appears to produce better EFS for patients with stage II-IV DAWT than Regimen I albeit with increased toxicity.

O-027

Renal Tumor - Clinical

MALIGNANT RHABDOID TUMOR OF THE KIDNEY (MRTK) – DATA OF 52 PATIENTS TREATED ACCORDING TO PROTOCOLS OF THE GPOH (GERMAN SOCIETY OF PAEDIATRIC ONCOLOGY AND HEMATOLOGY)

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Objectives

To analyze the data of 52 consecutive patients having MRTK registered in the framework of SIOP 9/GPO, 93-01/GPOH, 2001/GPOH and EU-RHAB between 1991 and 2013 in Austria, Switzerland and Germany.

Methods

All children having a histologically proven MRTK entered onto above studies were eligible for analysis. Median Follow up was 5.3 years.

Results

22 patients presented with metastatic disease most frequently to the lungs (n=18). Simultaneous MRTK and AT/RT occurred in 3 patients. 1 patient died before treatment. 13 patients underwent upfront surgery and 38 received preoperative treatment (19 Dactinomycin and Vincristine (AV), 18 AV plus Doxorubicin (AVD), 1 unknown). Mean response to AVD was significantly better than to AV (63% volume reduction vs. 15% increase in volume, p=0.002). Local stage distribution after surgery was 5, 13 and 29 for stage 1, 2 and 3 respectively (5 undetermined). 37 patients achieved a complete remission during the treatment course: 20 were in continuous CR at the end of treatment. 29 patients died: 27 due to progressive disease, 2 due to postoperative bleeding. 2 year event free (EFS) and overall survival (OS) were 35 and 39% respectively. Age younger than 10 months (2.7 RR, 95%CI: 1.2-5.7) and local stage III (3.3 RR, 95%CI: 1.4-7.9) are significant risk-factors in Cox-regression analysis. 2y OS for patients with stage IV was 28% (n=14/22) compared to 48% (n=15/30) for localized MRTK. Patients having achieved a macroscopic complete remission and a local stage III had a significantly improved 2y OS if undergoing flank irradiation (36% vs. 18%, p=0.05, n=19). Patients having achieved a macroscopic CR show 52% and 50% 2y OS for localized and metastatic MRTK respectively.

Conclusions

Younger patients especially with metastatic disease still have an appalling prognosis. Early histologic diagnosis and intensive postoperative treatment including irradiation are important in the treatment of MRTK.

O-028

Renal Tumor - Clinical

TREATMENT AND OUTCOME OF PATIENTS WITH RELAPSED CLEAR CELL SARCOMA OF THE KIDNEY (CCSK): A COMBINED SIOP AND AIEOP STUDY

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Objectives

Clear Cell Sarcoma of the Kidney (CCSK) is an uncommon pediatric renal tumor. Relapses occur in about 15% of the patients. Detailed clinical information on relapsed CCSK is scarce. The current study aims to describe outcome of patients with relapsed CCSK treated according to recent European protocols, in order to find a rationale for creating future international CCSK relapse treatment protocols.

Methods

We analysed prospectively collected data of all CCSK patients who developed a relapse after complete response to initial therapy, entered onto International Society of Pediatric Oncology (SIOP) and Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) trials between 1992 and 2012.

Results

Thirty-seven of 237 CCSK patients (16%) treated according to SIOP and AIEOP protocols developed a relapse. Median time from initial diagnosis to relapse was 17 months (range, 5.5 months - 6.6 years). 35/37 relapses (95%) were metastatic; the most common sites of relapse were brain (n = 13), lungs (n = 7) and bone (n = 5). Relapse treatment consisted of chemotherapy (n = 30), surgery (n = 19) and/or radiotherapy (n = 18), followed by high dose chemotherapy and autologous bone marrow transplantation (ABMT) in 14 patients. 22/37 patients (59%) achieved a second complete remission (CR); 15 of whom (68%) developed a second relapse.

Five-year event-free survival (EFS) after relapse was 18% (95% CI: 4 - 32%) and 5-year overall survival (OS) was 26% (95% CI: 10 - 42%).

Conclusions

In this largest series of relapsed CCSK patients ever described, overall outcome is poor. Relapses tend to occur late, so extensive follow-up is desirable. Most relapses are metastatic and brain relapses are more common than previously recognized. Intensive treatment aiming for local control, followed by high dose chemotherapy and ABMT, seems to be of benefit to enhance survival. Novel development of targeted therapy is urgently required.

O-029

Renal Tumor - Clinical

GAIN OF 1Q AS A BIOMARKER IN PRE-TREATED WILMS TUMOUR IN THE SIOP WT 2001 TRIAL: A SIOP RENAL TUMOURS BIOLOGY CONSORTIUM STUDY

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Objectives

To further improve outcomes for Wilms tumor (WT), there is a clinical need for molecular biomarkers with sufficient sensitivity and specificity for use in risk stratification. The SIOPWT2001 trial, that enrolled over 4,000 patients from 261 centres in 28 countries, aimed to evaluate the utility of loss of heterozygosity (LOH) of 1p/16q in relation to histological risk group assessed after pre-operative chemotherapy and incorporate analysis of new potential biomarkers such as gain of 1q.

Methods

The SIOP-RTSG biology consortium contributed 911 frozen tumour samples from SIOPWT2001 trial patients in 7 countries for molecular analysis of 1p/16q LOH (microsatellite analysis) and copy number assessment at 1p/16q, 1q, and several other loci of interest in WT (MLPA analysis). Analyses were conducted in 3 laboratories, with exchange of a blinded quality assurance sample set.

Results

To date, analysis of 365 tumours shows LOH 1p(10%), LOH16q(18%) and combined LOH(3%), with a significant association of LOH 16q with anaplastic histology but not with the SIOP high risk 'blastemal-type' WT. Gain of 1q is found in 98/420(23%), with increased frequency in blastemal (50%) and anaplastic (44%) WT but similar, lower frequency across all other histological subtypes (mixed:21%; regressive:23%; epithelial:21%; stromal:19%). Preliminary survival analysis of 304 cases showed significant hazard ratios of 3.1 (1.8-5.4) for relapse and 2.7 (1.2-6.2) for death for 1q

gain/normal, respectively. Final assessment of 1q gain in multivariate analysis incorporating histological risk group, tumour stage and patient age for all 911 patients is planned for April 2014, once the full molecular dataset is integrated with the international clinical trial database.

Conclusions

Gain of 1q is a potential adverse biomarker for WT. Its association with high risk histological features after pre-operative chemotherapy and independent impact on survival require assessment in a larger number of patients before consideration for clinical use.

O-030

Renal Tumor - Clinical

RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN CHILDREN AFTER SURGERY FOR UNILATERAL RENAL TUMOR

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Objectives

Chronic kidney disease (CKD) is associated with increased risk for cardiovascular diseases and overall mortality. We analyzed the characteristics of a cohort of patients with CKD long after surgery for unilateral renal tumor during childhood to identify modifiable risk factors for CKD.

Methods

A single-center observational study of 60 children who underwent nephrectomy and 12 children who underwent nephron-sparing surgery (NSS) for unilateral renal tumor. Glomerular filtration rate was estimated (eGFR) with the Modification of Diet in Renal Study or the Schwartz formulas as appropriate for age. CKD was defined as an eGFR < 90 ml/min/1.73m².

Results

At a mean \pm SD age of 27 ± 15 years after surgery, CKD was present in 32 patients (44%). Older age ($p=0.01$), nephrectomy ($p=0.008$), pre-operative renal dysfunction ($p=0.02$), higher tumor stages ($p=0.001$), blood hypertension ($p=0.001$), albuminuria ($p=0.03$), and acquired renal cyst ($p=0.03$) were more frequently associated with CKD. Adjuvant therapy, second tumor prevalence and co-morbidities did not influence the CKD development.

Conclusions

After surgery for unilateral renal tumor during childhood, main risk factors for CKD in some subjects included 50% ablation of renal parenchyma, age-related decline in renal function, and adaptive renal hyperfiltration.

In children with unilateral renal tumor nephrectomy might no longer be regarded as the gold standard surgical treatment when NSS is feasible.

O-031

Brain Tumours Biology 1

MOLECULAR CLASSIFICATION OF EPENDYMAL BRAIN TUMORS

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Objectives

Histopathological grading of ependymoma according to the WHO classification of CNS tumors is extremely challenging. A comprehensive molecular stratification scheme is absolutely essential and contemporary, since modern technologies reached routine practise. During the past decade, the biological understanding of ependymomas has improved significantly; especially molecular subgroups based on transcriptomic alterations were defined. Two distinct biological entities of ependymoma were identified by several studies (designated Group-A, CIMP-positive and Group-B, CIMP-negative), which show striking differences in genetic characteristics and clinical outcome. A similar consensus for supratentorial and spinal ependymoma is lacking.

Methods

We studied genome-wide DNA methylation (Illumina HumanMethylation450) in 308 primary ependymal tumors, including ependymomas, subependymomas (SE), and myxopapillary ependymoma (MPE) of distinct localizations. To identify meaningful molecular subgroups, we conducted unsupervised hierarchical clustering. Gene expression profiling was used to validate these molecular subgroups, to identify differentially expressed and epigenetically silenced genes.

Results

DNA methylation data showed that ependymal brain tumors can be classified into several molecular subgroups. Group-A tumors (CIMP-positive), Group-B tumors (CIMP-negative), MPE, and SE formed robust distinct clusters. Supratentorial ependymomas can be classified into two principle molecular subgroups, one of is associated with highly recurrent RELA fusion, displays a poor prognosis, and occur in young children and infants. Notably, a significant number of ependymomas previously classified by histology as WHO Grade II/III look like SE by DNA methylation, and also have extremely good survival.

Conclusions

In summary, using genome-wide DNA methylation analysis we could delineate meaningful molecular subgroups of ependymal brain tumors including supratentorial ependymoma. Diagnoses of tumors with challenging histopathological features can now be supported easily by this DNA methylation technology. Hence, this approach offers the opportunity to replace the current ambiguous histopathological grading system with an unbiased molecular classification that readily distinguishes biologically, genetically, and clinically meaningful subgroups of ependymal brain tumors.

O-032

Brain Tumours Biology 1

POSTERIOR FOSSA EPENDYMOMA SUBGROUPS HAVE DISTINCT THERAPEUTIC AND PROGNOSTIC IMPLICATIONS

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Objectives

Recent integrated genomic studies has shown that posterior fossa ependymoma comprise two distinct molecular subgroups, the CIMP+ve group and CIMP-ve group where CIMP+ve patients are typically younger and have a worse prognosis. Current standard of care for all posterior fossa ependymoma include surgery and conformal external beam radiation to the tumour bed, irrespective of extent of resection or subgroup. We sought to delineate the prognostic implications of external beam irradiation in a subgroup specific manner.

Methods

We assembled a cohort of 83 posterior fossa ependymoma's and were subgrouped using DNA methylation. Clinical details were ascertained through a retrospective chart review.

Results

In order to characterize treatment implications of ependymoma subgroups, overall survival was stratified by treatment with external beam irradiation. When restricting the analysis to CIMP +ve ependymoma with gross total resections, external beam irradiation confers a survival advantage ($p=0.063$). Subtotally resected CIMP +ve ependymoma have a dismal prognosis without any significant difference in survival with the administration of external beam irradiation ($p=0.75$). In CIMP -ve patients, administration of upfront external beam irradiation results in improved progression free survival ($p=0.082$), however, overall survival is 100% across all patients ($p=1$).

Conclusions

The survival benefit of adjuvant external beam irradiation in posterior fossa ependymoma is highly dependent on subgroup. In CIMP +ve cases, external beam irradiation has no benefit in patients with subtotally resected tumours, and these patients should be considered for enrolment in clinical trials. A significant proportion of CIMP -ve patients can be cured with surgical resection alone, and the remainder can likely be salvaged with irradiation at recurrence.

O-033

Brain Tumours Biology 1

EPIGENOMIC ALTERATIONS DEFINE LETHAL CIMP-POSITIVE EPENDYMOMAS OF INFANCY

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Objectives

Ependymomas are chemo-resistant tumours, which in children, commonly arise in the region of the brain known as the posterior fossa (PF). PF ependymomas comprise two clinically and molecularly distinct diseases termed PFA and PFB. While PFB ependymomas occur most often in older children, exhibit a large degree of chromosomal instability, and have a favorable prognosis, PFA ependymomas arise most often in infants, have very few chromosomal alterations, and are associated with poor survival. The purpose of our study was to characterize the mutational and epigenetic landscape of PF ependymoma to identify drivers of tumourigenesis and targets for therapy.

Methods

We performed whole-genome sequencing of 5 PF ependymomas, and whole-exome sequencing of 42 PF ependymomas. We undertook DNA methylation profiling of 79 ependymomas by MBD2-chip, 48 PF ependymomas by Illumina 450K microarrays, and 6 PF ependymomas by whole-genome bisulfite sequencing. These findings were supported by H3K27me3 ChIP-seq of 11 PF ependymomas.

Results

Our findings reveal that PF ependymoma harbour a stable mutational landscape, exhibiting zero recurrent mutations in coding space. This was in contrast to widespread epigenomic alterations, at the level of DNA and H3K27 methylation, distinguishing between PFA and PFB. We demonstrate that PFA ependymomas are characterized by DNA hypermethylation at CpG islands, described as a CpG island methylator phenotype (CIMP+), and that both DNA and H3K27 methylation converge upon genes known to be silenced by the PRC2 complex in embryonic stem cells. We show that PFA-CIMP+ ependymoma short-term cultures are highly sensitive to inhibitors of DNA methylation and inhibitors of H3K27me3 shown both *in vitro* and *in vivo*.

Conclusions

Our study represents the first subgroup specific therapy shown to be effective in PFA ependymoma, and suggests that agents which target DNA methylation and/or H3K27 tri-methylation in patients harbouring PFA-CIMP+ ependymoma may be efficacious to use in clinical trials.

O-034

Brain Tumours Biology 1

COMBINED MODEL OF MOLECULAR AND CLINICAL PROGNOSTIC MARKERS ENHANCES RISK STRATIFICATION OF MEDULLOBLASTOMA

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Objectives

Medulloblastoma comprises four distinct molecular subgroups – WNT, SHH, Group3, and Group4. Current medulloblastoma protocols stratify patients based on clinical features: patient age, metastatic stage, extent of resection, and histological variant. Stark prognostic and genetic differences between the four subgroups suggest that subgroup-specific molecular biomarkers could improve patient prognostication.

Methods

Molecular biomarkers were identified from a discovery set of 673 medulloblastomas from 43 cities around the globe. Combined risk stratification models were designed based on clinical and cytogenetic biomarkers identified by multivariate Cox proportional-hazards analyses. Identified biomarkers were tested using FISH on a non-overlapping medulloblastoma tissue microarray (n=453), with subsequent validation of the risk stratification models.

Results

Subgroup information improves the predictive accuracy of a multivariate survival model compared to clinical biomarkers alone. Most previously published cytogenetic biomarkers are only prognostic within a single medulloblastoma subgroup. Profiling a six-pack of FISH biomarkers (*GLI2*, *MYC*, 11, 14, 17p, and 17q) on FFPE tissues, we can reliably and reproducibly identify very low-risk and very high-risk patients within each of SHH, Group3 and Group4 medulloblastomas.

Conclusions

Combining subgroup and cytogenetic biomarkers with established clinical biomarkers substantially improves patient prognostication, even in the context of heterogeneous clinical therapies. The prognostic significance of most molecular biomarkers is restricted to a specific subgroup. We have identified a small panel of cytogenetic biomarkers that reliably identifies high-risk and low-risk groups of patients and which will make an excellent tool for selecting patients for therapy intensification and therapy de-escalation in future clinical trials.

O-035

Brain Tumours Biology 1

MAINTENANCE OF MOLECULAR SUBGROUP AFFILIATION IN METASTATIC MEDULLOBLASTOMA

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Objectives

Previous genomic and molecular analyses have revealed that medulloblastoma comprises four distinct molecular variants with distinct genetics, transcriptomes, and outcomes. Subgroup affiliation has been previously shown to remain stable at the time of recurrence, which likely reflects their distinct cells of origin. However, an important question that remains unanswered is subgroup stability in the metastatic compartment.

Methods

We assembled a cohort of 12-paired primary-metastatic tumors collected in the MAGIC consortium, and established their molecular subgroup affiliation by performing integrative gene expression and methylation analysis. Frozen tissues were collected and profiled using Affymetrix gene expression arrays and Illumina methylation arrays. Class prediction and hierarchical clustering were performed using existing published datasets.

Results

Our molecular analysis establishes the unequivocal maintenance of molecular subgroup affiliation in metastatic medulloblastoma. We further validated these findings by interrogating a non-overlapping cohort of 19-pairs of primary-metastatic tumors from the Burdenko Neurosurgical Institute using an orthogonal technique of immunohistochemical staining. We confirm the perfect concordance, identified using integrative molecular analysis, between molecular subgroup affiliation at both the primary site and metastatic lesions on the basis of immunohistochemical staining.

Conclusions

This investigation represents the largest reported primary-metastatic paired cohort profiled to-date and provides a unique opportunity to evaluate subgroup-specific molecular aberrations within the metastatic compartment. Although previous studies have shown the existence of clonal evolution of the metastatic compartment from its matching primary tumor, the maintenance of subgroup affiliation presents a treatment opportunity to target subgroup-specific events. Our findings further support the notion that medulloblastoma subgroups arise from distinct cells of origin, which are carried forward from ontogeny to oncology.

O-036

Brain Tumours Biology 1

RECURRENT MEDULLOBLASTOMA IS HIGHLY DISTINCT FROM ITS MATCHED PRIMARY TUMOR

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Objectives

Medulloblastoma (MB) is the most common paediatric malignant brain tumor. By the way of optimal surgery, radiation, and chemotherapy, medulloblastoma can be treated but despite the best therapy the disease recurs in 40% of the cases. We developed a protocol to study the genetic differences between primary and recurrent tumors *in vivo*, using our transposon mutagenesis driven mouse model.

Methods

Our novel murine model of metastatic MB is highly penetrant, has a short latency, and involves random secondary genetic events. The model is based on mobilizing the Sleeping Beauty transposon in the cerebella of *Ptch*^{+/-} mice. We performed sub-total surgical removal of the murine tumors, and then treated the mice by multi-fraction CT-guided craniospinal irradiation. By the way of next generation sequencing we identified mutated driver genes in the primary tumors as compared to the recurrences.

Results

70% of the mice treated with surgery and CSI recurred locally, a smaller fraction (30%) recurred distally with recurrent disease on the spinal cord. Recurrences are genetically divergent from their matched primary tumors. We have sequenced primary and recurrent tumors identifying several potential synthetic lethal genes in the primary and relapse drivers, which are only found mutated in the recurrences. We selected actionable targets and performed *in vitro* radiosensitization assays with small molecules inhibitors of the predicted driver genes, showing a reversal of radiation resistance.

Conclusions

Primary MBs are highly genetically different from the recurrences, urging the scientific community to develop different therapeutic approaches to efficiently target primary and recurrent human tumors. As our mouse model shows the same rate and pattern of recurrence observed in human patients is an extremely valuable translational platform to design new strategy against recurrent MB. Highly targetable events in genes known to play a role in cell-cycle, apoptosis and proliferation, are potential drivers of local and distal MB recurrence.

O-037

Bone Tumour - Fasanelli Session

**ZOLEDRONATE DOES NOT REDUCE THE RISK OF TREATMENT FAILURE IN
OSTEOSARCOMA: RESULTS OF THE FRENCH MULTICENTRE OS2006
RANDOMISED TRIAL**

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Objectives

Based on anti-tumour effect of zoledronate in vitro and in experimental models of rat osteosarcoma, we assessed whether zoledronate (Z) in combination with chemotherapy and surgery improved Event-Free Survival (EFS) in children and adults with osteosarcoma

Methods

Experimental treatment consisted of 10 Z-injections (4 pre and 6 postoperative), 4 mg/injection in adults, 0.05 mg/kg/injection in younger patients. Chemotherapy included methotrexate-etoposide-ifosfamide +/-adriamycine-cisplatin in children/adolescents, and doxorubicin-ifosfamide-cisplatin in adults. Balanced randomisation between Z+arm and Z-arm was stratified by centre, age, chemotherapy type and risk group (localised resectable disease versus unresectable primary and/or metastases). The study was planned as an open-label superiority trial, with three interim analyses (early stopping for efficacy or harm) disclosed to an independent data and safety monitoring board (DSMB). 470 patients (170 events) were required to achieve an 80%-power to detect a 13%-improvement of 3-year EFS (H1: 55% versus 68%, HR(event)=0.65) with zoledronate (2-sided alpha=0.05)

Results

A second interim analysis was performed after the inclusion of 318 patients (82% with a localised and resectable tumour) recruited between April-2007 and February-2014: 158 Z- and 160 Z+. No significant increase in toxicity was found in Z+, except expected hypocalcemia grade 2-4 (p<0.0001). With a median follow-up of 3.1 years, 106 events and 58 deaths were reported, including one treatment-related death. The risk of failure was not reduced in Z+ compared to Z-: HR(event)=1.31 [0.79–2.18],

p=0.17; HR(death)=1.42 [0.70–2.88], p=0.21. Results were similar after exclusion of eight Z+patients who had received ≤ 1 zoledronate-injection, and were homogeneous across the randomisation strata. Futility analysis, performed on DSMB request, showed that the probability of demonstrating a benefit was <0.0001 . Following DSMB recommendation, the trial steering committee decided to stop accrual in the trial

Conclusions

With current follow-up, the addition of zoledronate to chemotherapy did not reduce the risk of failure in osteosarcoma patients

O-038

Bone Tumour - Fasanelli Session

MODELING PRE-CLINICAL STANDARD-OF-CARE THERAPY AND IDENTIFICATION OF NOVEL AND REPURPOSED DRUG CLASSES WITH ACTIVITY AGAINST OSTEOSARCOMA

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Objectives

Treatment outcomes for osteosarcoma have stagnated with current therapies, yet many novel drug classes have not been explored nor integrated into existing regimens. We sought to screen novel agents and repurposed drugs for cytotoxicity against osteosarcoma, and to develop a preclinical model of human standard-of-care therapy, in order to integrate candidate compounds into existing treatment regimens.

Methods

With IACUC approval, orthotopic xenografts of human osteosarcoma were created in athymic nude mice. Femoral tumors and pulmonary metastases developed, recapitulating human disease. Early phase cultures of xenograft tumors and osteosarcoma cell lines were exposed to compounds from focused drug libraries in graded concentrations, both in insolation and in combination with standard-of-care agents. After 72 hours' exposure, an ATP cell viability assay was used to determine ec50 values and relative activity compared against a reference dose-response curve.

Results

373 compounds in 432 formulations were screened with this high-throughput assay. Drug sensitivity profiles of primary and metastatic tumors showed minimal differences. Using ec50 <10uM and relative activity >50% as a threshold, sensitivity and activity were highest with HDAC and proteasome inhibitors, and inhibitors of PI3K with MEK and PI3K with mTOR, and lowest with PARP, RAF, ERK and MEK inhibitors. Panobinostat and CUDC-907 were the HDAC inhibitors with greatest potency. As a class, HDAC inhibitors showed additive effects when combined with doxorubicin. Separately, using area-under-concentration-time-curve (AUC)-guided dosing, mice were subjected to a multimodal standard-of-care regimen incorporating methotrexate with leucovorin rescue, doxorubicin, cisplatin, ifosfamide and etoposide, and hind limb amputation for local control.

Conclusions

We identified classes of novel and repurposed drugs with activity against human osteosarcoma cells. HDAC inhibitors have particular efficacy, and their effects are potentiated when combined with doxorubicin. These and other identified compounds can be further tested using our preclinical standard-of-care regimen to prioritize agents for introduction into existing clinical protocols.

O-039

Bone Tumour - Fasanelli Session

WHOLE GENOME AND EXOME SEQUENCING REVEALS THE HETEROGENOUS LANDSCAPE OF CANCER GENES IN OSTEOSARCOMA

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Objectives

The aim of this study was to describe through unbiased next generation sequencing the somatic alterations that drive osteosarcoma.

Methods

A series of 126 osteosarcoma tumours along with normal tissue DNA from the same patients was selected based on the availability of DNA and subjected to whole genome (n=39) or whole exome (n=87) massively parallel sequencing. The series comprised paediatric / adolescent (n=67) and adult (n=59) osteosarcoma. Ten cases arose secondary to radiation or to an underlying cancer predisposition syndrome. All classes of mutations, i.e. substitutions, small insertion and deletions (indels), structural rearrangements, and copy number changes were called using the analysis pipeline of the Cancer Genome Project.

Results

The overall configuration of the genomes varied greatly, in terms of mutation burden, mutational signatures and processes including chromothripsis and kataegis, with no striking differences found between paediatric/adolescent and adult osteosarcoma. Focusing the analysis on the cancer gene landscape, cancer genes mutated at a high frequency included established osteosarcoma drivers such as *TP53* or *RB1*. Novel cancer genes such as *H3F3A*, previously not implicated in the pathogenesis of osteosarcoma, were also identified. However, these were generally mutated at a low frequency. A number of potential therapeutic targets were identified, including mutations in different tyrosine kinase receptors.

Conclusions

The landscape of cancer genes driving osteosarcoma was markedly heterogeneous. Although our study identified cancer genes not previously implicated in the pathogenesis of osteosarcoma, no novel driver mutated at a high frequency was identified. This lack of an osteosarcoma specific driver distinguishes osteosarcoma from other bone tumours that we and others have studied by unbiased sequencing. Nevertheless, our findings may guide efforts that utilise targeted therapeutics in osteosarcoma. Furthermore, our findings enable studies of clinical cohorts by targeted sequencing of the cancer genes we describe here, to investigate whether tumour genotype accurately predicts clinical outcome.

O-040

Bone Tumour - Fasanelli Session

LONG-TERM FOLLOW-UP OF THE CESS 81 AND CESS 86 EWING SARCOMA TRIALS

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Objectives

Since 1980 patients with Ewing sarcoma have been treated according to consecutive protocols (CESS) of the German Society of Pediatric Oncology and Hematology (GPOH)*. Post treatment surveillance also includes long term follow-up**.

Methods

673 patients (pts) entered into the CESS 81 (n=183) (1980-1985) and CESS 86 (n=490) (1985-1992) Ewing sarcoma trials were analyzed. 375 pts (59%) were male, 278 (41%) female. 549 pts (82 %) had localized, 124 (18%) metastatic disease. The median age at diagnosis was 14.8 years (range 0.7 - 41.4). The median age of survivors at last time of observation was 28.9 years (range 8.8 - 63.3). Median follow-up time of survivors was 15.5 years (range 0.3 - 30.6).

Results

315 pts (47%) were alive at last follow-up. Events were observed in 361 pts: local relapse in 19%, distant relapse in 64%, combined relapse in 13%, and secondary malignancies in 4%. 10-year event-free survival (EFS) was 0.49 (SE=0.02) in localized, and 0.21 (SE=0.04) in metastatic disease. 10-year overall survival (OS) was 0.54 (SE=0.02) in localized, and 0.23 (SE=0.04) in metastatic disease. Self-reported late morbidity was available from 128 of 315 survivors: 19.5% cardiovascular and 2% renal abnormalities, and secondary amputation (3.9%). 19.8% of the former patients rated their health status as less good or poor. 7.3% have been unemployed more than 1 year in the last 5 years. 62.2% had a handicapped pass, 9.9% with 100%.

Conclusions

Long-term observation is crucial in pediatric cancer survivors. Nearly half of patients of the earliest phase III Ewing sarcoma trials are long-term survivors. Of patients with recurrence approx. 90% died from disease. Patient-related outcome scores are currently investigated in a long-term observation study for inclusion into long-term follow-up guidelines and to better predict the long-term quality of survivorship.

*supported by Deutsche Krebshilfe **supported by BMBF/DLR 01ER0807

O-041

Bone Tumour - Fasanelli Session

PROGNOSIS OF CHILDREN AND ADOLESCENTS WITH SOFT TISSUE EWING TUMORS (STET) TREATED IN 3 CONSECUTIVE, PROSPECTIVE STUDIES OF THE COOPERATIVE WEICHSTEILSARKOM STUDIENGRUPPE (CWS)

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Objectives

Intensive chemotherapy (CHT) and aggressive local therapy are regarded as a golden standard in the treatment of Ewing sarcoma. However, the optimal CHT-intensity and the extent of local modalities are still not known. Different Ewing Sarcoma studies differ concerning CHT intensity and recommendation for local therapy. We present the therapy results of patients with STET treated in the three consecutive CWS-Studies CWS-91, -96 and 2002.

Methods

244 pts aged 1-21 yrs were registered in the CWS-91 (n=84), CWS-96 (n=116)- or CWS 2002P (n=44). 19 pts were in IRS Group I, 55 in II and 170 in III. In the CWS - 91 a combination EVAIA (Ifosfamide, Vincristine, Doxorubicin, Actinomycin D, VP16) was used. In the CWS-96 the patients were randomized between a 4 drug combination VAIA (Ifosfamide, Doxorubicin, Actinomycin D, Vincristine) vs. 6 drug CEVAIE (Etoposide instead of Doxorubicin, plus carboplatin and VP16). In CWS 2002P, VAIA plus maintenance CHT with Cyclophosphamide and Vinblastine were recommended. Irradiation was recommended depending on results of the primary or secondary resection.

Results

5 yr event-free-survival (EFS) and OS (overall survival) were 62.8% and 73.2 %. The EFS and OS by study were: CWS-91 64.1% and 71.9 %, CWS-96 56.9% and 70.1%, CWS 2002P 78.5% and 86.1% respectively. The 5 yr EFS for the VAIA was: 66.3% for the CEVAIE: 51.7% (p=0.053), the OS - 85.6% vs. 57.2% (p=0.032). 5yr EFS and OS for irradiated (n=172) vs. not irradiated patients were 63.0 % vs. 61.7%, and 71.6% vs. 79.5% respectively.

Conclusions

The prognosis improved from CWS-91/96 to CWS 2002P. The CEVAIE was inferior in OS in comparison to the standard regimen VAIA. The stratification criteria allowed for the correct allocation to irradiation. The addition of maintenance CHT in the CWS

2002P may be associated with improved prognosis and should be examined in a randomised way.

O-042

Bone Tumour - Fasanelli Session

DOES INTENSITY OF SURVEILLANCE AFFECT SURVIVAL AFTER SURGERY FOR SARCOMAS? RESULTS OF A RANDOMIZED NONINFERIORITY TRIAL

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Objectives

We hypothesized that a less intensive follow up protocol would not be inferior to the conventional follow up protocol in terms of overall survival (OS). We asked whether a chest radiograph follow up group was inferior to a CT scan follow up group in terms of detecting pulmonary metastasis; and whether a less frequent (6 monthly) follow up interval was inferior to a more frequent (3 monthly) follow up group in terms of detecting pulmonary metastasis and local recurrence

Methods

A prospective randomized single-center non inferiority trial was conducted between January 2006 and June 2010. 500 non metastatic patients were randomized to demonstrate non inferiority by a margin (delta) of 10% (hazard ratio [HR], 1.36). The primary end point was OS at 3 years.

Results

At minimum follow up of 30 months (median, 42 months; range, 30–81 months), 3 year OS and DFS for all patients was 67% and 52%, respectively. OS was 67% and 66% in chest radiography and CT groups, respectively (HR, 0.9; upper 90% confidence interval [CI], 1.13). DFS rate was 54% and 49% in chest radiography and CT groups, respectively (HR, 0.82; upper 90% CI, 0.97). OS was 64% and 69% in 6-monthly and 3-monthly groups, respectively (HR, 1.2; upper 90% CI, 1.47). DFS was 51% and 52% in 6-monthly and 3-monthly groups, respectively (HR, 1.01; upper 90% CI, 1.2).

Conclusions

Inexpensive imaging will detect the vast majority of recurrent disease in patients with sarcoma without deleterious effects on eventual outcomes. Although less frequent visits adequately detected metastasis and local recurrence, this trial could not conclusively demonstrate non inferiority in OS for a 6-monthly interval of follow up visits against 3 monthly. This might have been a function of a small sample size; longer follow up in larger populations may confirm this finding.

O-043

Supportive Care and Late Effects

STANDING ON PINS AND NEEDLES? PATTERNS AND SEVERITY OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA DURING THE FIRST YEAR OF TREATMENT

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Objectives

The study purpose was to describe vincristine-induced peripheral neuropathy (VIPN) patterns and severity in children with preB acute lymphoblastic leukemia (ALL) during the first year of treatment.

Methods

128 newly diagnosed children 1-18 years of age receiving vincristine 1.5 mg/M₂ (2mg maximum) per Children's Oncology Group (COG) treatment trials were recruited from four sites (Indiana University, University of Michigan, Vanderbilt University, Children's National). Neurologist-trained evaluators quantified VIPN based on patient-reported symptoms and physical examination using the Total Neuropathy Score-Pediatric Vincristine (TNS©-PV). Additional assessments were conducted using the NCI-CTCAE v.4.0. VIPN was assessed over the first year of therapy. Data were analyzed using descriptive statistics, correlations, paired t-tests, and cluster analysis. Vincristine dose density curves were calculated using the kernel density function.

Results

VIPN assessments (N = 1961) were performed on equal numbers of males and females. Most were Caucasian (87.7%) and non-Hispanic (78.1%). Mean age was 6.16 (SD 4.96) years (range 1-18). TNS©-PV and NCI-CTCAE score patterns were similar, but TNS©-PV scores revealed more granular details regarding specific signs and symptoms. Reflexes were affected most (mean/SD = 1.63/0.05, range 0-4). VIPN scores peaked 5-6 months post-diagnosis, approximately two months after reaching the maximum vincristine dose density, illustrating a coasting effect. VIPN did not improve in months 8-12 despite decreasing dose density. VIPN scores were positively associated with age ($p = .0095$) but not gender. Cluster analyses results revealed that some children ($n = 7$) experienced severe VIPN unrelated to dose density.

Conclusions

VIPN is most severe six months from the onset of ALL treatment and does not improve over the first year of treatment despite decreasing dose density. Cluster analysis identifies a cohort of children at risk for developing severe VIPN. Further

research is ongoing to elucidate a baseline predictive signature for identifying high-risk patients.

O-044

Supportive Care and Late Effects

GENETIC VARIANTS IN *SLC22A17* AND *SLC22A7* ARE ASSOCIATED WITH ANTHRACYCLINE-INDUCED CARDIOTOXICITY IN CHILDREN

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Objectives

The risk of anthracycline-induced cardiotoxicity (ACT), a serious adverse drug reaction of cancer therapy, is in part mediated by genetic variation. Recently, several genetic variants predictive of ACT in children were identified and replicated. This study was aimed to identify additional genetic variants associated with ACT and to assess whether these variants could improve a genotype-guided ACT risk prediction model.

Methods

We carried out a case-control association study in a discovery cohort of 78 serious ACT cases and 266 controls with replication in an independent cohort of 56 cases and 162 controls. Samples were genotyped for more than 4,500 single nucleotide polymorphisms (SNPs) in over 300 key genes pre-selected for relevance in drug transport, metabolism or toxicity. Predictive models including genetic and clinical risk factors were trained in the discovery cohort and assessed in the replication cohort.

Results

We identified significant genetic associations with ACT in the discovery cohort for two SNPs in *SLC22A17* (rs4982753) and *SLC22A7* (rs4149178) ($P=0.0078$ and $P=0.0034$, respectively), that were subsequently replicated ($P=0.0071$ and $P=0.047$; combined odds ratio 0.50 [95% CI 0.33-0.75] and 0.45 [95% CI 0.26-0.75]). Additional evidence for association was found for variants in *SULT2B1* and several genes related to oxidative stress. Adding the two *SLC22* variants to a risk prediction model improved the discriminative ability (Area Under Curve (AUC) from 0.75 to 0.78 for combined cohorts [$P=0.029$]).

Conclusions

We identified and replicated two novel genetic variants predictive of ACT. Addition of these variants to a risk prediction model further improved this model, which could be used for risk stratification of patients who may benefit from alternative treatment strategies, more intensive cardiotoxicity monitoring or preventive treatment measures.

O-045

Supportive Care and Late Effects

METABOLIC SYNDROME AND CARDIAC DYSFUNCTION IN ADULT SURVIVORS OF CHILDHOOD CANCER: RESULTS FROM THE ST. JUDE LIFETIME COHORT STUDY

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Objectives

Cardiac dysfunction after anthracycline chemotherapy and chest-directed radiotherapy (RT) is well established. The additional contribution of traditional cardiovascular risk factors and metabolic syndrome in aging survivors is less well defined.

Methods

Analysis included 1,679 ≥ 10 yr survivors (median age 31 yrs, range 18-59; Echo included systolic (3D EF, abnormal $<50\%$), diastolic function (grades 1-3 abnormal), global longitudinal (>-18.9) and circumferential (>-22.1) myocardial strain. Metabolic syndrome defined using NCEP-ATP III criteria. Logistic regression or Poisson regression was adjusted for current age, age at diagnosis, race/ethnicity, sex, chest RT and anthracycline exposure to calculate odds ratios (ORs) or relative risk (RR) and 95% confidence intervals (CI).

Results

Systolic dysfunction was detected in 5.1%, diastolic dysfunction in 10.2%, and abnormal strain in 43.1% (longitudinal) and 58.1% (circumferential). 27.8% of survivors had metabolic syndrome (obesity 29.2%, triglycerides $>150\text{mg/dl}$ 25.3%. HDL cholesterol abnormal 36.7%, hypertension 45.6% and diabetes 32.1%). Metabolic syndrome was associated with increased risk for diastolic dysfunction (OR 2.6, CI 1.8-3.7) and strain abnormalities (longitudinal RR 1.6, CI 1.4-1.8; circumferential RR 1.1, CI 1.0-1.2), but not reduced EF (OR 1.2, 95% CI 0.7-2.1).

Conclusions

Although EF is preserved, metabolic syndrome increases risk for diastolic dysfunction and systolic dysfunction detected by longitudinal myocardial strain, independent of chest RT and anthracycline exposure. Interventions that prevent metabolic syndrome may reduce cardiac risk and should be considered.

O-046

Supportive Care and Late Effects

ADVERSE SOCIAL OUTCOMES IN SURVIVORS OF CHILDHOOD CANCER: A MEDICAL RECORD LINKAGE STUDY

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Objectives

To determine the likelihood of adverse social outcomes such as not being married/registered partner, not living independently and using social benefits in adult childhood cancer survivors (CCS) compared to the general Dutch population.

Methods

We linked a complete cohort of 5-year CCS treated at Emma Children's Hospital/Academic Medical Center (N=1,647) with two administrative registers, the Municipal Personal Records Database (Dutch acronym: GBA) and the Social Economic Categories register (Dutch acronym: SECMBUS). We included CCS diagnosed between 1966-2001, aged above 18 years during the study period and alive at 1st January 1999. We retrieved anonymous social outcomes data from the last year that a person was registered in the GBA during 1999-2009 and compared it to a randomly selected sample of the general Dutch population obtained from GBA, matched on gender, year of birth and calendar year per CCS retrieved (sampling rate 1:20 at maximum). We conducted multivariate logistic regression analysis to estimate the likelihood of not being married/registered partner, not living independently and using social benefits compared to the general Dutch population. Furthermore, we used multivariate logistic regression within the CCS group to analyze patient-, cancer- and treatment-related associated risk factors for adverse social outcomes.

Results

After complete linkage, we obtained a group of 1,283 unique CCS and 25,188 reference persons (81% and 97.8% respectively, of individuals retrieved from GBA) with information on social outcomes. CCS had higher likelihood (odds ratio, 95% confidence interval) of not being married/registered partner (1.2, 1.1-1.4), not living independently (1.6, 1.3-1.9) and using social benefits (2.4, 2.0-2.8) compared to the general population. Radiotherapy (with or without surgery) increased the likelihood of using social benefits (2.6, 1.2-5.0) as well as a central nervous system tumor diagnosis (1.9, 1.1-3.4).

Conclusions

Targeted prevention of adverse social outcomes needs consideration to increase possibilities for survivors to develop socially in line with their peers.

O-047

Supportive Care and Late Effects

HOSPITALIZATIONS AMONG ADULT SURVIVORS OF CHILDHOOD CANCER TREATED WITH STEM CELL TRANSPLANTATION

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Objectives

Knowledge regarding the burden of morbidity after HSCT once pediatric cancer survivors reach adulthood is sparse. Frequency of hospitalizations can serve as a proxy measure of morbidity. The aim of the study was to assess the number of hospitalization episodes in long-term adult survivors of childhood malignancies treated with HSCT.

Methods

We used record linkage between the SickKids' clinical transplant database, the Canadian Province of Ontario's pediatric cancer registry (POGONIS) and health care utilization data housed at the Institute for Clinical Evaluative Sciences (ICES). The study population included all adult (> 5 years post transplant) survivors of childhood cancer treated with allogeneic/autologous HSCT at SickKids.

Results

242 long-term adult survivors were followed for a mean of 12.3 years (148 allogeneic and 86 autologous HSCT). Mean age at HSCT was 11.5y (SD: 4.7) and 11.0y (SD: 5.3) for the allogeneic and autologous groups, respectively. 262 hospitalizations were documented in adults post allogeneic HSCT, representing a rate of 0.15 hospitalizations per follow-up year. Univariate analysis revealed that age >10 years at cancer diagnosis (RR=3.53, 95% CI: 2.34-5.33), age >10 years at HSCT (RR=5.88, 95% CI: 2.89-11.85), and female gender (RR=1.70, 95% CI: 1.33-2.18) were associated with an increased rate of hospitalization. The underlying diagnosis, ALL vs. AML was not associated with increased rate of hospitalization despite the use of TBI among ALL patients. 106 hospitalizations were documented in adults post autologous HSCT, representing a rate of 0.09 hospitalizations per follow-up year. Age >10 y-o at time of HSCT (RR=2.29, 95% CI: 1.29-4.04) and female gender (RR=1.70, 95% CI: 1.15-2.52) were associated with increased rate of hospitalization.

Conclusions

Age > 10 years at time of HSCT and female gender were associated with increased risk for hospitalization. Our future studies focus on length of stay and the indications for these hospitalizations.

O-048

Supportive Care and Late Effects

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS IN PEDIATRIC TRANSPLANT RECIPIENTS

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Objectives

Recipients of solid organ transplantation (SOT) carry a substantially increased risk to develop posttransplant lymphoproliferative disorders (PTLD). Excess risk of cancer is largely due to immunosuppression and oncogenic virus infection. Objective: We performed a clinicopathological review of PTLD in pediatric transplantations in our institution.

Materials and Methods

Recipients of pediatric (age at transplantation <21 years) SOT were reviewed and PTLD were classified using the WHO criteria: PTLD, early, or PTLD, monomorphic; and the organ/sites of involvement as nodal or extranodal.

Results

In over 500 SOT performed, there were 40 PTLD developed in 26 patients, patient's age (mean 13.6, range 1 to 29) with 11 cases classified as early PTLD, and 29 cases as monomorphic PTLD. The latency period of PTLD onset ranged from 10 months to 11 years, involving nodal sites 16, extranodal sites 24, with GI tract, lung, upper aerodigestive tract and liver most commonly involved. Diffuse large B-cell lymphoma with 23 cases (79%) was the most common cancer type and associated with EBV infection. The cumulative incidence rate of PTLD in pediatric heart transplant and lung transplant recipients were 8.5% and 5.9% respectively.

Conclusions

PTLD are relatively common in pediatric recipients of SOT and commonly involving nodal and extranodal sites, and in particular, in organs with mucosa-associated lymphoid tissues (MALT). Oncogenic viruses, especially EBV play an etiologic role in the development of PTLD in the pediatric transplant population.

O-049

Neuroblastoma 1

A NEUROBLASTOMA RISK CLASSIFICATION MODEL FOR DEVELOPING COUNTRIES: A STUDY FROM THE INTERNATIONAL NEUROBLASTOMA (NB) RISK GROUP (INRG) DATABASE

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Objectives

Current methods for stratifying NB patients at diagnosis to INRG risk/pre-treatment groups are based on prognostic clinical, genomic, and histologic factors [Cohn et al, JCO 2009]. In developing countries, testing tumors for genomic biomarkers or histologic features is not possible; however, clinical tests serum ferritin and serum lactate dehydrogenase (LDH) are likely available.

Methods

Retrospective analysis included INRG patients with sufficient data for clinical risk factors and event-free survival (EFS). Survival tree regression was performed, considering only age (<18 months; ≥18 months), INSS stage (4; not 4), ferritin (<92; ≥92ng/mL), and LDH (<587; ≥587U/L). Patients were categorized into clinical pre-treatment risk groups by 5-yr EFS: very low (>85%), low (>75-≤85%), intermediate (≥50-≤75%), or high risk (<50%). EFS time was from diagnosis until first event (relapse/progression, second malignancy, death), or until last contact if no event occurred.

Results

From 8,800 INRG patients, 7,679 were able to be risk classified according to INRG definitions, including genomic and histological factors. Of 7,679, 3,509 had known age/stage/LDH/ferritin, and a clinical pre-treatment risk group was assigned: very low (n=1319), low (n=379), intermediate (n=550), and high (n=1261), with 5-yr EFS of 90±1%, 80±3%, 65±3%, and 27±2%, respectively. The clinical risk classification was the same as (58.1%) or similar to (12.8%) the INRG in 70.9% of patients. Based on 5-year EFS: INRG overestimated risk but clinical factors correctly assigned risk in 18.9% of patients; clinical factors overestimated (3.7%) or underestimated (6.4%) risk but INRG correctly assigned risk in 10.1% of patients.

Conclusions

In 89.9% of patients, clinical factors (age, stage, ferritin, LDH) do as well or better than clinical, genomic, and pathologic factors currently used in INRG risk/pre-treatment group assignment. The INRG-clinical pre-treatment risk stratification shows promise for developing countries to assign treatment intensity, whereby very low-risk

patients can be spared unnecessary, expensive chemotherapy.

O-050

Neuroblastoma 1

RISK FACTORS WITHIN THE EUROPEAN HIGH RISK NEUROBLASTOMA HR-NBL1/SIOPEN TRIAL

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Objectives

Evaluation of the unselected patient cohort of the HR-NBL1/SIOPEN trial including all non-randomised patients.

Methods

Since 02/02/2002, the trial accrued in 21 countries (175 centres) 2242 patients (pts) of whom 2022 had INSS stage 4 (eligibility <1year only pts with MycN amplification (MNA)) and 220 stage 2&3 with MNA of any age. The median age is 3.6yrs (range, 1 day-20yrs). Four randomised questions are addressed (R0/R1/R2/R3). After Rapid Cojec or modified N7 induction (R0/R3), pts with insufficient response received additional 2nd line treatments (i.e. TVD 2- 4 courses) to proceed to myeloablative therapy (MAT/R1; BUMEL, CEM or mIBG containing regimes). Local control aimed at complete surgical resection (achieved in 76%) and radiotherapy of 21 Gy only to the primary tumour site. Till 2007 maintenance treatment was 13cis RA alone. In 2007 ch14.18/CHO mAb based immunotherapy (IT) was introduced with a modification towards a randomised IL2 question in 2009 (R2). To date 428pts received ch14.18/CHO based IT by the 8 hour infusion scheme.

Results

In stage 4 pts MNA frequencies are: 66% in 1-1.5 yrs (116/177, 66%), 44% in 1.5-5yrs (449/1108) and 22% (79/363) > 5yrs. The 5-yrs EFS&OS for all pts is $0.31 \pm 0.01 / 0.41 \pm 0.01$ with rates of $0.28 \pm 0.01 / 0.38 \pm 0.01$ for stage 4, but $0.63 \pm 0.04 / 0.68 \pm 0.04$ in MNA stages 2&3 with lower rates in 24 infants ($0.44 \pm 0.12 / 0.43 \pm 0.12$). In stage 4 pts prognosis declines with age: infants and pts 1-1.5 yrs showed comparable outcomes ($n=186$, $0.39 \pm 0.07 / 0.47 \pm 0.08$), followed by pts of 1.5-5yrs ($n=1234$, $0.30 \pm 0.02 / 0.40 \pm 0.02$) and pts >5yrs ($n=402$, $0.15 \pm 0.02 / 0.28 \pm 0.03$). Partial response or better was more frequently observed in younger children with the following rates: 90%, 84%, 82%, 66%, 56% and 41% for age groups of 1-14 yrs of age.

Conclusions

Stage and age remain major prognostic factors whilst MNA pts clearly benefit from intensification.

O-051

Neuroblastoma 1

IMAGE DEFINED RISK FACTORS (IDRF) IN NEUROBLASTOMA: INCIDENCE, EVOLUTION DURING TREATMENT AND CORRELATION WITH SURGICAL OUTCOME

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Objectives

Describe IDRF prevalence among patients enrolled in the European Unresectable Neuroblastoma (EUNB) study, evaluate their modification after chemotherapy, and how influenced surgical outcome.

Methods

IDRF were those reported by the treating physicians, but imaging reports were reviewed for those coded as "other" and a more specific IDRF was assigned. When the only IDRF was related to the size of the tumour (big), the patient was excluded from the study. Surgical outcomes were related with IDRF response to chemotherapy.

Results

Of the 160 patients enrolled in the EUNB study, 17 were excluded (8 no imaging pre second surgery, 6 "big tumor", 3 stage 3 after first surgery). The 143 evaluable patients had a total of 228 IDRF. The most frequent were: encasement of carotid sheath in cervical tumours (n=4); infiltration of the left costo-vertebral junction in thorax (n=9); and infiltration of renal pedicles in abdomen (n=50).

Following chemotherapy 76 (33%) IDRF disappeared, but 33 new appeared.

Complete IDRF disappearance was observed in 33 patients (23%), decrease in number but persistence in 13 patients (9%), no change in 70 (49%), disappearance of some but appearance of new IDRF in 15 (10%), and IDRF number increase in 12 (8%).

Second surgery was not performed in 18 patients (3 because of CR or MRD after chemotherapy, and 15 because still inoperable). Of the 125 patients who underwent second surgery, 6 (5%) had a further biopsy, 30 (24%) had incomplete tumor excision; 36 (29%) had minimal residual, while 53 (42%) had complete resection. Complete resection or minimal residual were more frequent among children who had numerical reduction of IDRF (P=0.002).

Conclusions

Chemotherapy was effective in 33% of IDRF, but in 27 patients (19%) new IDRF appeared despite chemotherapy. Second surgery was more successful in

patients/tumors in which some chemotherapy related response was documented

O-052

Neuroblastoma 1

REVISED RISK ESTIMATION AND TREATMENT STRATIFICATION OF LOW- AND INTERMEDIATE-RISK NEUROBLASTOMA PATIENTS BY INTEGRATING CLINICAL AND MOLECULAR PROGNOSTIC MARKERS

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Objectives

Precise risk estimation is essential to avoid under- and overtreatment of neuroblastoma patients. To optimize neuroblastoma treatment stratification, we aimed at developing a novel risk estimation system by integrating gene expression-based classification and established prognostic markers.

Methods

Microarray-based gene expression profiles were generated from 709 primary neuroblastomas. Classification models were built using a training set of 75 tumors with contrasting courses of disease, and subsequently validated in an independent test set (n=634). Kaplan-Meier estimates and multivariate Cox regression analyses were used to assess the prognostic variables under investigation.

Results

The best-performing classifier (SVM_th10) consisted of 194 probes corresponding to 139 genes, and predicted patient outcome with an accuracy of 0.95 (sensitivity 0.93, specificity 0.97) in the validation cohort. The highest potential clinical value of the classifier was observed in current low- and intermediate risk (LR and IR, respectively) patients, in which the classifier significantly distinguished patients with diverging outcome (LR, 5-year OS 0.99 ± 0.01 vs 0.76 ± 0.11 ; IR, 5-year OS 1.0 vs 0.70 ± 0.09 ; both $p < 0.001$). In multivariate Cox regression models for non-high risk patients, the classifier outperformed risk assessment of the current German trial NB2004 (EFS, HR 5.07, 95%-CI 3.20-8.02, OS, HR 25.54, 95%-CI 8.40-77.66; both $p < 0.001$). Based on these findings, we developed a revised risk stratification system for LR/IR neuroblastoma patients by integrating established prognostic markers and the SVM_th10 classifier. According to this system, we newly identified patient subgroups with poor outcome (5-year EFS $18.5 \pm 7.8\%$), for whom we propose intensified treatment, and patient subgroups with beneficial outcome (5-year EFS $87.4 \pm 5.3\%$), who may benefit from treatment de-escalation.

Conclusions

Integration of gene expression-based classification and established prognostic markers improves risk estimation of LR/IR neuroblastoma patients. We propose to implement our revised risk assessment and treatment stratification system in the upcoming prospective clinical trial NB2013 LR/IR.

O-053

Germ Cell and Sex Cord-Stromal Tumours

MATURE AND IMMATURE TERATOMA: RESULTS OF THE SECOND PEDIATRIC AIEOP (ASSOCIAZIONE ITALIANA DI EMATOLOGIA ONCOLOGIA PEDIATRICA) ITALIAN STUDY

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Objectives

Teratomas (T) demonstrate a benign clinical behavior, however they may recur with malignant components or as T only, and in a small group of patients prognosis can be fatal. In the Protocol for Malignant Germ Cell Tumor (MGCT), in the context of AIEOP, we collected patients with T to evaluate prognostic factors, type of relapse and outcome.

Methods

209 patients were enrolled from 2004 to 2013. Initial evaluation and follow-up included clinical examination, tumour markers and imaging procedures. Surgical resection was recommended as unique treatment. Immature T (IT) were classified as grading 1–3.

Results

Mature T (MT) and IT were diagnosed in 139 and 70 patients, respectively (median age 42 months; F:M ratio 2.4:1). 113 patients had gonadal tumor (91 ovarian, 22 testicular) 96 extragonadal (61 sacrococcyx (SC), 12 mediastinum, 9 retroperitoneum, 14 other sites). 10 patients (4.8%) showed associated congenital malformation-syndromes. A tumor complete resection was performed in 175 patients, a partial resection in 21 and a biopsy in one. 15 events occurred: 4 patients had contralateral metachronous ovarian T; 1 with SC-MT developed an adrenal neuroblastoma; 10 patients relapsed locally (2/139 MT and 8/70 IT) within a median time of 7 months from diagnosis: 6 with MGCT component, 1 with malignant transformation and 3 with T only. Two patients died, one of progressive IT grade 3 and 1 for surgical complications. At a median follow-up of 60 months, the EFS, RFS and OS are as follows: 87%, 91% and 95%, respectively. Analyzing MT and IT separately, OS is 100% and 95% and EFS 96% and 86%, respectively.

Conclusions

T show good prognosis, especially the M ones. Surgery and follow-up remain the standard approaches, however, in some rare cases, especially with partial resection,

IT may progress, representing a real challenge in term of treatment.

O-054

Germ Cell and Sex Cord-Stromal Tumours

**OUTCOME OF CHILDHOOD MALIGNANT GERM CELL TUMOR (MGCT)
TREATED ON CARBOPLATIN BASED CHEMOTHERAPY –SINGLE CENTRE
EXPERIENCE IN PAKISTAN**

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Objectives

To study the clinicopathological features and outcome of children with MGCT treated on Carboplatin, Etoposide and Bleomycin (JEB) at CCH, Pakistan.

Methods

A retrospective study at CCH on children less than 16 years diagnosed with extracranial Germ cell tumor between January 1998 till 2013. They were treated on Carboplatin based chemotherapy including Etoposide and Bleomycin (JEB) without risk stratification. The demography, clinical presentations and primary site, histopathology, staging and treatment received, were reviewed. Outcome was analyzed.

Results

Total 75 patients included with male to female ratio 1:1. Median age of presentation was 3 years (range 1 month to 16 years). Median duration of symptoms was 2 months(15 days – 2 years). Abdominal distention and pain were the most common symptoms. 48/75 patients (64%) were Gonadal Germ Cell Tumor (GGCT) with 19(25%) ovarian and 29(39%) testicular tumors. Extragonadal tumors were 27 (36) with sacrococcygeal teratoma (20 %) being most common. Yolk sac tumor was the most common (56%) histopathological diagnosis followed by mixed GCT 16%, teratoma 12%, and dysgerminoma 9.3%. 14 gonadal tumors did not receive chemotherapy. 61/75 patients received 3-6 cycles of JEB chemotherapy. 51 patients (84%) completed the treatment, 1 left and 2 died during chemotherapy, 7 (12%) had progressive disease. 20 patients had Stage I disease, 6 stage II, 18 stage III and 17 had stage IV disease, with 100 %, 60%, 71% and 59% overall survival(OS) respectively. For patients who received chemotherapy, OS is 76 % ; for GGCT 89% and for extragonadal 58%. OS of whole cohort is 81% (59/75) .

Conclusions

Carboplatin based chemotherapy has shown good survival for children with GGCT. The suboptimal survival in extragonadal cases could be due to advanced disease and poor local control.

O-055

Germ Cell and Sex Cord-Stromal Tumours

OVARIAN SERTOLI LEYDIG CELL TUMORS IN CHILDREN AND ADOLESCENTS: AN ANALYSIS OF THE EUROPEAN COOPERATIVE STUDY GROUP ON PEDIATRIC RARE TUMORS (EXPERT)

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Objectives

To analyze ovarian Sertoli-Leydig cell tumors (SLCTs) for potential prognostic markers and their use for treatment stratification.

Methods

Forty-four patients were included. Patients were prospectively reported to the German MAKEI studies (n=23), French TGM protocols (n=10), Italian TREP registry (n=6), and the Polish Pediatric Rare Tumor Study group (n=5). Tumors were classified according to WHO and staged according to FIGO.

Results

Median age was 13.9 (0.5–17.4) years. All patients underwent resection by tumor enucleation (n=8), ovariectomy (n=17), adnectomy isolated (n=18) or with hysterectomy (n=1). FIGO-stage: Ia 24 pts, Ic 17 pts, II/III 3 pts. One patient had bilateral tumors. Four patients (stage Ia: 3, stage Ic: 1) developed a metachronous contralateral tumor. Otherwise, all stage Ia patients remained in complete remission. Among 20 patients with incomplete resection or tumor spread (stage Ic-III), 8 relapsed, and 5 patients died. Eleven patients were initially treated with 2–6 cycles of cisplatin-based chemotherapy. Of these, seven patients are in continuous remission. Poor histological differentiation was associated with higher relapse rate (5/13) compared to intermediate (3/18) and high differentiation (0/4). Tumors with retiform pattern or heterologous elements showed a high relapse rate, too (5/11). After a median follow-up of 62 months, event-free survival is 0.70 ± 0.07 , relapse-free survival 0.81 ± 0.06 , and overall survival 0.87 ± 0.05 .

Conclusions

Prognosis of SLCTs is determined by stage and histopathologic differentiation. Complete resection with careful avoidance of spillage is a prerequisite of cure. The impact of chemotherapy in incompletely resected and advanced stage tumors remains to be evaluated.

O-056

Germ Cell and Sex Cord-Stromal Tumours

SEX CORD STROMAL TUMORS IN CHILDREN AND TEENAGERS: RESULTS OF THE TGM95 STUDY

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Objectives

Sex cord stromal tumors (SCT) are rare in children and teenagers, accounting for 2% of malignant gonadic tumors. We present the results of the National SFCE TGM95 trial for ovarian and testicular SCT.

Methods

Between 1995 and 2005, in France, children (<18years) with ovarian and testicular SCT were prospectively registered. Primary gonadal resection was recommended whenever feasible with complete and "non-mutilating" surgery. Patients with disseminated disease or incomplete resection received neoadjuvant or adjuvant 4-6 cycles of VIP (etoposide 75mg/m²/D1-5, ifosfamide 3g/m²/D1-2, cisplatin 20/mg/m²/D1-5, every 3 weeks).

Results

Thirty-eight ovarian SCT were registered. Median age was 10.7y [0.58-17.7]. Endocrine symptoms were present in 21 cases. Histological diagnoses were: juvenile (23) and adult (3) granulosa cell tumors, Sertoli-Leydig cell tumors (11), and mixed germ cell-SCT (1). Primary oophorectomy +/-salpingectomy led to complete resection in 23 patients who did not receive adjuvant treatment. Two relapsed after 4-5 years (1 peritoneal and 1 contralateral) and achieved 2nd complete remission with surgery and VIP. Fifteen patients had primary incomplete resection due to tumor rupture and/or malignant ascites: 11 received VIP and had no recurrence (median follow-up: 5.8y), 4 did not receive chemotherapy and relapsed between 2-18 months, with fatal outcome in 2 cases with Sertoli-Leydig cell tumors. Five-year OS and EFS were 94.4% and 85.3%.

Eleven patients had localized testicular tumors (median age 0.83y [0-8.8]): juvenile granulosa cell tumors (4), Sertoli and/or Leydig cell tumors (5), and not otherwise specified SCT (2). Treatment was surgery alone with inguinal orchiectomy. None relapsed (median follow-up 5.3y).

Conclusions

In childhood ovarian SCT, surgery should be complete and non-mutilating. If complete resection is non-feasible, neoadjuvant chemotherapy is necessary. Tumor rupture is a formal indication for adjuvant chemotherapy which is efficient to prevent recurrences. In childhood testicular SCT, prognosis is excellent with inguinal orchiectomy, raising the debate on testis sparing surgery.

O-057

Epidemiology 2

EARLY DIAGNOSIS: THE INFLUENCE OF TRAINING OF PRIMARY HEALTH CARE PROFESSIONALS FOR SUSPICION OF PEDIATRIC CANCER IN BRAZIL

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Objectives

In Brazil, cancer is the leading cause of death by disease among children and adolescents 1-19 years for all regions. As in Brazil the time between symptoms and diagnosis of pediatric cancer is long and many patients are referred to treatment at advanced stages, NGO Instituto Ronald McDonald (IRM) developed the Early Diagnosis Program to build capacity of primary health care workers. In the context of primary health care, the program called Family Health Strategy (ESF) covers approximately 50% of the population. Thus, it is considered crucial for changing this scenario, the dissemination of knowledge about the main signs and symptoms of the disease among these professionals, evaluating the performance of health primary care professionals in suspicion of pediatric cancer in Brazil.

Methods

Training health workers in order to promote early diagnosis of childhood cancer. The live learning course has a 24 hour workload per training within weeks. The classes include discussions with health managers on local content that covers everything from the organization of the national policy for cancer care, to the role of each ESF professional in early diagnosis of cancer. The book, freely distributed by IRM, was developed in partnership with Brazilian Society of Pediatric Oncology and National Cancer Institute. Besides, a multicenter survey to measure the impact of the program in each location where the projects were executed was performed.

Results

The program exists since 2008 and already trained 14,885 professionals of 2,254 teams in 14 states. It impacted 2,367,089 0-19 years children and adolescents with an investment of R\$ 4.748.825,25 (US\$ 2,016,101.06).

Conclusions

In regions where the program was implemented there was a 23% increase in the number of children referred with suspected cancer. The average delay time of referral for diagnosis fell by 61% in those who received the training (13-5 weeks).

O-058

Epidemiology 2

FETAL MACROSOMY AS A RISK FACTOR FOR CHILDHOOD NON-HODGKIN LYMPHOMA: A NATIONWIDE SWEDISH COHORT STUDY

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Objectives

Birth weight has been explored as a risk factor for several types of childhood (0-14 years) cancer. This nationwide Swedish cohort study aims to evaluate the association between crude and adjusted characteristics of fetal growth (birth weight, length, head circumference, ponderal index, small-SGA, appropriate-AGA and large for gestational age-LGA) and non-Hodgkin lymphoma (NHL) risk.

Methods

All 3,444,136 singleton live births were included, among whom 515 incident NHL cases aged 0-14 years were diagnosed in 1973-2007, as identified through linkage with the Swedish Cancer Register. Proportional hazards models were used to estimate the Hazard Ratio (HR) and 95% confidence intervals (95% CI) of NHL. The core multivariable model included infant sex, maternal education and maternal age at delivery, birth order of the index child (1+ child) and gestational age, the latter omitted in the analyses with SGA, AGA, LGA variables, as appropriate.

Results

Male sex was associated with a doubled NHL risk (HR=2.00, 95% CI: 1.66-2.41). LGA birth weight, but not birth weight *per se*, was associated with an 80% increase in NHL risk (HR=1.83, 95%CI: 1.20-2.79). In the subgroup analyses by sex, the latter association was confined particularly to girls (HR=3.37, 95% CI: 1.90-5.97). Other growth variables were not consistently associated with NHL risk, possibly due to smaller variation or measurement errors.

Conclusions

Fetal macrosomy seems to represent a considerable risk factor for childhood NHL, whereas its effect may differ by gender. An approach to assess the association solely using crude birth weight, as a proxy, seems inadequate, given that more elaborate LGA indices may portray accelerated intrauterine growth as a more meaningful component. Future studies should aim at disentangling the physiological mechanisms underlying the relevance of sex-specific associations.

O-059

Epidemiology 2

LATE MORTALITY AMONG 5-YEAR SURVIVORS OF EARLY ONSET CANCER: A POPULATION-BASED REGISTER STUDY

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Objectives

To investigate cause-specific long-term mortality among 5-year survivors of early onset cancer (aged 0-34 years at diagnosis), with follow-up for death extending from 1971 through 2012.

Methods

The 5-year survivor cohort was identified via the Finnish Cancer Registry. Mortality data was extracted from National Death Certificate files of Statistics Finland. A total of 16,769 cancer survivors who survived for at least 5 years and were aged less than 35 years at cancer diagnosis were identified. A healthy sibling cohort and general population data served as reference.

Cause-specific cumulative mortality among 5-year cancer survivors, standard mortality rates (SMRs) compared to general population data and hazard ratios (HRs) for causes of death compared to the healthy sibling cohort were analyzed.

Results

The overall standardized mortality ratio (SMR) of cancer patients was 4.6-fold, (95% CI 4.4-4.8). Highest SMRs were found for malignancies (12.8, 95% CI 12.3-13.3), infectious (4.8, 95%CI 2.9-6.7) and cardiovascular diseases (1.9, 95% CI 1.7-2.1). Malignancies and cardiovascular diseases accounted for largest death numbers. Childhood and YA cancer survivors with the same primary cancer diagnosis displayed elevated overall SMRs in the same range, with the exception of markedly higher values after childhood Hodgkin lymphoma. The highest cumulative non-malignancy-related mortality was due to cardiovascular disease with a steady rise throughout the follow-up, but strongly dependent on the primary cancer diagnosis and age at diagnosis. Different from survivors of YA malignancies, no reduction of cumulative cardiovascular mortality was observed in childhood cancer survivors towards the recent treatment periods. However, overall and malignancy-related mortality showed a declining tendency towards the most recent periods after both, childhood and YA cancer.

Conclusions

Our findings on non-malignancy-related mortality stress the need to set up long-term individual follow-up with a focus on cardiovascular late effects for early onset cancer survivors, especially for YA cancer survivors still lacking those.

O-060

Epidemiology 2

CREATION OF COMPOSITE INDICES TO ASSESS THE IMPACT OF ECONOMIC AND CULTURAL FACTORS ON OUTCOMES IN PEDIATRIC HEMATOLOGIC MALIGNANCIES

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Objectives

The contribution of socioeconomic factors to racial and ethnic disparities in pediatric cancers remains understudied, partly due to the complexity of synthesizing the effects of multiple individual factors. In this study, we aimed to construct and utilize a composite index to analyze the impact of socioeconomic factors on survival in common pediatric hematologic malignancies .

Methods

Standardized values of seven different county-based disparity variables from the U.S. Census were utilized to calculate two indices: economic index (utilizing levels of poverty, income, education, crowding, and unemployment) and cultural index (utilizing levels of language isolation and immigration), with high values indicating greater social disadvantage. Selection of factors included test for face validity through consensus, evaluation of correlations between factors, and confirmation of pre-established domains using principle component analysis (PCA). We obtained survival outcomes from 18 SEER registries for all patients under the age of 19 who were diagnosed with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin-lymphoma (HL), or non-Hodgkin lymphoma (NHL) from 2000–2010. Survival distribution functions of disadvantaged and advantaged counties were compared using Log-rank test. Cut-off values for comparisons were defined as the median of each index within the cohort.

Results

The construction of the two indices was supported by PCA, which revealed two main latent variables from the set of seven chosen variables. Economic disadvantage (high index score) was associated with lower survival rates for ALL ($p<0.001$), AML ($p=0.005$), HL ($p=0.036$), and NHL ($p=0.02$). Differences were not significant when counties were stratified by cultural domain.

Conclusions

Our study resulted in the creation of an index that synthesizes a variety of census-derived measures of SES. Economic factors showed strongest impact during validation. Cultural factors appear less significant in mediating outcomes, but may be combined with economic factors to create a composite index in the future.

O-061

Neuroblastoma 2

INTEGRATED ANALYSES OF EPIGENETIC REGULATORY GENES IN NEUROBLASTOMA

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Objectives

Neuroblastoma (NB) is one of the aggressive pediatric solid tumors of childhood. Because NB displays remarkable clinical heterogeneity, heterogeneous genetic targets have been implicated in their pathogenesis. Recently, high-throughput genome-wide screenings have been applied to discover tumor-specific mutations of ALK, ATRX, and ARID1A/B in NB. However, since overall frequencies of recurrent mutation rate of these genes are relatively low, molecular basis of NB has not been completely elucidated. Meanwhile, previous genome-wide methylation studies suggest epigenetic aberrations may be also important, but little is known about their roles in the pathogenesis of NB. To elucidate the role of epigenetic regulators in the pathogenesis of NB, target capture 'deep' sequencing which enabled minor clones detections and array based methylation analysis were carried out.

Methods

Target capture followed by deep sequencing of 80 epigenetic regulatory genes using next-generation sequencing (Illumina HiSeq 2000) was performed in 24 NB specimens. An extended cohort of 96 NB specimens was analyzed for deep sequencing of selected genes. Additionally, genome-wide methylation analysis (Illumina Infinium HumanMethylation450 BeadChip Kit) was performed in 50 NB specimens.

Results

Among the 80 epigenetic regulators, 9 genes including polycomb and trithorax group related genes were mutated in 24 cases. Although these mutations were mostly found in single cases, ASH1L mutations were detected in two cases. Subsequent deep sequencing revealed that novel ASH1L mutations were observed in total of 9/197(4.5%) cases of NB. On the other hand, based on the methylation profiles, 50 NB cases were divided into 2 subgroups independently of the clinicopathological findings, such as age, stage, and MYCN status.

Conclusions

Our results indicated that not only genetic alterations but also epigenetic regulation may play important roles in the pathogenesis of NB. Comparing expression patterns, genetic alterations, and methylation profiles would be necessary to disclose the roles of epigenetic regulation in NB.

O-062

Neuroblastoma 2

SURVIVAL FOLLOWING LONG-TERM INFUSION OF ANTI-GD2 ANTIBODY CH14.18/CHO IN COMBINATION WITH INTERLEUKIN-2 IN A PILOT COHORT OF HIGH-RISK NEUROBLASTOMA PATIENTS CORRELATES WITH FC-GAMMA RECEPTOR POLYMORPHISMS

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Objectives

Treatment using long-term infusion (LTI) of anti-GD₂ antibody ch14.18/CHO and subcutaneous interleukin-2 (IL-2) may improve outcome in high risk neuroblastoma (NB).

Methods

53 NB patients received 5/6 cycles of 6x10⁶ IU/m² s.c. IL-2 (d1-5; 8-12), LTI of 100 mg/m² ch14.18/CHO (d8-17) and 160 mg/m² oral 13-cis-RA (d19-32) in a single center program. Effector cells (NK- and T-cell subsets), ch14.18/CHO levels and GD₂ specific killing of neuroblastoma cells by ADCC and CDC were analyzed. KIR/KIRL mismatch and Fcγ-receptor polymorphisms were determined with a validated PCR-based method for, KIR, HLA, FCGR2A (H131R), -3A (V158F) and -3B (NA1/NA2). Clinical response was assessed following INRG criteria by mIBG, MRI/CT, BM and catecholamines.

Results

LTI of ch14.18/CHO translated into the expansion of effector NK- (3x) and T-cells (2x) combined with a pro-inflammatory cytokine response (IL-2, IL-6, IL-8, IFNγ). Effective levels of ch14.18/CHO (12.48 ± 0.93 µg/ml) at the end of antibody infusion was associated with GD₂ specific activity against NB cells in functional assays (CDC, ADCC, WBT). Interestingly, ch14.18/CHO levels and functional parameters before subsequent treatment cycles indicate persistent anti-NB activity measurable for the entire treatment period of 6-7 months. Response rates were 41.7 % in mIBG (15/36), 31.8 % MRI/CT (7/22), 28.6 % bone marrow- (6/21) and 38.1 % in catecholamines (8/21). An overall response of 30% (12/40), EFS of 32.4 % (observation 3.2 years, mean: 1.6 years) and an OS of 66.8% (observation 3.9 years, mean: 3.1 years) was observed. Patients with high affinity FCGR alleles are associated with a longer event-free survival (P = 0.025), which supports NK-cell mediated ADCC as the mechanism of action.

Conclusions

Survival following LTI of ch14.18/CHO correlates with high affinity FCGR supporting ch14.18/CHO mediated ADCC as the primary mechanism of action.

O-063

Neuroblastoma 2

MYELOABLATIVE THERAPY (MAT) AND IMMUNOTHERAPY (IT) WITH CH14.18/CHO FOR HIGH RISK NEUROBLASTOMA: UPDATE AND NEWS OF RANDOMISED RESULTS FROM THE HR-NBL1/SIOPEN TRIAL.

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Objectives

The HR-NBL1/SIOPEN trial randomised 2 essential treatment concepts: Randomisation R1 investigated BUMEL superiority whilst randomisation R2 tested the benefits of adding subcutaneous interleukin 2 (scIL2) to ch14.18/CHOMAB immunotherapy(IT).

Methods

After Rapid Cojec induction patients (pts) were randomised in R1 (296 BuMel, 302 CEM) till 09/2010. Median follow up is 6.2 years. Eligibility included complete bone marrow remission and ≤ 3 , but improved mIBG positive spots. Local control included surgery and radiotherapy of 21 Gy. R2 was initiated in 2009 aiming at 400pts receiving ch14.18/CHOMAB as 8-hour infusion with 20mg/m² over 5 days and 13 cis RA over a total of 5 IT cycles. The schedule requires high dose morphine to control for neuropathic pain. R2 addressed a scIL2 question, using a dose of 6x10E6/m²/day over 5 days twice in a weekly interval, given in week 2 in parallel with ch14.18/CHOMAb.

Results

The superiority of BuMel in EFS and OS over CEM (3-years EFS&OS 50%/61% vs. 38%/52%; $p < 0.001$) is maintained with a significantly lower relapse and progression rate with BuMel (48% vs. 58%) as major factor. Severe toxicity rates (ICU, toxic deaths) are below 10%, but are higher for CEM ($p = 0.012$). Hence the MAT toxicity profile favours BuMel in spite of a VOD rate of 24% (grade 3: 4%) vs. 10% in CEM (Grade3: 1%). In August 2013, R2 reached the target and the randomisation is currently suspended with last patient out in 01/2014. The R2 population undisclosed for treatment arms shows currently a 2 year EFS/OS of 56%/68%. The scIL2 arm carries a significantly higher toxicity burden related to IL2 associated side effects like fever and capillary leak with a number of pts in the IL2 arm stopping treatment early.

Conclusions

BuMel is maintained as SIOPEN standard treatment whilst disclosed and detailed R2 results are expected for SIOP2014.

O-064

Neuroblastoma 2

SIGNIFICANT PROGNOSTIC RESULTS OF THE SIOPEN MIBG SCORING METHOD IN 2 COOPERATIVE INDEPENDENT HIGH RISK NEUROBLASTOMA TRIALS

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Objectives

Harmonised evaluation standards of MIBG scintigraphy for (re)staging of neuroblastoma (NB) are an international aim. In the HR-NBL1/SIOPEN trial population a SIOPEN score (SISCO) >3 was associated with a significantly poorer event free survival (EFS) on pre and post induction mIBG. This analysis validates the SISCO prognostic value in the independent dataset (DS) of the Children's Oncology Group (COG) protocol A3973.

Methods

SIOPEN scoring evaluates mIBG uptake in 12 skeletal regions (scored 0-6/region, maximum of 72), MIBG scans from mIBG-avid stage 4 NB pts in 2 collaborative trials were reviewed by the SIOPEN Nuclear Medicine review committee: the COG-A3973 (DSA; n=216) and SIOPEN HR-NBL1 trial (DSB; n=343). Predefined categories from DSB were used with a SISCO of 0, 1-3, 4-17 and ≥18. The median follow-up time was 7.1 and 5.5y, respectively.

Results

Both DS showed a significantly superior EFS with a SISCO ≤3 at diagnosis [5-yr EFS in DSA: 51%±7% vs 34%±4%, p=0.047 and in DSB 47%±7% vs 26%±3%, p=0.007]. A post induction SISCO of ≤3 also revealed a significant superior outcome [5-yr EFS in DSA: 43%±5% vs 16%±6%, p=0.004 and in DSB 36%±4% vs 14%±4%, p<0.001]. Pts with a SISCO of 0 post induction have the best outcome in both DS. In MYCN amplified pts, the pre and post-induction SISCO of ≤3 showed a significant impact in both groups, whilst in MYCN non-amplified pts this effect is only seen post induction. A SISCO ≤3 has independent statistical significance in Cox models including age and MYCN.

Conclusions

A SIOPEN score ≥ 3 of mIBG scans carries relevant prognostic significance for the management of patients with high-risk NB at diagnosis and at the end of induction chemotherapy in the HRNBL1/SIOPEN trial and was confirmed in the independent COG A3973 data set.

O-065

Neuroblastoma 2

HISTORICAL GOLD STANDARD FOR TIME-TO-PROGRESSION (TTP) AND PROGRESSION-FREE SURVIVAL (PFS) FROM RELAPSED/REFRACTORY NEUROBLASTOMA MODERN ERA (2002-14) PATIENTS

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Objectives

Early phase trials of investigational agents in pediatric patients (pts) with relapsed neuroblastoma (NB) historically used a "response" (RECIST) endpoint, which is challenging because NB in bone and bone marrow isn't 'measurable'. TTP and PFS are better suited to measure therapeutic benefit in NB, especially for targeted agents and immunotherapies. Historical data on PFS/TTP exist in small potentially biased cohorts. We studied the largest cohort to date of relapsed/refractory NB pts, treated with modern era frontline and relapse therapy. We determined PFS, OS, & TTP, for use as historical comparators in future Phase 2 studies.

Methods

489 NB enrollments (consecutive 11/2002-1/2014), from 384 distinct pts, on 36 Phase 1 (27) or 2 (9) Children's Oncology Group trials were analyzed for PFS (relapse, progression, disease death), overall survival (OS) (any death), & TTP, starting from Phase 1,2 trial enrollment. If pts were on multiple trials, enrollments were analyzed as if independent. For PFS, non-disease deaths were censored. Using RECIST, only 2 Phase 2 trials met the prospective response rate bar for success. For high-risk pts, planned frontline therapy included HSCT; 11.6% received ch14.18 antibody.

Results

From relapse study enrollment: 1-year & 4-year PFS/OS were 19±2% & 8±3%/56±3% & 14±4%, respectively; median TTP was 63 days(95% CI: 56,79). Median follow-up in pts without progression was 9.7 mos. Risk factors at diagnosis within subgroups were: 88% of 230-INSS stage 4; 92% of 230-≥18 mos old; 18% of 189-MYCN amplified; 49% of 180-diploid; 94% of 172-unfavorable histology. Only MYCN amplification was prognostic of worse PFS after relapse study enrollment (p<0.001). Median time from diagnosis to first relapse/progression was 22 mos(95% CI: 19,25) (n=214).

Conclusions

PFS/TTP/OS from this representative comprehensive historical COG early-phase trial NB cohort should be used in Phase 2 trials as the gold standard comparator to identify promising new agents for NB.

O-066

Neuroblastoma 2

HUMANIZED ANTI-GD2 ANTIBODY (HU14.18K322A) GIVEN WITH CHEMOTHERAPY +/- PARENTAL NATURAL KILLER (NK) CELLS IN CHILDREN WITH RECURRENT OR REFRACTORY NEUROBLASTOMA

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Objectives

Preclinical studies demonstrate that anti-GD2 antibodies, acting via antibody-dependent cell-mediated cytotoxicity (ADCC), enhance the effects of chemotherapy; however, it is unknown if chemotherapy combined with Hu14.18K322A is feasible and effective in children with neuroblastoma. This study evaluates the safety and feasibility of administering a unique humanized anti-GD2 antibody (Hu14.18K322A) with chemotherapy and parental NK cells to enhance ADCC.

Methods

Pediatric patients with recurrent or refractory neuroblastoma were eligible to receive six courses of Hu14.18K322A (40mg/m²/dose, days 2-5) in combination with alternating courses of cyclophosphamide/topotecan (courses 1,2), irinotecan/temozolomide (courses 3,4) and ifosfamide/carboplatin/etoposide (courses 5,6). Parental NK cells were administered with courses 2, 4 and 6.

Results

Ten heavily pretreated patients, median age 6.5 years (range, 2.8–13.5), including 7 with prior anti-GD2 treatment, completed 40 courses. One patient developed unacceptable toxicity characterized by prolonged thrombocytopenia (>35 days). Four patients came off study for adverse events (hu14.18K322A allergy, prolonged viral infection, surgical death and myelodysplastic syndrome). Common toxicities included grade 3-4 myelosuppression (10/10 patients) and grade 1-2 pain (10/10 patients). Eight patients received 19 NK cell infusions. The median number of NK cells infused per dose was 18.2×10^6 /kg (range, 6.2×10^6 /kg- 47.8×10^6 /kg). Responses to therapy included: 2 complete responses (CR), 1 very good partial response (VGPR), 2 partial responses (PR) and 5 with stable disease (SD). Five patients (2CR, 1VGPR, 1PR, 1SD) and 2 patients (1CR, 1VGPR) who received NK cell infusions had measureable donor NK cells on days 7 (chimerism range, 2%-100%) and 14 (chimerism range, 1%-64%) respectively. None of the patients progressed on therapy. One patient remains in CR 9 months after completing therapy.

Conclusions

Administration of concurrent chemotherapy, Hu14.18K322A and parental NK cells is safe, feasible and resulted in clinically meaningful responses in patients with neuroblastoma. Accrual to the trial is ongoing.

O-067

Brain Tumours Biology 2

MICRORNA EXPRESSION IN ATYPICAL TERATOID/RHABDOID TUMORS (AT/RT): NEW POTENTIAL THERAPEUTIC TARGETS?

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Objectives

Atypical Teratoid/Rhabdoid Tumors (AT/RT) are aggressive pediatric tumors of the central nervous system. As there is no effective treatment, new therapeutic options are needed. MicroRNAs (miRNAs) are small noncoding RNAs that post-transcriptionally modulate entire sets of genes. Modulating miRNAs may provide a new avenue on cancer treatment.

Methods

We compared the miRNA expression profiles of 10 AT/RT to 4 Meduloblastoma (MB) and the gene expression (GE) profiles of 14 AT/RT to 6 MB. Illumina V2 MicroRNA Chips and Illumina HT-12 whole genome expression arrays (Illumina, Inc., CA, USA) were used for analysis. Total RNA was isolated using Trizol Reagent (Invitrogen, CA, USA). Fold changes (FC) were calculated, and *t-test* was applied to assess the significance of differentially expressed genes. MiRNAs with $-1.5 \leq FC \leq 1.5$ (p-value < 0.05) and mRNAs with $-2 \leq FC \leq 2$ (p-value < 0.05) were selected. Ingenuity Pathway Analysis (IPA, www.ingenuity.com) was used to determine pairing of highly predicted miRNA-mRNA with inverse expression correlation and to determine enriched biological functions of differentially expressed genes. Selective miRNA/mRNAs were validated by real-time PCR.

Results

Among 85 differentially expressed miRNAs and 1002 differentially expressed mRNAs, miRNAs-mRNAs pairs were established with 10 miRNAs and 53 mRNAs. Among them, miR-663 was the most up-regulated in AT/RT (FC=4.81). Accordingly, the following predicted targets were found to be significantly down-regulated: CDK5R1 (FC=-5.24) that regulates expression of CDK5, and NCAM1 (FC=-4.51), both of them essential for neural development.

Conclusions

The down-regulation of genes involved in neural development regulated by miR-663 in AT/RT may indicate that this miRNA might be concurring for the poor differentiated nature of these tumors. We speculate that manipulating this specific miRNA could induce differentiation of AT/RT cells lowering its aggressive behavior.

Acknowledgments: Research Funded by The Rally Foundation for Childhood Cancer Research in memory of Haley Trainer and Dr. Ralph and Marian C. Falk Medical Research Trust.

O-068

Brain Tumours Biology 2

USING *DROSOPHILA MELANOGASTER* FOR THE IDENTIFICATION OF GENES INVOLVED IN THE BIOLOGY OF ATYPICAL TERATOID/RHABDOID TUMORS

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Objectives

The majority of atypical teratoid/rhabdoid tumors (AT/RT) is characterized by inactivation of one single gene, *SMARCB1*. However, only little is known on targetable downstream pathways. We therefore aimed to perform a broad functional screen of genes potentially involved in the detrimental effects of *SMARCB1* deficiency.

Methods

Using *Drosophila melanogaster* and the Gal4-UAS system, a modifier screen was performed in order to identify pathways involved in the phenotype associated with ubiquitous or glial-specific knockdown of *snr1*, the fly homolog of *SMARCB1*. The functional role of identified genes and pathways was investigated in human rhabdoid tumor cell lines BT16, A204 and G401 as well as AT/RT tumor samples from the European Rhabdoid Tumor Registry EURHAB.

Results

Silencing of *snr1* expression in *Drosophila melanogaster* resulted in a lethal phenotype as well as increased volume and proliferation of the larval fly brain. Crossing *snr1* knockdown flies with strains expressing specific RNAi shifted the lethal phenotype in 70/1015 screened candidate genes. These included *merlin kibra* and *expanded*, whose products represent a key upstream regulator of the hippo pathway. In *SMARCB1*-deficient human rhabdoid tumor cell lines, silencing of *NF2*, *WWC1* and *FRMD6*, the homologues of *merlin*, *kibra* and *expanded*, resulted in reduced proliferative activity on MTT and BrdU assay, while cytotoxicity was unaltered. Furthermore, YAP1, the main effector of the hippo pathway was over-expressed in AT/RT and associated with shorter progression-free survival and overall survival.

Conclusions

Highlighting the role of hippo signaling in *SMARCB1*-deficiency and the biology of AT/RT, these results demonstrate that fly models can be employed for the identification of clinically relevant pathways in human cancer.

Supported by IZKF Münster (Ha3/016/11).

O-069

Brain Tumours Biology 2

DELINEATING TRANSFORMING MECHANISMS AND THERAPEUTIC TARGETS OF THE C19MC ONCOMIR CLUSTER

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Objectives

Central nervous system-primitive neuro-ectodermal tumors (CNS-PNETs) represent a distinctly aggressive and clinically heterogeneous class of embryonal brain tumors with poorly understood biology. We have recently shown that CNS-PNETs with C19MC amplification and/or high LIN28 expression comprise a single molecular entity that spans various histologic categories and anatomic compartments. These tumors, classified as 'Group 1', are distinguished by highly primitive neural gene signatures. Taken together with our prior observations that C19MC miRNAs alters human neural stem cell (hNSC) phenotypes, these findings suggest C19MC OncoMiRs may critically modulate cell differentiation and growth pathways to promote tumorigenesis.

Methods

To elucidate molecular mechanisms of C19MC-mediated tumorigenesis, we combined miRNA target prediction algorithms with comparative gene expression analyses of primary C19MC amplified tumors and hNSCs with stable expression of 5-oncogenic C19MC miRNAs.

Results

These analyses revealed multiple cell cycle regulatory tumor suppressors as candidate C19MC gene targets including p21, p27 and p130 (RBL2), which displayed highly conserved C19MC binding sites. We observed that p21, p27 and RBL2 were directly and synergistically targeted by C19MC miRNAs in cell lines with stable 5-C19MC OncomiRs expression. Significantly, miRNA *in-situ* hybridization and immuno-histochemical analyses confirmed p21, p27 and RBL2 as bonafide gene targets in primary C19MC-amplified human tumor cells. We observed stable 5-C19MC miRNA expression conferred a proliferative phenotype in hNSCs, thus suggesting C19MC OncomiRs may synergize to activate pro-growth pathways. Recently, we identified gene fusions of C19MC and *TTYH1* and demonstrated that the distinct methylation landscape of Group 1 CNS-PNETs correlated with C19MC targeting of RBL2 with consequent up-regulation of DNMT3B. Consistent with these observations, growth of primary Group 1 CNS-PNET cells was robustly inhibited by 5-azacytidine and Vorinostat treatment.

Conclusions

These studies collectively suggest that C19MC OncoMiRs promote tumorigenesis by targeting cell cycle regulators to modulate the epigenome and provides one of the first rational therapeutics for these devastating tumors.

O-070

Brain Tumours Biology 2

SIGNIFICANCE OF TUMOR ASSOCIATED MACROPHAGES IN MEDULLOBLASTOMA

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Objectives

Children with medulloblastoma can be subgrouped into at least four molecular categories, offering the potential for targeted therapeutic approaches to reduce treatment related morbidities. Little is known about the role of tumor microenvironment in medulloblastoma or its contribution to these molecular subgroups. Tumor microenvironment has been shown to be an important source for therapeutic targets in both adult and pediatric neoplasms. In this study, we investigated the hypothesis that expression of genes related to tumor-associated macrophages (TAMs) correlate with the medulloblastoma molecular subgroups and contribute to a diagnostic signature.

Methods

Gene expression profiling using Human Exon Array (n=168) was analyzed to identify medulloblastoma molecular subgroups and expression of inflammation-related genes. Expression of 45 tumor-related and inflammation-related genes was analyzed using a custom-built TaqMan Low Density Array (TLDA) card in 83 medulloblastoma samples to build a gene signature predictive of molecular subgroups. TAMs in medulloblastomas (n=54) comprising the four molecular subgroups were assessed by immunohistochemistry (IHC).

Results

A 31-gene medulloblastoma subgroup classification score inclusive of TAM-related genes (*CD163*, *CSF1R*) was developed with a misclassification rate of 2%. Tumors in the Sonic Hedgehog (SHH) subgroup had increased expression of inflammation-related genes and significantly higher infiltration of TAMs than tumors in the Group 3 or Group 4 subgroups ($p<0.0001$ and $p<0.0001$, respectively). IHC data revealed a strong association between location of TAMs and proliferating tumor cells.

Conclusions

Our study reports the first evidence of the presence of TAMs in medulloblastomas and provides a novel 31-gene TLDA signature that accurately determines medulloblastoma molecular subgroups. These data suggest that SHH tumors have a unique tumor microenvironment and interactions of TAMs and SHH tumor cells may contribute to their pathogenesis revealing TAMs as a potential therapeutic target.

O-071

Brain Tumours Biology 2

H-PRUNE, THROUGH NEGATIVE REGULATION OF NM23-H1, ENHANCES TGF- β SIGNALING IN MEDULLOBLASTOMA

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Objectives

Brain tumors are the most common cause of childhood oncological death and medulloblastoma (MB) is the most frequent and highly invasive embryonal tumor that arises in the cerebellum and disseminates through the cerebrospinal fluid to coat the brain and spinal cord. Recent studies have revealed that MB comprises at least four distinct molecular sub-entities, which differ in terms of cell-of-origin, clinicopathologic features and disease outcome. Within these molecular groups, metastatic disease at diagnosis was characteristic in Group-3 subtype even though the mechanisms of metastatic cells dissemination are still poorly studied.

Methods

In our study, we identified h-Prune as one of the most differentially expressed and functionally relevant genes in MB Group-3. In this group TGFBR1 is highly amplified and network analysis studies illustrate that TGF- β signaling activation is unique to Group-3. Moreover the Group-3-enriched MB oncogene OTX2 is a prominent target of TGF- β signaling in the developing nervous system.

Results

H-Prune, was identified as NM23-H1-binding protein and NM23-H1 was found as negative regulator TGF- β signaling by preventing activation of SMADs proteins. Here we found that h-Prune through negative regulation of NM23-H1 enhance TGF- β signaling, while h-Prune silencing by RNA interference in several well established MB cell lines resulted in a strong inhibition of cell migration, proliferation and adhesion, suggesting that h-Prune is required for growth of MB cells. Further, we demonstrated that h-prune silencing negatively regulate OTX 2 protein quota in MB immortalized cell line, and finally knockdown of h-prune model impairs the tumor engraftment in orthotopic xenograft.

Given the relevance of h-Prune in MB, accordingly with the effects of its silencing, *in vitro* and *in vivo*, we also presented a new drug against h-prune able to impair its protein stability.

Conclusions

Our findings in primary tumors, together with functional studies in MB cell lines, provide strong evidence for an important role of h-Prune in the progression and metastatic dissemination, suggesting future ways for rational tailored-pharmacological therapy for Molecular Group-3 MBs.

O-072

Brain Tumours Biology 2

**CHROMOSOME ENGINEERING AND STEM CELL DIFFERENTIATION
TECHNOLOGIES TO MODEL SOMATIC COPY NUMBER ABERRATIONS IN
MEDULLOBLASTOMA**

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Objectives

Medulloblastoma is the most common malignant brain tumour of childhood and a major cause of oncologic death in children. Recent progress in genetic analysis has revealed a number of chromosome abnormalities in medulloblastoma. Chromosome 17 aberrations including loss of 17p, gain of 17q and isochromosome i17q, are seen across medulloblastoma subgroups. A chromosome “17p deletion” knock-out mouse model has been developed, however, this model is embryonic lethal at an early stage of development likely due to haploinsufficiency of critical developmental genes, it is unclear if neuronal precursors can form when mouse 17p equivalent region is deleted. Mouse embryonic stem cells cultured under serum-free of embryoid body-like aggregates (SFEBq) conditions can differentiate into many cell types of the brain including cerebellar progenitor cells. We hypothesize that differentiation of 17p deletion ES cells into cerebellar progenitor cells is not embryonic lethal.

Methods

The SFEBq method was optimized for use with chromosome engineered mouse embryonic stem cells harboring an 18 million bp deletion equivalent to human 17p deletion. EBs were differentiated into cerebellar progenitor cells and intracranially injected into NOD scid gamma (NSG) immunodeficient mice.

Results

Mouse ES cells with 17p equivalent deletion were successfully differentiated into cerebellar precursors *in vitro*. 17p deletion cells were more proliferative in Ki67 staining comparing to the parental floxed cells without 17p deletion. Immunofluorescence staining with Math1 and Neph3 demonstrates “17p deletion” ES cells give rise to granule cell precursor, purkinje cells and other GABAergic neurons.

Conclusions

SFEBq allows us to generate cell types of the cerebellum chromosome engineered with a mouse equivalent 17p deletion. These cells are more proliferative but insufficient to cause medulloblastoma. The addition of Oncogene overexpression or gene knockouts will allow us to model the events that transform cerebellar progenitors into medulloblastoma.

O-073

Rare Tumours

PEDIATRIC MALIGNANT MESOTHELIOMA: THE EUROPEAN EXPERT GROUP EXPERIENCE

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Objectives

Mesothelioma is an exceptional tumor that arises from the surfaces of the pleural and peritoneal cavities, pericardium, or tunica vaginalis. In adults, most patients need medical oncological therapies and long-term survival is very uncommon. Very little is known about the characteristics of this tumor in a pediatric setting.

Methods

The European EXPeRT group of pediatric very rare tumors reviewed retrospectively children and adolescents (< 18 year) diagnosed in Europe with mesothelioma between 1987 and 2013.

Results

22 patients (pts) were identified, 6 males and 16 females, mean age 11.2 years (range 3 months-17.9 y). Primary tumour was located into the peritoneum in 13 pts, pleura in 3, vagina in 1 case, pericardium in 1, and multiple sites in 4 pts. Metastasis at diagnosis were present in 9 patients. Histology was epithelioid for all cases. Chemotherapy was delivered to 19 patients, cisplatin-based regimen, added to Pemetrexed in 9 patients. Additional cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (cCHIP) was performed in 6 patients as first line therapy, and for 3 patients after relapse or progressive disease. Ten patients went into complete remission after cCHIP and cisplatin-based chemotherapy. At a median of 59 months follow-up, 10 patients remain in first complete remission, 4 with residual stable images, one with progressive disease, 5 patients died, two patients are lost of follow-up.

Conclusions

Mesothelioma is a very rare tumour in pediatric population. Pediatric mesothelioma seems to be different from its adult counterpart with less primary pleural localization and a much better outcome despite frequent relapses.

This series provides interesting insight into the safety and effectiveness of treatment of pediatric mesothelioma patients highlighting the role chemotherapy cisplatin based with pemetrexed, cCHIP. Establishment of European recommendations are recommended.

O-074

Rare Tumours

PEDIATRIC MELANOMA: ANALYSIS OF 52 CASES FROM THE FRENCH PEDIATRIC RARE TUMOR GROUP (FRACTURE)

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Objectives

to describe the clinical presentation, treatment and evolution of malignant skin melanomas (MM) occurring in children.

Methods

a descriptive, retrospective, multicenter national study of children and adolescents (

Results

52 patients from 7 French centers were included. The median age was 15 years (ranges: 5-18), 12 were less than 10 years old. 45% of the tumors were amelanotic and 84% were raised. The Breslow thickness was >4mm for 35% of tumors. Histology showed superficial spreading (n=16), spitzoid (n=15) or nodular presentation (n=13). At diagnosis, the disease was localized in 40 patients, and 2 had metastasis. Clinical lymph node involvement was present in 5. Primary excision was performed in 49 patients. Sentinel lymph node biopsy was performed in 19 patients and was positive in 5. Sixteen patients relapsed and 10 died after progressive disease despite various treatments (surgery, chemotherapy, and immunotherapy). The five-year event-free (EFS), relapse-free (RFS) and overall (OS) survivals were respectively 62.7% [95%CI: 45.3 – 76.0], 72.3% [95%CI: 55.6 – 83.7] and 75.5% [95%CI: 56.8 – 87.1]. On Cox univariate analysis, older age at diagnosis had a negative impact on OS (HR: 1.3 [95%CI: 1.1 – 1.7], p: 0.04). Clark level (II/III vs. IV/V), Breslow thickness and AJCC staging were not significant prognostic factors for EFS and OS. Differences between children and adolescents will be discussed.

Conclusions

Pediatric melanoma is a very rare pathology. It can be amelanotic and concerns mainly adolescents. Primary surgical resection of primary and involved nodes is the optimal management for early stages. Therapy for advanced stages or relapses is unclear and prognosis remains dismal. As efficacy of targeted therapy is unknown in pediatric MM, international cooperative clinical and biological studies are warranted.

O-075

Rare Tumours

NASOPHARENGEAL CARCINOMA IN CHILDREN AND ADOLESCENTS 1989-2014: DEMOGRAPHIC, CLINICAL, THERAPEUTICAL CHARACTERISTICS AND LONG TERM OUTCOME

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Objectives

The aim of this study was to evaluate the demographic, clinical and therapeutic characteristics and long-term outcome in childhood and adolescent nasopharyngeal carcinoma (NPC) retrospectively in a single center.

Methods

From November 1989 to January 2014 the files of 85 patients <18 years with NPC were treated in Istanbul University Oncology Institute. All patients received three courses of neoadjuvant chemotherapy (1989-1994; cisplatin-based regimens; 1995-2008: Bleomycin, etoposide and cisplatin - BEP; since 2008- :EP) followed by radiotherapy given both to the primary tumor and to the metastatic cervical lymph nodes.

Results

Sixty-four boys and 21 girls, median age 14 yrs (6-18), presented mostly with a lump in the neck, headache, and ear and nose problems. Median follow-up time was 118 months (1mo.-24 years). Eighty-eight % of the biopsies (n=75) of NPC were WHO type III tumors. Most patients had advanced stage tumors (III=40, IVA=17, IVB=23) with 2 distant metastatic sites (IVC=2) according to AJCC staging system.

Chemotherapy was followed with radiotherapy 60Gy to the primary tumor and involved lymph nodes, and 50-54Gy to the cervical nodal region. The 10-year overall (OS) and event-free survival (EFS) rates were 79.5% and 78.7%, respectively. When patients before 1994 were excluded from the analysis, there was no significant difference in 10 yr-OS and EFS in patients who received BEP or EP (88.6 vs 87.1 and 86.2 vs 88.5, respectively). Eight patients died due to relapse disease.

Secondary malignancy developed in two patients. Two others died with causes unrelated to malignancy. Late effects included hypothyroidism, neck fibrosis, xerostomia, bony hypoplasia, skin problems and hearing loss.

Conclusions

Children and adolescents with advanced NPC had a relatively good rate of long-term survival. Neoadjuvant therapy and radiotherapy leads to high locoregional control and thus survival in advanced stage NPC; EP seems to be as effective as BEP. Survivors should be followed for long-term morbidities.

O-076

Rare Tumours

SALIVARY GLAND CARCINOMAS IN CHILDREN AND ADOLESCENTS: THE ITALIAN TREP PROJECT EXPERIENCE

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Objectives

Salivary glands carcinomas (SGC) are extremely rare in pediatric age, with an annual incidence of 0.8-1.4 per million persons <20 years. We report clinical features of a series of children/adolescents with SGC prospectively registered in the Italian TREP (*Rare Tumors in Pediatric Age*) project.

Methods

Diagnostic/therapeutic guidelines were developed and disseminated between Italian pediatric oncology/surgical centers. In the 2000-2012 period, 720 cases of rare pediatric tumors by 39 different centers were registered: 17 patients had SGC. The number of SGC expected each year in Italy is 6.8 in the 0-17 years population, so the observed/expected ratio was 0.19.

Results

SGC mainly arose in the parotid (14 cases), in most cases they were low-grade tumor (14 cases); clinical presentation was often favorable, with low-stage disease; they had low-grade tumor (12 T1 tumor, i.e. size <2 cm, without extraparenchymal extension, 4 regional nodal involvement). All patients underwent surgical resection, achieving histologically-free margins in 9/17. Concerning patients with parotid gland tumor, 13/14 received parotidectomy (10 total, 3 superficial), 1 had a tumorectomy. Post-operative facial nerve injury was reported in 2 cases. Adjuvant radiotherapy was given to 6 cases, due to incomplete resection associated to N1 tumor and/or T3 tumor. The overall prognosis was good: only one patient with a huge high-grade T4N3 tumor had tumor progression and died of disease. The other 15 cases were alive in first continuous remission, 1-8 years after diagnosis. Noteworthy, in 4/17 cases SGC was a second tumor, 6-9 years after a primary cancer (i.e. acute lymphoblastic leukemia, osteosarcoma, Ewing sarcoma and Hodgkin disease).

Conclusions

This series represents the firstly-reported prospective national-based cooperative series of pediatric SGC. The compliance to TREP recommendations was high. These tumors are rarely managed by pediatric oncologists/surgeons. Larger international cooperation and networking with otolaryngologists/head-neck surgeons expert on

adult SGC are advisable.

O-077

Rare Tumours

TRACHEOBRONCHIAL MUCOEPIDERMOID CARCINOMA IN PEDIATRIC POPULATION- KEY CLINICAL PATHOLOGICAL ISSUES

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Objectives

Mucoepidermoid carcinoma was first identified as malignant tumor of major salivary glands, and later also described in tracheobronchial tree, from submucosa mucous glands. Though extremely rare in the pediatric population, tracheobronchial is the second most common primary neoplasm for the location. The most common for is carcinoid tumor. Large series study of this entity in childhood is very scarce in medical literature and the molecular mechanism.

Methods

We retrieved 40 pediatric cases of tracheobronchial mucoepidermoid carcinoma from literature and our institution and analyzed their most relevant clinicopathological features. The age cutoff is 20 years old.

Results

The gender distribution appears to be equal in this population. Presentation age ranges from 3 months to 20 years (mean= 9 year). Pneumonia, especially recurrent pneumonia manifested by cough and fever is the most salient presentation feature. Less than one third of the cases have hemoptysis. The typical endoscopic finding is a well-defined polypoid endobronchial/ intraluminal mass. The intermediate grade cases were more frequently encountered in pediatric population (about 50%), but no high grade case was observed. One case regional lymph node metastasis was identified. All study group patients survived with surgical resections alone. On molecular pathology level, translocation t(11;19) and t(1;11) have been detected , some associated with cyclin D1 immuno positivity. 30% of the cases tested were positive for EGFR gene mutation L861Q. One case was tested positive for ERCC1.

Conclusions

Slow growth, insidious course featuring recurrent pneumonia is characteristic of pediatric mucoepidermoid carcinoma. The most important differential diagnosis to be considered include: carcinoid, adenoid cystic carcinoma. The other differentials include- inflammatory myofibroblastic tumor, histoplasmosis nodules, chondroid hamartoma, infantile fibrosarcoma, neurofibroma, hemangioma, and bronchogenic cyst. Mucoepidermoid carcinoma is resistant to radiotherapy and chemotherapy, surgical options do well. In term of prognosis, compared with adult cases, pediatric cases fared better, with 100% survival rate and rare recurrences.

O-078

Rare Tumours

CLINICAL ANALYSIS OF PLEUROPULMONARY BLASTOMA IN THE LARGER CHINESE PEDIATRIC HEMATOLOGY AND ONCOLOGY CENTER

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Objectives

Retrospectively analyzed pleuropulmonary blastoma (PPB) in 4 larger Chinese Pediatric Oncology center in recent years. And provide a basis for multi-center collaborative treatment of PPB in China

Methods

The clinical features, pathological findings and outcome of PPB cases observed from 1999 to 2011. Clinical data, surgical notes and summaries of treatment were taken from the charts and correlated with outcome by standard statistical methods.

Results

The series included 30 patients (12 males, 18 females) with a median age of 36 months (19~156months), a median of 15 days(5-180days) from onset to diagnosis. In ten patients developed with lung involvement only. Site of extrapulmonary involvement have mediastinal, pleura, pericardial,abdominal lymph nodes and liver. Tumor size was between 5 and 10 cm in seven patients, more than 10 cm (max 16×15×12cm³) in nine patients, and unknown in fourteen patients. Two patients had type 1, eight patients type 2, and thirteen patients type 3 . Histologic subtype was unknown in seven patients.

At diagnosis, twelve patients had total resection, 2 had recurrences and died, 2 had lost, 8 were complete remission(CR); three patients had partial resection. The remaining patients had biopsy only at initial surgery. Of fourteen patients were treated by chemotherapy. Nine patients received CAV/IE regimen for 3-8 courses. Three received IVAD regimen and Cisplatin for 7-12 courses. Two received IVADand IVA regimen for 12 courses. 6 got CR, 1 partial remission ,6 had recurrences and died, 1 was lost. Those patients had total surgery or partial resection before and/or after chemotherapy.

Conclusions

PPB is an aggressive neoplasm. Achieving total resection of the tumor at any time of treatment (both before and/or after chemotherapy) resulted in a significantly better prognosis, whereas extrapulmonary involvement at diagnosis resulted in a significantly worse prognosis.

O-079

**Leukemia/MDS/Bone Marrow Transplantation – Clinical
TO COMPARE ROLE OF HYDROXYUREA AND HYPERHYDRATION VERSUS
HYPERHYDRATION ALONE TO DECREASE TOTAL LEUKOCYTE COUNT IN
CHILDREN OF ACUTE LEUKEMIA WITH HYPERLEUKOCYTOSIS:A
RANDOMIZED CONTROL TRIAL**

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Objectives

Acute leukemia with hyperleukocytosis (TLC > 1,00,000/cu.mm) is an oncological emergency. Hydroxyurea is used to treat hyperleukocytosis, but evidence is limited.

1. To demonstrate that addition of hydroxyurea to conventional management causes a significant decline in total leukocyte count when compared to conventional therapy alone in newly diagnosed children of acute leukemia with hyperleukocytosis.
2. To demonstrate difference in complications (tumor lysis, pulmonary complications, CNS complications, hemorrhagic complications and mortality) and time taken to initiate chemotherapy in both the groups.

Methods

48 children were randomized in two groups. One group received conventional treatment (intravenous fluids 3 liter/m² as 5% dextrose saline with 40 meq/liter of sodium bicarbonate and oral Allopurinol 300 mg/m²/day). Other group in addition received hydroxyurea (75mg/kg/day).

Results

Treatment response in hydroxyurea group was seen in (83.3%) patients, were as in conventional group it was (29.2%). The difference was significant (P value < 0.05). There was no significant difference in complications (P value > 0.05). Bleeding complication were petechiae (25%), ecchymosis (16.7%), melena (8.3%), epistaxis (6.3%) and retinal hemorrhage (6.3%). Respiratory complications were tachypnea (41.7%), cough (22.9%), respiratory acidosis (10.4%) and infiltrate on chest radiograph (10.4%). CNS complications were papilledema (8.3%), photophobia (8.3%) and headache (4.2%). Median duration to start chemotherapy was less in hydroxyurea group (P value < 0.05). There was no significant adverse drug effects of hydroxyurea observed.

Conclusions

Addition of hydroxyurea to conventional treatment leads to rapid and early decline in TLC without any significant adverse drug effect. Hydroxyurea treatment should be given with standard conservative treatment including intravenous fluids, alkalinization and allopurinol.

O-080

**Leukemia/MDS/Bone Marrow Transplantation – Clinical
MONITORING MRD IN CHILDHOOD AML USING A SET OF SEVEN GENES – A
SIMPLE METHOD WITH STRONG PROGNOSTIC IMPACT**

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Objectives

This study evaluated the prognostic impact of a simple and highly standardized assay for monitoring minimal residual disease (MRD) in acute myeloid leukemia (AML).

Methods

The expression of seven leukemia associated genes (WT1, PRAME, CCL23, GAGED2, MSLN, SPAG6, and ST18) was measured by TaqMan Low Density Arrays in bone marrow of 114 children with AML and 52 healthy controls. Patients were treated according to multicenter study AML-BFM 2004. Samples were collected and analyzed prospectively at standard time points (diagnosis, day15; day28). The lab that measured the MRD was blinded to the clinical course of the patients.

Results

Relapse free survival (RFS) was 95% (n=19; SE=5%) if expression of all genes was down to normal by day15, 63% (n=41; SE=8%) if expression was elevated on day15 but normalized by day28, and 38% (n=21; SE=11%) in patients who still showed elevated expression of at least one gene on day28 (p<0.001). The prognostic impact was still highly significant (p=0.002) when patients were stratified for established risk factors. Day15 was the most relevant time point for measuring treatment response.

Conclusions

This method is strongly predictive of outcome in childhood AML. It can easily be adopted by other groups because TaqMan Low Density Arrays are a commercially available, fully standardized method.

O-081

**Leukemia/MDS/Bone Marrow Transplantation – Clinical
TOXICITY IS ASSOCIATED WITH AGE IN NOPHO-AML 2004**

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Objectives

Due to the high intensity treatment of childhood acute myeloid leukemia (AML) almost all patients experience severe toxicities, some life threatening. Children ≥ 10 years with AML have worse outcome compared to younger children, in part due to treatment related mortality. We investigated if a range of toxicities were age-dependent in the NOPHO-AML 2004 protocol.

Methods

We reviewed toxicities registered in the database of the NOPHO-AML 2004 protocol, including all protocol patients from the Nordic countries and Hong Kong (n=320) censoring patients at time of HSCT.

Results

Treatment-related mortality (after day 10 of diagnosis) occurred in 11/315 (3.5%). During therapy, sepsis/septic shock was significantly more common in 10-17 year olds compared to 2-9 year olds (22% vs 8.5%, $p=0.01$). Admission to the intensive care unit was more common in 10-17 year olds compared to 2-9 year olds (24% vs 13%, $p=0.051$). This difference was also seen for infants compared to 2-9 year olds, but not significantly (13% vs 23%, $p=0.28$). Other noteworthy differences were seen that did not reach significance: assisted ventilation was more common in infants and 10-17 year olds compared to 2-9 year olds (13% and 12% vs 6.8%); Creatinine was elevated to more than 3 x normal more often in infants and 10-17 year olds compared to 2-9 year olds (6.7% and 3.7% vs 0.8%); Bilirubin was elevated to more than 3 x normal more often in infants compared to 2-9 year olds (10% vs 2.6%). The only toxicity seen more often in 2-9 year olds was central neurotoxicity (7.6% vs 1.9% for 10-17 year olds, $p=0.094$).

Conclusions

Infants and 10-17 year olds experienced more toxicity during AML treatment. This was especially true for admission to the ICU, sepsis and assisted ventilation.

O-082

**Leukemia/MDS/Bone Marrow Transplantation – Clinical
MOLECULAR AND CYTOGENETIC ANALYSES OF PEDIATRIC ACUTE
MYELOID LEUKEMIA PATIENTS WHO DID NOT OBTAIN COMPLETE
REMISSION AFTER INDUCTION THERAPY: A REPORT FROM JPLSG AML-05
STUDY**

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Purpose

Recent improvement of risk-stratified chemotherapy has increased the long-term survival rate of the patients with pediatric acute myeloid leukemia (AML). However, some subgroups still have poor prognosis despite intensive chemotherapy with hematopoietic stem cell transplantation (HSCT), indicating the necessity of more specific identification of the subgroups. Prognosis of the patients with non-complete remission after induction therapy (non-CR) is considered to be extremely poor, but little is known about the molecular characteristics. In this study, we report the molecular identification of pediatric AML cases with non-CR.

Patients & Methods

We analyzed 369 pediatric AML cases enrolled in the AML-05 study in Japan. After induction therapy, 53 of the cases (19.6%) did not achieve CR. AML1-ETO, CBFB-MYH11, MLL-rearrangement, NUP98-NSD1, CBFA2T3-GLIS2, NUP98-JARID1A, FLT3-ITD, KIT, N-RAS, WT1, MLL-PTD, and NPM1 were detected by RT-PCR and MLPA methods.

Results

WBC count was significantly higher in non-CR cases (48,200 vs 18,250)(p

Conclusions

Conventional chemotherapy and HSCT were thought to be insufficient for pediatric AML patients with non-CR, who had distinct biology. Therefore, novel targeted therapies against such genetic mutations are expected.

O-083

**Leukemia/MDS/Bone Marrow Transplantation – Clinical
REFRACTORY CYTOPENIA OF CHILDREN AND ACQUIRED APLASTIC
ANEMIA: A CLINICAL AND PATHOLOGICAL STUDY OF 130 CASES**

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Objectives

Explore the clinical characteristics and histopathological morphology features of bone marrow biopsies between refractory cytopenia of children (RCC) and acquired aplastic anemia (AAA), and facilitate the diagnosis, differential diagnosis and treatment of RCC and AAA.

Methods

We retrospectively analyzed clinical data and histopathological morphology of bone marrow biopsies in RCC or AAA patients from January 2011 to December 2012 in our hospital.

Results

There were totally 130 patients studied. The final diagnoses of them were RCC in 78 cases (60.0%) and AAA in 52 cases (40.0%). The ratio of RCC and AAA in this study was 1.5:1. The median WBC count, absolute neutrophil count, blood platelet count, hemoglobin level, and reticulocyte count were all higher in RCC children than AAA (*P*micromegakaryocyte was found in 61.5% (48/78) of them. In AAA group, 88.5% (46/52) of them had cellularity of bone marrow biopsy specimens under 5%; megakaryocyte was not found in 98.1% (51/52) of them. The response rates of immunosuppressive therapy (IST) using CSA±rabbit anti-thymocyte globulin for patients with RCC and AAA at 3 months were 59.5% and 26.9% (*P*=0.011), and at 6 months 75.0% and 38.1% (*P*=0.007).

Conclusions

RCC and AAA are not uncommon in childhood bone marrow failure disorders. RCC patients showed milder cytopenia and bone marrow hyperplasia than AAA. Patchy distribution of hematopoietic cells, erythroid islands with a marked left shift and micromegakaryocytes are decisive histomorphological patterns used to separate RCC from SAA. IST is an effective therapy in patients with RCC and AAA, and the outcome of IST for patients with RCC is superior to that of patients with AAA.

O-084

**Leukemia/MDS/Bone Marrow Transplantation – Clinical
CHEMOTHERAPY-BASED CONDITIONING FOR CHILDREN WITH ACUTE
LYMPHOBLASTIC LEUKEMIA AS PREPARATIVE REGIMEN FOR ALLOGENEIC
HEMATOPOETIC STEM CELL TRANSPLANTATION: AN EBMT PAEDIATRIC
DISEASES WORKING PARTY STUDY**

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Objectives

Total body irradiation (TBI) is the backbone for conditioning regimen in children with high risk acute lymphoblastic leukemia (ALL). Some situations preclude the application of TBI, e.g. young patient's age, pre-existing morbidities or centre's facilities. To get detailed outcome information of children who received non-TBI conditioning, the EBMT Paediatric Diseases Working Party initiated a longitudinal retrospective study.

Methods

We identified 1728 children and adolescents with ALL who received a first HSCT between 2000 and 2012 and who were registered in the EBMT data base with a majority transplanted from unrelated donors and bone marrow.

Results

The stem cell source was bone marrow in 43,6% and peripheral blood stem cells in 37,8%. 18,1% received cord blood. For 90,8% of patients the centres intended a myeloablative conditioning, and for 9,8% a reduced toxicity or a reduced intensity conditioning regimen was chosen. The preferred non-TBI conditioning regimen was a combination of busulfan and cyclophosphamide (48%), followed by a triple-drug regimen consisting of busulfan, cyclophosphamide and etoposide; the remaining patients received different combinations like fludarabine/thiotepa/melphalan or treosulphan. At time of analysis, 51,4% of patients were alive. Causes of death were relapse (49,8%) or transplant related complications (42,7%). Patients transplanted after 2008 had an overall survival of 60,9% with comparable relapse incidence but lower incidence of non-relapse mortality. Compared to the whole cohort, children who were transplanted below the age of 4 years had a lower relapse incidence (28,6%) and an overall survival of 56,3%.

Conclusions

More than 50% of children with ALL who received a TBI-free conditioning regimen for allogeneic HSCT from different donors in different remission status are alive. This observation justifies and requests a prospective evaluation whether TBI is still superior compared to conditioning regimen with chemotherapy only in comparable cohort of patients.

O-085

Liver Tumours

TRANSARTERIAL EMBOLIZATION FOR PRIMARY HEPATIC MALIGNANT TUMOR IN PEDIATRIC PATIENTS: A 10-YEAR SINGLE INSTITUTION EXPERIENCE

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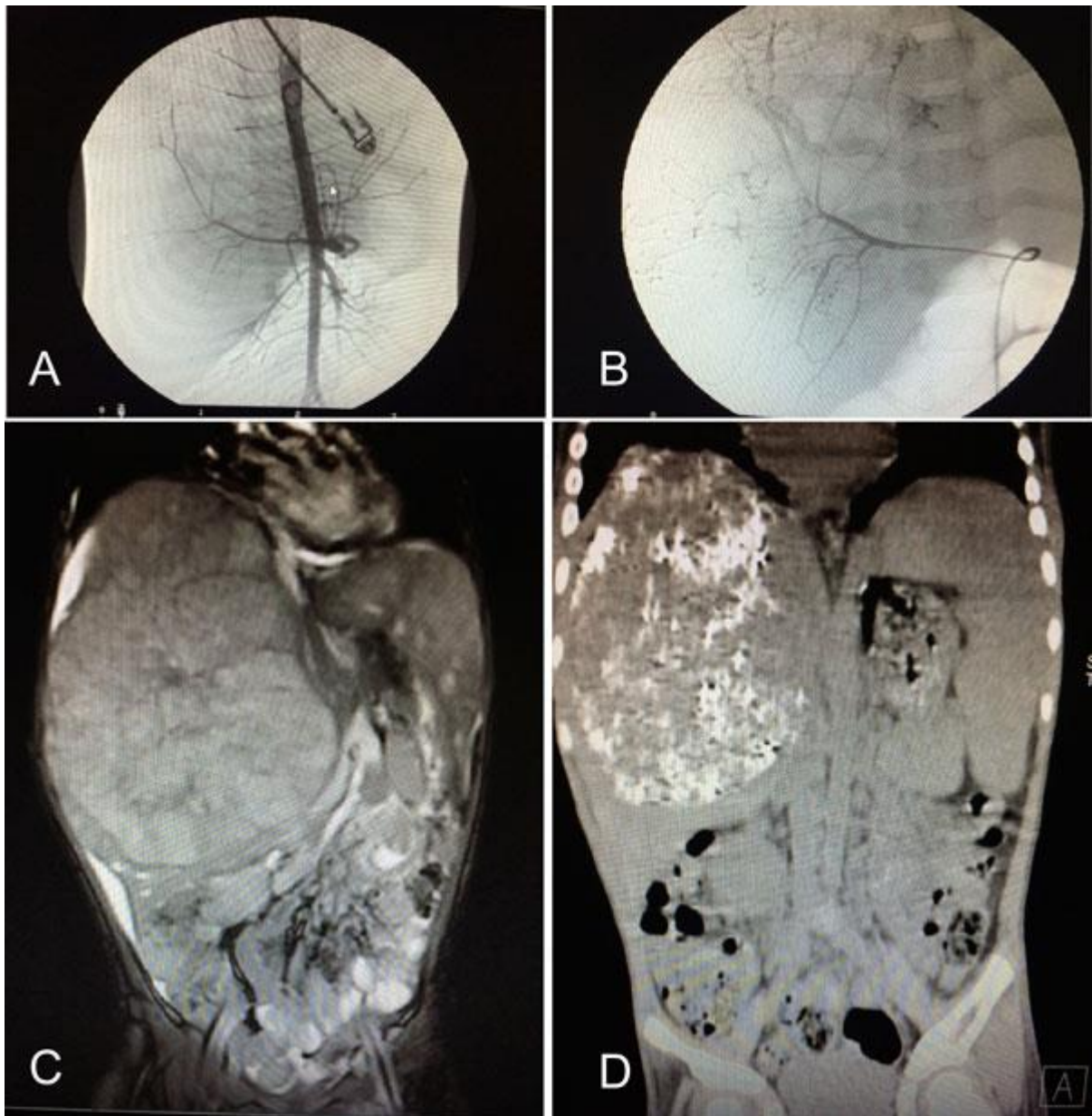
Objectives

The purpose of this study is to evaluate the feasibility and efficacy of transarterial chemoembolization (TACE) in treating pediatric primary hepatic malignant tumor (PHMT).

Methods

From 2000 to 2009, 29 patients (age between 4 months and 14 years) with initially unresectable PHMT were enrolled in this study. Twenty-four cases were hepatoblastoma (HB); 3 cases were hepatic carcinoma (HC); 2 cases were undifferentiated embryonal liver sarcoma (UELS). After percutaneous puncture biopsy, all patients received TACE (1-3 times), chemotherapy, and surgery. Follow-up materials were obtained in all patients. The tumor response, survival rate, and complications were analyzed.

Results



Following TACE, there was a visible reduction in tumor size as well as a dramatic decrease in AFP levels (in patients with hepatoblastoma). The tumor volumes (evaluated using CT or MRI) decreased by between 50.1 and 81.3%, with a mean value of 67%. Multiple metastasis masses were found in one patient with HB after TACE; 2 patients with PRETEXT stage IV tumor (1 HB and 1 HC) remained unresectable after 2 times of TACE. Complete surgical resection was achieved in other 26 patients (89.7%). All patients who underwent surgery (26 cases) received a follow-up at least 5 years. One patient was found to have lung metastasis lesion 6 months after surgery. The 5-year event free survival (EFS) rate was 86.2% (25/29). Complications included fever, transient impairment of hepatic function and abdominal pain.

Conclusions

TACE is a safe and promising method with a low rate of severe complication in treating pediatric PHMT.

O-086

Liver Tumours

**RESULTS OF SURGICAL TREATMENT IN CHILDREN WITH
HEPATOBLASTOMA IN THE NETHERLANDS (1990-2013): A NATION WIDE
ANALYSIS**

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Objectives

Surgical resection remains the cornerstone for a successful treatment in hepatoblastoma. A better insight in the results of surgery may improve the outcomes for hepatoblastoma patients even more. Therefore, the aim of this study was to review the results of surgery in the treatment of hepatoblastoma in the Netherlands retrospectively, focusing on surgery related complications, complete resection of the intrahepatic tumour, morbidity, surgical mortality and long term survival.

Methods

A retrospective chart review was performed on all patients treated for hepatoblastoma at one of the Paediatric Surgical Centers at the Academic Hospitals in Amsterdam, Nijmegen, Groningen and Rotterdam between 1990 and 2013.

Results

A total of 100 patients were included. Among the 73 patients who underwent partial liver resection, pathology report showed complete tumour resection in 64 patients and microscopic tumour residue in 2 patients. In 41 out of 70 patients, one or more complications were reported (59%). Thirty-four patients reported haemorrhage that needed transfusion (49%). Nine patients developed biliary complications of whom 8 needed one or more additional surgical interventions. Overall, 5 year survival was 83%. In the group of 73 patients who had partial hepatectomy 5 year survival was 93% and in the group of 18 patients who had initial transplantation 5 year survival was 82%.

Conclusions

Partial liver resection in children with hepatoblastoma is associated with high complication rates.

O-087

Liver Tumours

GEMCITABINE AND OXALIPLATIN FOR THE TREATMENT OF PEDIATRIC PATIENTS WITH HEPATOCELLULAR CARCINOMA.

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Objectives

Pediatric patients with hepatocellular carcinoma (HCC) are often treated with hepatoblastoma-directed therapy despite distinct histologies and natural histories. Patients with unresectable or metastatic disease fare poorly with less than 20% overall survival indicating a need for new therapeutic approaches. Adult studies have demonstrated HCC responses to Gemcitabine and Oxaliplatin (GemOx) as either front-line or retrieval therapy. We compiled data from pediatric oncologists regarding their experience treating pediatric HCC patients with GemOx.

Methods

An international working group comprised of Children's Oncology Group (COG), Société Internationale d'Oncologie Pédiatrique (SIOP), Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH), and Japanese Study Group for Pediatric Liver Tumors (JPLT) members met in Tübingen Germany in March 2014 to discuss prospective treatment strategies for pediatric HCC patients. We designed a secure electronic survey to collect de-identified patient information regarding histology, age, dose, response, and toxicity.

Results

Of 50 physicians polled, 20 responded. Eight physicians treated 24 patients (10 conventional, 14 fibrolamellar, FL) with GemOx. Patient age ranged from 4-24 years. All patients received Gemcitabine 1000mg/m² and Oxaliplatin 100mg/m² with the majority receiving q2 week dosing. GemOx was given first-line once and second-line two-thirds of the time. Using RECIST criteria, seven patients (29%) achieved an upfront partial response (PR) and seven patients (29%) achieved stable disease for a duration of 3-16 months (2 and 6 patients with FL, respectively). PR was sustained for 4-5 cycles; no patients became resectable. Ten patients progressed. Eleven patients experienced toxicities including grade 3-4 cytopenias, grade 3 nausea/vomiting and fever/neutropenia, and hepatopathy, neuropathy, or allergic reaction.

Conclusions

This is the most comprehensive report to date of GemOx use in pediatric patients with HCC. In the retrieval setting, response rates are more promising than those reported for adults (18%). These results support the potential trial of GemOx as first-line therapy in pediatric HCC.

O-088

Liver Tumours

UNDIFFERENTIATED EMBRYONAL SARCOMA OF THE LIVER – MULTICENTER GERMAN-POLISH EXPERIENCE OF THE CWS AND PPGGL GROUPS.

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Objectives

Liver sarcomas are rare, representing 6%-13% of primary hepatic tumors, among which undifferentiated embryonal sarcoma of the liver (UESL) prevails. The aim of our study was to assess the outcome of UESL in a multinational study.

Methods

Between 1994-2007, 25 patients with UESL were treated in CWS-96 and CWS-2002 trials in Germany and Poland. Median age at diagnosis was 7,5 years (4 months – 19 years). 12 patients were males, 13 - females. Lesion involved: single hepatic lobe in 22 cases (right – 15, left – 7), both lobes - 1 case and in 1 - ?. Tumor was multifocal in 1 case. The tumor size was 5-10 cm in 8 cases and greater than 10 cm in 17. Four children had distant metastasis on presentation (all disappeared following chemotherapy). Fifteen patients received preoperative chemotherapy.

Results

Good response to chemotherapy was observed in 2 cases, partial - in 9, progressive disease in 3, missing data - 1. Postoperative chemotherapy was administered in 20 children. Local radiotherapy was used in 3 children. Tumor resection was performed in 20 patients (10 - primary and 10 - delayed). Complete (R0) resection was achieved in 14 patients (12 are alive). Resection margins were positive (R1) in 5 patients (4 - alive). One child with macroscopically incomplete resection (R2) is alive. Five tumors never became operable: all of them died. The median FU was 153 months (83– 228). Seventeen patients (68%) are alive with no evidence of disease. Eight patients (32%) died (progression – 3, relapse – 3, therapy-related death – 2). Three patients relapsed. All, who were not operated on and/or relapsed, died.

Conclusions

Patients with UESL of the liver have good prognosis (68% ANED) when treated with multimodal therapy. Complete resection was traditionally considered the cornerstone of the treatment for UESL however in our experience even microscopically incomplete (R1) resection was associated with relatively good survival.

O-089

Liver Tumours

MDM4 IS A POTENTIAL NOVEL THERAPEUTIC TARGET IN HEPATOBLASTOMA

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Objectives

Hepatoblastoma (HB) is the most common malignant liver tumor of childhood which continues to have poor outcomes in those with unresectable and/or metastatic disease. The majority of HB patients at diagnosis have a wild type p53 tumor suppressor gene and have endogenous mechanisms of p53 down-regulation. MDM4 and MDM2 are the major negative regulators of p53. Copy number gain or amplification of MDM4 has been observed in a subset of HB patients. We hypothesize that MDM4 is the primary regulator of p53 function in hepatoblastoma and that blocking MDM4 will cause tumor cell death due to uninhibited p53 tumor suppressor activity.

Methods

An MTT assay to measure cytotoxicity was performed on the HB cell lines Huh-6, HepG2, HepT1, and PDCL-1 (a patient-derived cell line) which were treated with varying concentrations of NSC207895 (MDM4 inhibitor) or Nutlin-3a (MDM2 inhibitor). CaspaseGlo3/7 luciferase assay was used to assess caspase-3 and -7 activity in HepG2 cells treated with NSC207895. Western blot was used to measure expression levels of p53, p21, BAX, PUMA, and β -actin in HepG2 and HepT1 cells treated with NSC207895.

Results

Huh-6, HepG2, and HepT1 were all tested with Nutlin-3a and did not show significant cell death ($IC_{50} > 25\text{mM}$). MDM4 inhibition with NSC207895 caused significant cell death in Huh-6 ($IC_{50}=1.27\mu\text{M}$), HepG2 ($1.62\mu\text{M}$), HepT1 ($2.05\mu\text{M}$), and PDCL-1 ($0.66\mu\text{M}$). A 3.4-fold increase in caspase-3 and -7 activity was observed in HepG2 after 6 hours of exposure to NSC207895 ($p = 0.03$), indicating induction of apoptosis. By Western blot, expression of total-p53 and its downstream transcriptional targets, p21, BAX and PUMA, were increased in HepG2 and HepT1 cells 8 hours after exposure to NSC207895.

Conclusions

Our data supports the hypothesis that p53 activity is suppressed by MDM4 in hepatoblastoma and inhibition of MDM4 may be a viable therapeutic strategy.

O-090

Liver Tumours

DEVELOPMENT OF A NOVEL WEB-BASED CONSULTATION SERVICE FOR A PAEDIATRIC RARE TUMOR: THE SIOPEL CLINICIAN ONLINE CONSULTATION SERVICE

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Objectives

Because liver tumors in children are quite rare, individual clinician experience is usually limited. Yet the treatment decisions which must be made can be complex and diagnostic dilemmas are common. This is especially true with relapsed/refractory patients. Optimal care requires coordination between disciplines. In an effort to improve care, clinicians representing the four major international trial groups, cooperated to develop a novel web-based consultation service.

Methods

Supported by a grant from ENCCA, representatives from SIOPEL, GPOH, COG, and JPLT developed a web-based service accessed through the SIOPEL home-page. Clinicians may submit a consultation request for assistance in diagnosis, radiographic or pathologic evaluation, and management of non-clinical-trial-eligible patients. The request is directed to a specific discipline or groups of disciplines (surgery, oncology, radiology, pathology) or to all disciplines. The request is reviewed by one of two moderators and then sent to a panel of recognized experts in each of these four disciplines, representing all cooperative groups. The panel provides evidence-based information regarding diagnosis and treatment options, with the website facilitating an opportunity for online discussion amongst the experts. These options are summarized and circulated back to the panelists and treating institution. The treating institution must attest to ultimate responsibility for making management decisions in order to gain access to the site. Total consultation time is seven days.

Results

This consultation service is in final development and is anticipated to be launched in July, 2014.

Conclusions

This service represents an opportunity to enhance the care of children with rare tumors and facilitates education of clinicians caring for such challenging patients. It may serve as a model for cooperative management of other paediatric rare malignancies.

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under the project ENCCA, grant agreement n° 261474

O-091

Renal and Rare Tumours

COMPREHENSIVE MOLECULAR CHARACTERIZATION OF CLEAR CELL SARCOMA OF THE KIDNEY (CCSK): A CHILDREN'S ONCOLOGY GROUP TARGET PROJECT

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Objectives

Clear Cell Sarcoma of the Kidney (CCSK) is a rare childhood renal tumor that comprises approximately 5% of all primary renal tumors in children. The molecular background of CCSK is poorly understood. In the current study we aim to identify recurrent pathogenetic changes that result in the development or progression of CCSK.

Methods

Through the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative a genome-wide analysis of 13 CCSK samples was performed, including the OMICs platforms gene expression profiling (Affymetrix 133+2.0), SNP array analysis (Affymetrix SNP array 6.0), whole genome sequencing (Complete Genomics) and RNA-Seq (Illumina Truseq).

Results

Gene expression analysis showed enrichment of multiple gene sets, of which most were involved in Sonic Hedgehog and Akt/PI3K pathways. No significant recurrent copy number changes were identified. Whole genome sequencing revealed an extremely low somatic mutation rate; non-recurrent variants were identified in 10 of 13 cases, verified by RNA-Seq. Apart from a t(10;17)(q22;p13) translocation identified in one case, no significant fusions or mutations were detected in other cases by RNA-Seq.

Conclusions

Although gene expression analysis continues to show Sonic Hedgehog and Akt/PI3K pathway activation, we report no recurrent copy number changes, no recurrent fusions and no recurrent somatic mutations to explain this. Hence, our results suggest that the genome of CCSK is rather stable.

O-092

Renal and Rare Tumours

HYPOMETHYLATION OF GLIPR1 IS A POTENTIAL MARKER OF BLASTEMA IN WILMS' TUMOR

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Objectives

Wilms' tumor (WT) is a tumor variably composed of an admixture of blastema, epithelium and mesenchyma. In pretreated children, residual blastema carries a poor prognosis. However, blastema is not easily discriminated from the other components. *Glioma pathogenesis related 1 (GLIPR1)* gene was previously shown to be hypomethylated in WT and expressed in blastema, being correlated with clinical aggressiveness in other neoplasms.

The objective of this study was to determine whether *GLIPR1* hypomethylation can differentiate blastema from other components of WT.

Methods

Forty-eight patients with WT from 2 institutions, admitted between 1998 and 2012, in which an homogenous sample for DNA extraction was available were enrolled. Four normal adult kidneys, 8 fetal kidneys, 3 dysplasias, and 16 renal non-WTs served as controls. The study was approved by the ethics committee. Upon pathology review, areas with more than 90% or with less than 10% blastema were selected and macrodissected. DNA was extracted and bisulfate treated for quantification of *GLIPR1* promoter methylation using real time methylation-specific PCR, with beta-actin as control for DNA input. Cases were considered hypomethylated when methylation levels were lower than those of normal adult kidneys. Non-parametric tests were used for statistical analysis.

Results

WT patients comprised 47 children (median age 42 months; range 6months – 10yrs) and one adult. Overall, 54 areas were selected in WT, 30 with more than 90% and 24 with less than 10% blastema. *GLIPR1* hypomethylation was observed in 52 (96%) WT samples, in all fetal kidneys and dysplasias. Although methylation levels significantly differed between WT and normal adult kidney ($p=0.001$), no statistically significant difference was depicted between malignant and benign renal tumors ($p=0.166$). The areas of blastema displayed significantly lower levels of *GLIPR1* methylation compared to non-blastema ($p=0.017$).

Conclusions

In WT, *GLIPR1* hypomethylation levels may discriminate blastema from non-blastema, eventually providing a clinically useful biomarker if confirmed in further studies.

O-093

Renal and Rare Tumours

RENAL TUMORS WITH EXTENSIVE VASCULAR DISEASE: MANAGEMENT CHALLENGES IN A PEDIATRIC SERIES FROM THE HOSPITAL FOR SICK CHILDREN

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Objectives

Pediatric renal tumors have long been recognized, but their ideal management in the instances of vascular invasion remains controversial. We described the clinical behavior of patients diagnosed with renal tumors and extra renal vascular involvement at The Hospital for Sick Children in Toronto, Canada

Methods

A retrospective analysis was conducted in patients diagnosed from 1990 to 2012. Data collected included: age, gender, symptoms at presentation, staging, pathology report, radiological evidence of intravascular thrombus [i.e. renal veins (RV), inferior vena cava (IVC) and right atrium (RA)], intraoperative findings, therapeutic protocol implemented and anticoagulation; for outcomes, tumor and/or thrombus recurrence, thromboembolic phenomena and survival.

Results

Of 289 patients with renal tumors identified, 273 were included: Wilms (225), Renal Cell Carcinoma (RCC, 28), Clear Cell Sarcoma of the Kidney (CCSK, 11), others (25). The median age of the group was 4.4 years (4 days - 18 years).

Extra renal vascular disease was identified in 22 patients, with a median age 6 years (1.2 years - 16 years), including Wilms tumors (16/225, 7%), RCC (3/28, 11%), CCSK (2/11, 18%) and PEComa of kidney (1/2, 50%). Vascular involvement comprised exclusive evidence of RV microscopic disease (2), radiological findings without intraoperative/ pathology confirmation (5), macroscopic RV involvement (8) and macroscopic RV/IVC vascular disease (7).

Treatment escalation because of vascular disease included neoadjuvant chemotherapy (12; Wilms [11], RCC [1]), intraoperative thrombectomy (2; Wilms), and cavotomy (5; Wilms [3], RCC [1], CCSK [1]). No patient was placed under cardiopulmonary bypass.

Anticoagulation was administered in 2/22 patients for their tumor related thrombus, without complications. One patient had evidence of pulmonary embolism on a Chest CT.

Conclusions

Renal tumors with vascular invasion are a rare and challenging entity. Treatment included mostly cancer-related therapies and the role of vascular surgical approaches and/or systemic anticoagulation remains to be clarified.

O-094

Renal and Rare Tumours

LONG TERM OUTCOME IN ADOLESCENTS AND ADULTS TREATED FOR NEPHROBLASTOMA – A RETROSPECTIVE ANALYSIS OF THE SIOP 2001 GPOH TRIAL

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Objectives

Wilms tumor (WT) in adults are very rare. Since 2002 the renal tumour study centre in Germany registered 50 cases of WT older than 15 years of age. They were uniformly treated according to SIOP pediatric WT protocols or the adapted adult WT guidelines. Our intention was to identify risk factors for relapse in adolescents and adults with WT.

Methods

We retrospectively analyzed patients older than 15 years treated for WT in German hospitals. For data collection the same forms were used as in children.

Results

Out of 50 patients, 12 were treated with neoadjuvant chemotherapy, all other underwent primary surgery. Initial tumor volume was documented for 25 cases with a mean tumor volume of 682ml (813-2259ml). 11 patients had metastasis at time of diagnosis. Central pathology review was done in 43 patients (86%). Local stage distribution after primary surgery compared to preoperative chemotherapy was 44% versus 50% in stage I, 13% versus 30% in stage II and 44% versus 20% in stage III. Overall survival (OS) in patients with primary surgery is 60% vs. 80% in metastatic versus non-metastatic patients at time of diagnosis. Multivariate analysis including age at diagnosis, sex, metastasis at time of diagnosis, time to treatment, initial treatment, histological subtype and local stage as confounders revealed local stage III to be independent risk factor for relapse (OR:18, p<0.025).

Conclusions

Our data shows that local stage III is the main risk factor for relapse in adolescent and adult WT patients similar to WT patients below age of 15. With our data we emphasize to register this group of patients prospectively in a multicentre trial. Molecular genetic analysis need to be done in all of them to understand the aetiology of adult nephroblastoma and to find new treatment approaches.

O-095

Renal and Rare Tumours

THE SIGNIFICANCE OF RENAL DYSFUNCTION BEFORE SURGERY IN CHILDREN WITH UNILATERAL RENAL TUMOR

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Objectives

In adults with kidney tumor, baseline renal dysfunction (RD) is considered a significant risk factor for progressive renal function decline after nephrectomy. As in children with unilateral renal tumor (URT) no data are available on renal function outcome of children with baseline RD, we evaluated long-term post-operative renal function in a cohort of children with URT and baseline RD.

Methods

We retrospectively identified 54 children with URT who underwent surgery at our institution between 1982 and 2011. As serum creatinine poorly reflects renal function, we estimated glomerular filtration rate (eGFR) by indexing serum creatinine measurements to age, sex, and race. Update bedside Schwartz equation or the MDRDS equation, as appropriate for age, were used to calculate eGFR. RD was defined as $eGFR < 90 \text{ ml/min/1.73m}^2$.

Results

Of 52 children with sufficient data to evaluate baseline eGFR, 30 (57%) presented with baseline RD. During the second decade of life after surgery, 25 patients with baseline RD, despite the excision of 50 per cent of renal parenchyma, presented a significant increase in mean \pm SD eGFR (64.41 ± 17.33 vs $91.69 \pm 13.87 \text{ ml/min/1.73m}^2$; $p=0.001$). Five children with baseline RD who underwent nephron-sparing surgery (NSS) presented during the second decade of life after surgery a mean \pm SD eGFR similar to that of subjects with two healthy kidneys (66.7 ± 19.5 vs $123.4 \pm 18.9 \text{ ml/min/1.73m}^2$; $p=0.001$). Overall at follow-up, none of 12 patients who underwent NSS and 17 of 40 who underwent nephrectomy presented a persistent or newly acquired RD. Four of the 5 patients with post-nephrectomy new-onset RD presented baseline $eGFR < 100 \text{ ml/min/1.73m}^2$.

Conclusions

In children with URT, baseline RD appears to be a paraneoplastic clinical manifestation in subjects with reduced renal reserve capacity.

Renal tumor associate with baseline renal dysfunction may be a clinical surrogate marker for low nephron number endowment.

O-096

Renal and Rare Tumours

EMBRYONAL SARCOMA OF THE LIVER; A POPULATION BASED ANALYSIS USING THE SEER DATABASE

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Objectives

Embryonal Sarcoma of the Liver (ESL) is a rare entity in adults; 90% of cases occur in children. Previous case series of this rare tumor have reported overall survival of localized disease as high as 70%. However, as recent as 2012 May et al. described 5 patients currently alive and disease free in their first remission (38 to 205 months from time of diagnosis). The incidence and survival of patients with ESL has not been studied using a retrospective population-based analysis. Our objective was to evaluate incidence, organized by patient demographics, as well as long-term survival of this malignancy using the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry.

Methods

The SEER 18 database was searched for patients diagnosed with ESL between 1990 and 2010. Data analyzed included patient demographics, incidence, and survival.

Results

60 cases between the ages of 0 and 19 years were identified, representing 7% of all liver tumors in children. Median age at diagnosis was 9 years (0-19 years). The tumor was more common in boys than girls (52% vs. 48%). Most tumors were undifferentiated grade IV tumors (81%). Although 52% of tumors were localized at diagnosis, 27% had regional, and 20% had distant disease. All patients had surgical resection; only 6 patients received radiotherapy (SEER does not collect info on chemotherapy). Cause-specific survival by stage was 88%, 79%, and 56% respectively. We report an overall 1-year, 5-year, and 10-year cause-specific survival for ESL of 91%, 80%, and 75%.

Conclusions

This population-based analysis of ESL allows for a more accurate assessment of survival outcomes than previously possible in case series. Our analysis demonstrates that the prognosis for ESL has improved over time. Prognosis is excellent for localized disease.

O-097

Lymphoma

INCREMENTAL VALUE OF PET AND ROLE OF EARLY INTERIM PET ON RESPONSE PREDICTION AND OUTCOME OF PEDIATRIC NHL

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Objectives

Primary

To study the role of early interim PET in Pediatric NHL in terms of response prediction & final outcome.

Secondary

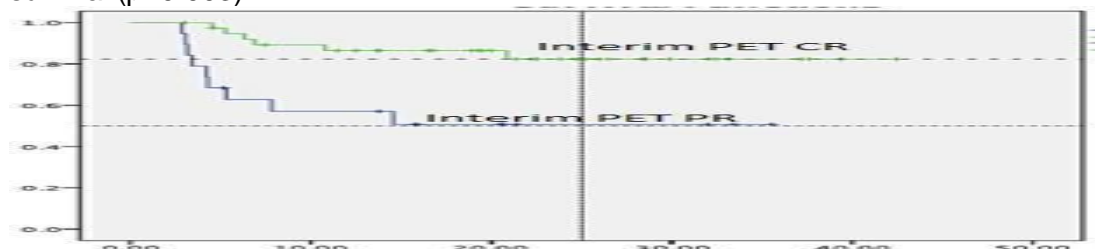
To study the incremental value of baseline PET over bone marrow for staging.

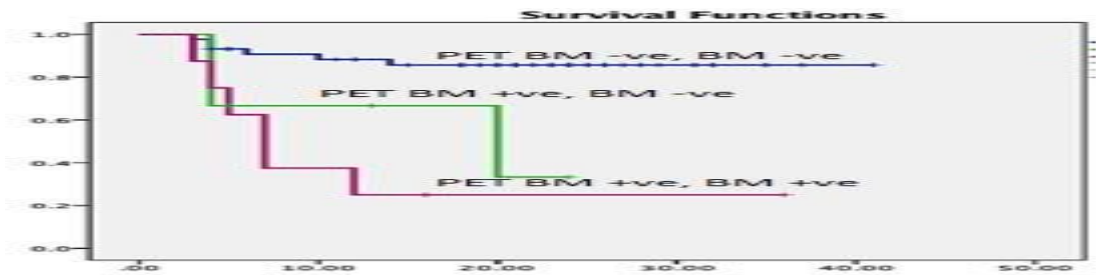
Methods

Newly diagnosed, chemo-naïve cases of pediatric (0-18 yrs) NHL (non lymphoblastic), having an interim PET/CT scan were included in the study from January 2009 to December 2011. FDG-PET (PET-2) was done after 2 cycles of chemotherapy. All patients were treated on MCP 842 protocol (8 cycles). The relation of CR and PR in interim PET/CT scan with PFS and OS was analyzed using Kaplan-Meier survival analysis. Post completion of therapy, patients were followed up as per the institutional protocol.

Results

58 patients were included in study, of which 46(79.3%) had advanced disease (stage III/IV). The median age of presentation was 8 yrs (3-18) with a median follow up of 21.4 months (3-43). All the BM positive patients (8/8) had uptake on PET, however 5(8.6%) patients had marrow uptake on PET only, upstaging the disease. Patients with BM involvement on only PET had significantly lower PFS/OS as compared to PET negative marrow, and only marginally better PFS/OS as compared to conventional Stage IV. Interim PET showed CR in 39/58(67.2%) of patients, PR in 17/58(29.30%) of patients and progressive disease in 2/58(3.4%). All the patients who were in CR in interim PET continued to be so at end of treatment. Response at interim PET could predict progression free survival (PFS) ($p < 0.000$) and overall survival ($p < 0.003$)





Conclusions

PET/CT scan in pediatric NHL picks up additional sites of marrow involvement leading to clinically relevant upstaging of disease with poor prognostic significance. Interim PET/CT significantly predicts PFS and OS in NHL making it a important for response assessment , prognostication and a risk adapted strategy in future.

O-098

Lymphoma

PROGNOSTIC IMPACT OF CYTOGENETIC ABNORMALITIES IN CHILDREN AND ADOLESCENTS WITH MATURE B-CELL NON-HODGKIN LYMPHOMA: A REPORT FROM JAPANESE PEDIATRIC LEUKEMIA/LYMPHOMA STUDY GROUP (JPLSG)

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Objectives

There is only limited information about cytogenetic abnormalities and their prognostic importance in childhood mature B-cell non-Hodgkin lymphoma (B-NHL)

Methods

We performed a review of 79 abnormal karyotypes in childhood mature B-NHL treated on JPLSG B-NHL03.

Results

A total of 63% of cases were classified as Burkitt lymphoma (BL) or Burkitt-like lymphoma (BLL), 27% were classified as diffuse large B-cell lymphoma (DLBCL) and 10% were others. A total of 11% were stage I, 14% stage II, 24% stage III, 9% stage IV and 42% acute leukemia (Murphy staging). As compared with other 242 patients without abnormal karyotypes, there was a significant over-representation of advanced stage, especially patients with leukemia and with high LDH level. Almost all cytogenetic aberrations in whole population occurred at the same incidence as previously reported in childhood B-NHL (FAB/LMB96 study) except for rearranged MYC/8q24 (R8q24) (51%). The incidence of cytogenetic aberrations in BL/BLL was not distinct from those of reported except for R8q24 (68%). The pattern of chromosomal alterations in DLBCL was similar to those of reported. The prognostic value of cytogenetic abnormalities on event free survival (EFS) was studied by Cox model controlling for the clinical risk factors : der(9p) and del(17p) were independently associated with a significant inferior EFS (hazard ratio: 4.79 ($P=0.033$) and 9.19 ($P=0.002$), respectively). The adverse prognosis of del(17p) was observed only in BL/BLL. There is no tendency of EFS to decrease in the patients with +7q or del(13q) which were previously reported as prognostic factors in childhood mature B-NHL.

Conclusions

Cytogenetic risk factors in our study were different from reported in childhood mature B-NHL. Our results emphasize the significant biological difference in ethnicity and the development of cytogenetic risk-adapted therapy in childhood mature B-NHL.

O-099

Lymphoma

THE CLINICOPATHOLOGICAL FINDINGS, TREATMENT AND OUTCOME OF JUVENILE MYCOSIS FUNGOIDES: CUTANEOUS T-CELL LYMPHOMA WITH FREQUENT FOLLICULAR INVOLVEMENT AND GOOD RESPONSE TO SKIN TARGETED THERAPY

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Objectives

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. About 75% of cases are diagnosed after age 50 years.² While studies from North America and Europe report a 0-5% rate of occurrence before age 20 years, several reports suggest that juvenile MF is much more common in Asian countries with prevalence of up to 25%. We aimed to evaluate the characteristics of juvenile MF in a large cohort.

Methods

Data were collected on all patients with MF aged ≤18 years at clinicopathological diagnosis who attended the Dermatology Department of Rabin Medical Center between 1994-2012 and were followed prospectively.

Results

The sample included 50 patients (30 male; mean age 11.4 years at diagnosis); 18 (36%) had Fitzpatrick skin type ≥IV. All were diagnosed with early-stage disease (IA-IIA) except 1 (tumor-stage, IIB). Eight had only classical MF lesions and 42 had other variants, alone or in combination, mainly hypopigmented MF (n=29) and delicate but clear clinicohistologic features of folliculotropic MF (FMF) (n=18). Among the various skin-targeted therapies applied, psoralen+UVA (PUVA) (systemic/bath) proved very efficient for FMF.

The vast majority of young patients present with early-stage disease and with unusual variants, especially hypopigmented MF. A novel finding of our study is the high percentage of FMF which affected one-third of our patients, was characterized by more superficial clinical features and histopathologically by fewer infiltrates than adult FMF and showed a good response to PUVA.

During follow-up of 0.25-15 years (mean 4.5), 2 patients progressed from stage IA to IB or IIA.

Conclusions

Reported here is the largest series of juvenile MF and the first to focus on FMF. FMF is not uncommon in children/adolescents and is characterized by more superficial clinical features and fewer heavy infiltrates than adult FMF, with good response to PUVA. The prognostic significance of childhood FMF remains unclear.

O-100

Lymphoma

MACROPHAGE POLARIZATION IN PEDIATRIC CLASSICAL HODGKIN LYMPHOMA CORRELATES WITH EPSTEIN-BARR VIRUS STATUS AND OUTCOME

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Objectives

We have shown recently that in Epstein-Barr virus (EBV)-associated pediatric classical Hodgkin lymphoma (cHL) the tumor microenvironment (TUM) is characterized by a cytotoxic/Th1 profile and higher numbers of CD14+, CD68+ and CD163+ cells when compared to adult cHL. The objectives of this study were to evaluate the macrophage polarization (MP) in the TUM of pediatric cHL (3 to 18y, median: 14y) and its impact on the survival.

Methods

MP was analysed by double-immunohistochemistry combining CD68 or CD163 with pSTAT1 (M1-macrophages) and CD68 or CD163 with CMAF markers (M2-macrophages). Expression levels of STAT1 and LYZ genes were investigated by RT-qPCR. Results were analyzed in context of age, histological characteristics, EBV-status, clinical follow-up and our previous study of T-cell populations in these cases. 100 cHL cases were studied, including 69% nodular sclerosis (NS) and 23% mixed cellularity (MC) cases.

Results

44.8% of cases were EBV-positive. Patients ≤ 14 years displayed higher numbers of CD168+pSTAT1+ cells ($P=0.01$), when compared with the oldest age-group. Higher numbers of CD163+pSTAT1+ macrophages were observed in cases with cytotoxic/Th1 tumor microenvironment profile, as disclosed by the ratios FOXP3+/CD8+ cells > 1.5 and FOXP3+/TBET+ cells > 1.5 ($P < 0.0005$ and $P = 0.04$, respectively). EBV+ cases exhibited high numbers of CD68+pSTAT1+ ($P=0.02$) macrophages. The level of *STAT1* and *LYZ* expression was associated the numbers of CD68+pSTAT1+ macrophages and EBV presence. Better overall-survival was observed in cases with high numbers of CD163+pSTAT1+ macrophages ($P = 0.04$). Worse progression-free survival (PFS) was observed in cases with high numbers of CD163+CMAF+ macrophages ($P = 0.02$). Gene expression was not associated with survival.

Conclusions

Our results suggest that in pediatric cHL macrophage polarization may depend on EBV status of HRS cell, and that a predominant M2 polarization is associated with worse PFS.

O-101

Lymphoma

POST KIDNEY TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

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Objectives

Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous group of lymphoid disorders that may complicate transplantation. Due to the clinicopathologic heterogeneity and patient's peculiarities, there is not a unified treatment approach.

Methods

In this retrospective (1987-2013) monocentric study we have enrolled 15 patients(M/F 11/4) with PTLD after kidney transplantation.

Results

Median age at diagnosis was 11.5 years(4-29 years). Median time at PTLD was 72 months(1-156 months). In 3 cases it was an "early PTLD" at 1, 5 and 6 months after transplant, in the major part(12/15, 80%) it was a "late-onset PTLD"(21-156 months). PTLD was an "early lesion" in 2 cases; polymorphic in 3; monomorphic in 9(B-cell lineage in 7 patients and T-cell lineage in 2); unknown in one. Treatment was surgical in 3 cases, anti-CD20 antibody in one, chemotherapy in 11, of whom 9 that derived from B-cell lineage received in association anti-CD20 antibody. The chemotherapy was administrated according to AIEOP protocols, without Methotrexate and reducing the doses. Nine patients received autologous EBV-specific cytotoxic T-lymphocyte at the end of treatment to consolidate the remission.

The complete remission was achieved in 93% of patients. Three patients developed a second PTLD, in two cases with the same histological type, respectively 97 months after the first plasmacytic hyperplasia and 11 months after the first polymorphic hyperplasia; in the third with a monomorphic PTLD 24 months after an extramedullary plasmocytoma. The patient with plasmacytic hyperplasia developed, 45 months after the second form, a PTLD Hodgkin-like that treated with chemo and radiotherapy obtained remission. One patient died for an HIV-related infection and one for disease. Thirteen patients are alive disease free with a median follow-up of 59 months(3-197 months). The therapy was well tolerated. 80% of patients maintained a good function of allograft-kidney.

Conclusions

A multidisciplinary approach allows a good clinical course of this post-transplant complication.

O-102

Lymphoma

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN RELAPSED ALK + ANAPLASTIC LARGE CELL LYMPHOMA OF CHILDREN AND ADOLESCENTS: A STUDY ON BEHALF OF THE SFCE AND SFGM-TC

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Objectives

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is an option for the treatment of relapsed anaplastic large cell lymphoma (ALCL) in children. To date, few paediatric reports have assessed its efficiency and tolerance.

Methods

We analyzed the data of 34 patients under 18 years (median age 7.4y [1.1-17]) prospectively registered in the SFGM-TC (Société Française de Greffe de Moelle et de Thérapie Cellulaire) database, who received an allo-SCT for the treatment of an ALCL ALK+ between 1993 and 2011. At transplant, 28 patients (82.4%) were in complete remission (CR) whereas 6 (17.6%) had a detectable disease. Conditioning regimens were mostly myelo-ablative (n=31). Most donors were unrelated (n=22) including 9 HLA-matched donors, 3 HLA-mismatched donors and 10 cord blood units.

Results

Median follow-up was 6.0 years [range 1.1-12.5]. The 5-year overall and progression-free survivals were respectively 70.0% (SE=8.0%) and 58.1% (SE=8.6%) on the whole series, and 94.7% (SE=5.1%) and 73.7% (SE=10.1%) in patients who received allo-SCT after a first relapse. Six patients relapsed after a median time of 141 days [35-235]. Durable CR was obtained in 4/6 patients after donor lymphocytes injection (n=1) or Vinblastine-corticosteroid treatment (n=3). Overall, the 5-year cumulative incidence of relapse and treatment-related mortality (TRM) was 17% (SE=7%) and 24% (SE=8%), respectively. Eventually, 10 patients died; 8 due to transplant toxicity and 2 of progressive disease. Five of the ten patients transplanted before 2004 died of TRM contrasting with three of the 24 patients transplanted in 2004 or later (Hazard ratio of TRM=5.2, 95% CI, 1.2-21.9, p-value=0.02).

Conclusions

In children with high-risk relapse of ALK+ ALCL, allo-SCT is a valid therapeutic option. However, the high level of TRM raises the question of its place in the area of new-targeted agents. When allograft is required, reduced-intensity conditioning could help reducing toxicity in these heavily pre-treated patients.

O-103

Rhabdomyosarcoma

GENOME-WIDE EPIGENETIC AND COPY NUMBER ANALYSES IN RHABDOMYOSARCOMA

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Objectives

Rhabdomyosarcoma (RMS) is a common pediatric soft tissue sarcoma and histologically classified into two major subtypes, alveolar (ARMS) and embryonal (ERMS). Most cases of ARMS have a characteristic fusion between the *PAX3/PAX7* and *FOXO1* genes, and the ERMS subtype commonly harbors loss of heterozygosity (LOH) at 11q15. However, epigenetic alterations underlying the pathogenesis of RMS are largely unknown. To explore the epigenetic basis of RMS, we performed genome-wide micro array based methylation and copy number analyses in 30 cases with ERMS and 17 cases with ARMS.

Methods

DNA methylation microarray analysis of 50 RMS cases was performed using Infinium HumanMethylation450 BeadChip (Illumina). In addition, copy number analysis was performed using GeneChip® 100K/500K arrays and Cytoscan® (Affymetrix). To determine DNA methylation profiles, we selected probes with variance ranked in the top 1% for unsupervised clustering analysis.

Results

Unsupervised hierarchical clustering identified 4 distinct subtypes. Interestingly, these 4 subtypes were correlated with clinical features and genomic alterations, including fusion status and copy number gains of chromosomes 2 and 8, and 11q LOH. Most cases with fusion negative ERMS were classified as clusters 3 and 4, whereas all fusion positive cases were classified as either clusters 1 or 2. Importantly, among these clusters, cluster 4 was significantly associated with favorable outcome (Fisher's exact test p value < 0.002).

Conclusions

In our analyses, we could separate RMS cases into 4 distinct methylation subtypes which are associated with clinicopathological findings. Our integrated epigenetic analyses enhance our understanding of the genetic and epigenetic mechanisms underlying pathogenesis of RMS.

O-104

Rhabdomyosarcoma

THE ROLE OF PET-CT IN THE MANAGEMENT OF CHILDHOOD

RHABDOMYOSARCOMA: SYSTEMATIC REVIEW

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Objectives

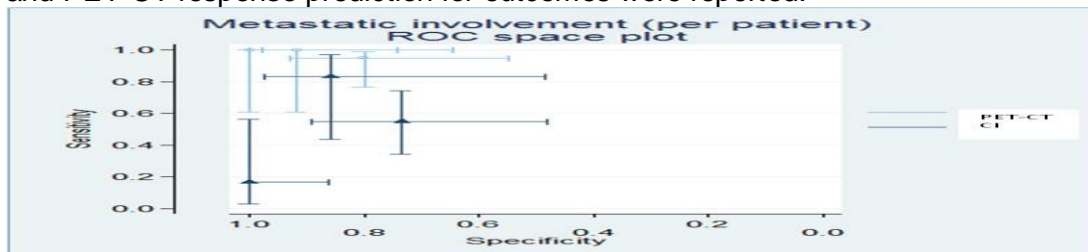
Rhabdomyosarcoma (RMS) has an incidence of 4.6 per million children and adolescents. Management depends on risk stratification. Current staging includes computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, and bone marrow biopsy. Advanced functional imaging has potential to improve staging accuracy and management strategies.

Methods

We conducted a systematic review (PROSPERO 2013:CRD42013006128) of the diagnostic accuracy and clinical effectiveness of functional imaging in histologically-proven paediatric RMS. Ten databases were searched to November 2013. Eligible studies compared positron emission tomography, with or without CT, or diffusion weighted (DWI) MRI to conventional imaging at any point in ≥ 10 RMS patients. Limited, heterogeneous data required narrative synthesis; sensitivity and specificity were plotted in receiver operating curve space.

Results

Eight studies (six PET-CT, two PET, with 272 RMS patients) were included. No studies of DWI-MRI met inclusion criteria. Pooled estimates were not calculated due to sparseness of data. Limited evidence indicated initial PET-CT results were predictive of survival. PET-CT was reported to change management of 7/40 patients in three studies. For nodal involvement PET-CT sensitivity ranged from 80% to 100% and specificity from 89 to 100%; for conventional imaging sensitivity was 67% to 86% and specificity 90% to 100%. For distant metastatic involvement PET-CT sensitivity ranged from 95% to 100% and specificity from 80% to 100% compared with sensitivity 17% to 83% and specificity 43% to 100% for conventional imaging. Very sparse data on particular metastatic sites and PET-CT response prediction for outcomes were reported.



Conclusions

PET/PET-CT may increase initial staging accuracy in paediatric RMS, specifically the detection of nodal involvement and distant metastatic spread. PET-CT should be further assessed in this population, ideally in a representative, unbiased and transparently selected patient cohort (i.e. those entering a randomised controlled trial of treatment).

Funding: Children's Cancer and Leukaemia Group (UK).

O-105

Rhabdomyosarcoma

THE ROLE OF DOXORUBICIN IN THE TREATMENT OF RHABDOMYOSARCOMA: PRELIMINARY RESULTS FROM THE EPSSG RMS2005 RANDOMIZED TRIAL

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Objectives

Doxorubicin is an effective drug against rhabdomyosarcoma (RMS), but its value when incorporated into an established multidrug regimen remains controversial. Previously, evidence for lack of benefit may have related to its use at low dose intensity. The EpSSG RMS2005 study incorporated a randomization to explore the benefit of early dose intensification with doxorubicin in high risk non-metastatic patients.

Methods

From June 2005 to October 2013, 481 patients (age >6 months, <21 years) were randomized between 9 cycles standard IVA (n=241) (ifosfamide 3g/m² day 1,2; vincristine 1.5mg/m² day 1, actinomycin-D 1.5mg/m² day 1) and IVADo (n=240), an experimental arm consisting of 4 cycles IVA with doxorubicin 30mg/m² on day 1,2 followed by 5 cycles of IVA. Tumor response was evaluated after the 3rd cycle and local treatment (surgery and/or radiotherapy) was delivered after the 4th cycle. The statistical plan was to randomize 500 patients in order to detect, with 80% power, a 35% relative reduction in events in the experimental arm (HR=0.65).

Results

An interim analysis was performed including 448 patients (223 IVA, 225 IVADo) with adequate follow up data. 134 patients had at least 1 event (65 IVA, 69 IVADo). At median follow-up 37 (14-56) months, 3-year event free survival was 67.2% (95% CI: 59.7–73.6) for IVA and 64.8% (95% CI: 57.3–71.2) for IVADo. 3-year overall survival was 83.0% (95% CI: 76.2–88.0) and 79.1% (95% CI: 72.3–84.5) respectively. Toxicity was greater with IVADo. Futility analysis led to a recommendation from the DMC to stop the randomization earlier than planned.

Conclusions

The addition of dose intense doxorubicin to standard chemotherapy failed to show an improvement in the outcome of patients with high-risk non metastatic RMS. The EpSSG RMS2005 trial continues to evaluate the role of maintenance therapy (cyclophosphamide/vinorelbine).

Supported by Città della Speranza Foundation

O-106

Rhabdomyosarcoma

ALVEOLAR RHABDOMYOSARCOMA WITH NODAL INVOLVEMENT, A GROUP WITH UNFAVOURABLE OUTCOME: EXPERIENCE OF THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA GROUP (EPSSG)

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Objectives

Alveolar rhabdomyosarcoma(aRMS) with nodal involvement(N1) accounts for up to 10% of all RMS. Results from most previous European co-operative studies suggested very poor survival (3-5 year EFS 25-39%), comparable to that of stage IV disease, although outcome was better in one more recent study (SIOP MMT95: 3yr EFS 57%). In the EpSSG RMS2005 protocol, aRMS/N1 received intensified initial chemotherapy (IVADo: ifosfamide, vincristine, dactinomycin, doxorubicin) and additional maintenance chemotherapy with systematic local treatment to primary and nodal sites.

Methods

98 aRMS/N1 patients (8.2% of all (n=1198) patients) were enrolled in EpSSG RMS2005 from October 2005 to October 2013. After primary surgery/biopsy, all received 4 cycles IVADo, 5 cycles IVA and 6-months maintenance therapy with cyclophosphamide and vinorelbine. Local treatment scheduled after IVADo included radiotherapy to primary site and/or nodes with or without secondary surgical resection of the primary and/or involved nodes.

Results

The incidence of adverse prognostic factors was high: 50% patients were >10 years age; 90% had gross residual disease (IRS Group III) after initial surgery/biopsy; 63% primary tumours were locally invasive (T2); 76% had primary size >5 cm and 82% occurred at unfavourable sites. At median follow-up of 49 months, 3-year EFS was 56.2% (95%CI: 44.2%-66.2%). Outcome data were available in 81 patients. Eight (10%) demonstrated refractory disease with early progression and died; 28 (34%) relapsed (22 after

completion of therapy) with median time to relapse 11.5 (11-18) months: 27/28 of these died.

Conclusions

Patients with aRMS/N1 may benefit from intensification of therapy although 10% fail to respond to initial chemotherapy and prospects for salvage of those who relapse are poor. Additional strategies are needed to further improve outcome for this high risk group and enrolment in phase I/II studies is justified for those who do not achieve early local control or who relapse.

O-107

Rhabdomyosarcoma

PROTON THERAPY FOR NON-METASTATIC RHABDOMYOSARCOMA: EARLY CLINICAL OUTCOMES

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Objectives

This study reports early toxicity and disease control in children with non-metastatic rhabdomyosarcoma (RMS) treated with proton therapy (PT).

Methods

From February 2007 through November 2013, 66 patients with a median age of 4.1 years (range, 0.6-15.3 years) were treated with PT for non-metastatic RMS. The most common primary sites were parameningeal (28), orbital (14), and bladder/prostate (13). The median tumor size was 5 cm (range, 2-15 cm). Thirty-six patients were Intergroup Rhabdomyosarcoma Study (IRS) stage 3 and 62 patients were IRS Group III. Patients received chemotherapy per the EPSSG RMS 2005 (n= 40) or contemporary COG (n= 26) protocols. The median interval between the start of chemotherapy and radiotherapy was 15 weeks (range, 3-60). The median follow-up is 1.5 years. Various patient and treatment factors were examined to identify predictors for disease control outcomes.

Results

The actuarial 2 year overall survival, progression free survival, local control, and freedom from distant metastases was 89%, 85%, 88%, and 94%, respectively. On multivariate analysis, tumor size > 5 cm, parameningeal site, and duration of induction chemotherapy >15 weeks were each associated with significantly lower rates for local control and progression free survival (p<0.05 for both). Of note, children with >5 cm parameningeal tumors had inferior rates of local control compared to all other tumors (54% vs 95%, p<0.002). Permanent toxicity was limited to 9 patients with cataracts, 1 patient requiring a unilateral hearing aid, and 4 patients requiring hormone replacement therapy.

Conclusions

To date, this is the largest cohort of children with RMS treated with PT. Early data suggests that highly conformal radiation does not compromise early tumor control or increase early toxicity in a group of young patients with unfavorable risk characteristics. Consistent with previous reports, we do not recommend delaying radiation beyond week 13 in patients with non-metastatic disease.

O-108

Rhabdomyosarcoma

**LONG-TERM EVALUATION OF ORBITAL RHABDOMYOSARCOMA IN CHILDREN:
THE INSTITUT CURIE EXPERIENCE**

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Objectives

Orbital rhabdomyosarcoma (ORMS) is associated with an excellent survival rate greater than 85%, and is considered to be a favorable site for this tumor. Treatment is based on combination chemotherapy together with best local therapy, sometimes surgery but more often radiation therapy. Local therapy is associated with frequent and potentially severe late sequelae and pediatric oncology groups have therefore tried for many years to reduce these sequelae without jeopardizing the outcome of ORMS in response to an adapted treatment strategy. A retrospective single-center analysis was set up in order to more clearly define the long-term status of ORMS survivors.

Methods

Among the 95 patients with localized ORMS treated at the Institut Curie between 1975 and 2010, 82 survivors were analyzed in this study.

Results

Median age at diagnosis was 6 years [range: 8 months – 19 years], and median follow-up was 8.5 years [range: 7 months -24 years]. The 5-year globe conservation rate was 90.4%. Ophthalmic dysfunction was present in 79% of patients. Impaired visual acuity (VA), defined by VA<20/20 on the affected eye, was present in 62% of patients; 38% of them had severe visual disability with VA<20/200. Late effects on orbitofacial structure were present in 39.8% of patients. Ocular or palpebral sequelae were present in 79% of survivors, mainly cataract (42%), ocular surface lesions such as keratoconjunctivitis (40%) and eyelid abnormalities (29%). General late effects were rare.

Conclusions

These data suggest that ocular and orbital late effects are frequent after treatment of ORMS, indicating the need for systematic long-term ophthalmologic follow-up of these patients. Radiation therapy is an important part of the total burden of therapy.

O-109

Retinoblastoma

THE DLX2 HOMEODOMAIN GENE REGULATES THE P107 TUMOUR SUPPRESSOR IN MOUSE RETINA DEVELOPMENT: IMPLICATIONS FOR MOUSE AND HUMAN RETINOBLASTOMA

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Objectives

Retinoblastoma is the most common malignant eye tumour of childhood. In humans, sporadic or germline mutations of the retinoblastoma gene Rb-1 are implicated in almost all cases. However, mutations of Rb-1 and either of its pocket protein family members, p107 or p130, are necessary to induce tumours in mouse models of the disease. The developmental regulation of p107 is relatively unknown. Dlx homeobox genes encode homeodomain-containing transcription factors expressed in ganglion cells, amacrine and horizontal cells of the embryonic and adult retina.

Methods

Chromatin immunoprecipitation (ChIP) was performed on embryonic mouse retina tissues (E18.5) using a polyclonal antibody to DLX2. Electrophoretic mobility shift assays (EMSA) were used to confirm specific protein:DNA interactions. Reporter gene assays were performed using luciferase reporter constructs containing the p107 promoter. p107 gene expression was assessed in the Dlx1/Dlx2 double knockout mouse (DKO). DLX2 expression was assessed in mouse models of retinoblastoma and human retinoblastoma samples.

Results

ChIP demonstrated that DLX2 occupies several regions of the p107 gene promoter in vivo. EMSA confirmed specific DLX2 transcription factor:p107 promoter DNA complexes in vitro. Co-expression of Dlx2 activated p107-luciferase promoter gene expression in vitro. p107 expression was reduced in the Dlx1/Dlx2 DKO mouse retina at E18.5. DLX2 was expressed in the nuclei of Chx10:Rb-p107 conditional DKO retinoblastoma as well as in almost all human retinoblastoma tissues we studied.

Conclusions

The homeodomain transcription factor DLX2 directly activates expression of the tumour suppressor p107, a member of the Rb pocket protein family essential for cell cycle regulation. Expression of DLX2 in both mouse and human retinoblastoma supports that these developmental tumours are partially differentiated and contributes to our knowledge regarding the cell of origin. Future studies will determine whether modulation of DLX2 expression regulates cell proliferation and differentiation of retinoblastoma.

O-110

Retinoblastoma

IMPACT OF RB1 MUTATION PRENATAL DIAGNOSIS ON CHILDREN AT RISK FOR RETINOBLASTOMA

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Objectives

Canadian Guidelines for Retinoblastoma Care¹ recommend testing infants for their affected parent's *RB1* mutation prenatally or at birth; infants carrying the *RB1* mutation may be delivered late pre-term [HD1] or near-term (36, 37 weeks gestation) to optimize opportunities for minimal impact treatment of small tumors. We evaluate effects of gestational age at first eye examination on outcomes of children carrying an *RB1* mutation.

Methods

We retrospectively studied infants carrying their family's *RB1* mutation, born between 1 June 1996 and 31 May 2013 and treated at SickKids. Information collected included: affected parent; sex; gestational age at birth, *RB1* testing and first eye exam; pregnancy or perinatal complications; type of sample tested and *RB1* mutation; locations of first and subsequent tumors; International Intraocular Retinoblastoma Classification and Tumour Node Metastasis staging; treatments delivered; last followup date; and overall and visual outcomes.

Results

Twenty infants carried their parent's *RB1* mutation, detected prenatally in 12 and after birth in 8. Nine were tested prenatally and electively delivered at 36-37 weeks gestation and 3 were spontaneously premature. All infants not tested prenatally were born at term. All newborn infants had weekly eye examinations. Vision-threatening tumors were present at birth in 25% (3/12) of infants delivered early or born prematurely and 75% (6/8) of full-term infants; posterior tumors appeared age 1 to 6 months in 9 infants. All patients eventually developed bilateral retinoblastoma. Good vision was maintained in all children born early; treatments included focal therapy (all) and later chemotherapy (5), stereotactic radiation and enucleation of one eye due to chemotherapy intolerance (1). Full-term infants received focal therapy (8), chemotherapy (5), and enucleation of one eye (2); bilateral macular tumors blinded one child.

Conclusion: Prenatal molecular detection and early delivery facilitated optimal outcomes.

1. National Retinoblastoma Strategy Canadian Guidelines for Care. Canadian Journal of Ophthalmology. 2009;44:S1-88.

O-111

Retinoblastoma

A PROSPECTIVE SINGLE INSTITUTION TRIAL USING TOPOTECAN BASED CHEMOTHERAPY FOR THE TREATMENT OF BILATERAL INTRAOCULAR RETINOBLASTOMA

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Objectives

To evaluate efficacy of systemic chemo-reduction using topotecan for advanced intraocular retinoblastoma.

Methods

27 newly diagnosed bilateral retinoblastoma patients (14 males, median age 7.9 months), worse eye Reese- Ellsworth (RE) group IV-V, received 11 cycles of chemotherapy: topotecan and vincristine (TV) x 2 followed by three alternating courses of carboplatin and vincristine x 2 and TV x 1. Intensive focal therapy was applied after the first 2 cycles. Event free survival (EFS) was defined as avoidance of external beam radiation (EBRT) and enucleation.

Results

Of 54 eyes, 42 were RE IV-V and 37 were International Classification (IC) C-E. 24 patients (89%) completed all prescribed chemotherapy; one was removed due to persistent viral infection and two had progressive disease requiring EBRT. All eyes received focal therapy. Seven patients received subconjunctival carboplatin during therapy, and six received plaque brachytherapy during follow-up. Eleven eyes were enucleated: one at diagnosis, nine with progressive disease including three eyes treated with EBRT, and one which developed neovascular glaucoma. At 8 years, cumulative incidence of EBRT was 2.4% (SE±2.4) and EFS for patients was 66.7% (SE± 38.5). Ocular survival for RE group IV-V eyes was 76.2% (SE±26.3) and 70% (SE± 27.0) for IC group D-E eyes. All patients experienced thrombocytopenia (41 episodes in 275 courses, 15%). There were 29 episodes of febrile neutropenia (10%). Fifteen patients had a documented source of infection (40% viral etiology). Grade 3 diarrhea was present in 9/27 patients, and one patient reacted to carboplatin. All patients are alive with median follow up was 7.4 years.

Conclusions

Topotecan combined with vincristine, carboplatin and aggressive focal therapies is an effective regimen for the treatment of advanced retinoblastoma (RE IV-V) that avoids radiation and results in globe salvage with measurable vision. Toxicities were anticipated and managed with appropriate supportive care.

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Retinoblastoma

TREATMENT OF RECURRENT OR PROGRESSIVE INTRAOCULAR RETINOBLASTOMA: PRELIMINARY RESULTS OF A NATIONAL PHASE II STUDY OF THE SWISS PEDIATRIC ONCOLOGY GROUP

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Objectives

To determine the effectiveness and safety of injections of Melphalan via the ophthalmic artery (SOAC), or into the vitreous cavity (IVC), or of periocular Topotecan (POT), as salvage therapies for recurrent/progressive retinoblastoma (Rb) according to the site of recurrence/progression. To evaluate the eye preservation rate after 3 courses of SOAC, 3 courses of IVC, 2 courses of POT (no enucleation and/or radiotherapy).

Methods

National single arm phase II prospective study including patients (pts) with recurrent/progressive Rb between 6 months and 15 years of age after failure to prior treatment (chemoreduction/focal therapy, plaque therapy, external beam radiation), with RetCam images and ultrasound biomicroscopy for identification of tumor-free meridian mandatory for IVC. Each patient was enrolled and evaluated only for one treatment arm. Response was evaluated after each treatment course for retinal tumors and/or vitreous seeds. Treatment was stopped at any time in case of progression, toxicity or parental refusal.

Results

Thirty-one pts were registered, 14 (4 with unilateral and 10 with bilateral disease) were eligible after failure to prior chemotherapy only (12) or chemotherapy/radiotherapy (2). Salvage treatment consisted of SOAC in 7, IVC in 5 and POT in 2 pts. Response was favorable in 3/7 SOAC, 5/5 IVC and 2/2 POT administrations. There was no enucleation or radiotherapy after a median follow-up of 7 months (1-16). Six out of 14 pts needed further treatment, 5 in the same eye (SOAC 1, IVC 1, combined SOAC/IVC 3), 1 in the contralateral eye (combined). Ocular hemorrhage in 2/14 eyes after SOAC was the worst adverse event observed, treated successfully with anti-VEGF.

Conclusions

In heavily pretreated Rb patients SOAC, IVC and POT are efficient in treating recurrent/progressive disease and preventing enucleation and/or radiotherapy. However, almost half of the treated eyes need further treatment for disease control. Treatment combinations should be considered in future.

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Retinoblastoma

EFFICACY OF SECOND COURSE OPHTHALMIC ARTERY CHEMOSURGERY FOR RETINOBLASTOMA THAT RECURS FOLLOWING PRIOR OPHTHALMIC ARTERY CHEMOSURGERY

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Objectives

Melphalan-based ophthalmic artery chemosurgery (OAC) has been highly effective for intra-ocular retinoblastoma, but some patients who achieve remission develop recurrence following completion of therapy. We aimed to evaluate the efficacy of second course OAC for such patients.

Methods

Single-arm, retrospective study of 32 eyes that underwent OAC at our centers between May 2006 and July 2013 and achieved remission, but suffered intra-ocular retinoblastoma recurrence at least 2 months off-therapy. Outcome measurements included Kaplan-Meier estimates of ocular progression-free survival (PFS) and ocular survival, and the Mantel-Cox test was used to compare curves.

Results

The eyes previously received a mean of 3.1 first course OAC infusions and developed off-therapy disease recurrence at a median of 4.4 months following completion of initial OAC. Median follow-up is 34 months following initiation of second course OAC. The Kaplan-Meier estimates of 2-year ocular PFS and ocular survival following second course OAC were 47.0% (95% confidence interval 27.8-64.0%) and 80.2% (95% confidence interval 58.5-91.3%), respectively. Presence of vitreous seeds (seen in 53% of eyes requiring second-course OAC) was significantly associated with inferior 2-year ocular PFS (33.6% [95% confidence interval 12.9-56.0%] versus 65.8% [95% confidence interval 32.0-85.8%]; $p=0.01$) and ocular survival ($p=0.01$). Factors not associated with ocular PFS included pre-OAC treatment history, age at initial OAC, early (<4.4 months) versus later recurrence, addition of new drug during second course OAC, and number of infusions during second course OAC.

Conclusions

Eyes with recurrent intra-ocular retinoblastoma following first course OAC treatment may be cured with second course OAC. However, a significant portion of the eyes may require additional therapy (third or fourth course OAC or other treatment modalities such as intra-vitreous chemotherapy), particularly if vitreous seeds are present at the time of initial OAC failure.

O-114

Retinoblastoma

AGE AND SITE-SPECIFIC RISKS OF SECOND MALIGNANT NEOPLASMS IN RETINOBLASTOMA SURVIVORS: A POPULATION-BASED STUDY

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Objectives

Retinoblastoma (RB) survivors have an increased risk of developing second malignant neoplasms (SMN). The aim of our study was to assess the site-specific, and age-specific risk of SMN among retinoblastoma survivors using population-based data.

Methods

We retrieved data from Surveillance Epidemiology and End Results (SEER) database (9 registries, 1973-2010). All children ages 0-19 diagnosed with RB (ICCC group V) were included in the study. Standardized incidence ratios (SIR) and corresponding 95% confidence intervals (95% CI) were calculated using SEERStat 8.1.2.

Results

Our cohort comprised 820 children with RB (mean age at diagnosis 1.8 years). 589 children (72.6%) had unilateral and 222 (27.4%) had bilateral RB. Thirty-one patients developed SMN (SIR=9.8, 95% CI 6.6-13.9). Children with bilateral RB had a higher risk of developing a head and neck second malignancy (HN-SMN) (n=12; SIR=93.7, 95%CI 48.4-163.8) than in other sites (n=14; SIR=23.2, 95%CI 12.7- 38.9). The observed increased risk of a HN-SMN was present even for those children with bilateral RB who did not receive RT (SIR=71.1, 95%CI 14.7-207.8), while a more modest risk of developing SMN at other sites was observed (SIR=22.2, 95%CI 7.2-51.8). Children with bilateral RB diagnosed < 1 year had higher risk of HN-SMN (RT: SIR= 168.8, 95%CI 72.9-332.6; Without RT: SIR=75.3, 95%CI 9.1-271.9) than those diagnosed > 1 year, corrected for use of RT (RT: SIR= 30.0, 95%CI 0.8-167.4; Without RT: SIR=64.0, 95%CI 1.6-356.7).

Conclusions

The risk of SMN among RB survivors is higher for patients diagnosed before one year of age. Children with bilateral RB are at an increased risk of SMN in the HN regardless of the use of RT. The need to use non-irradiating diagnostic studies of the HN should be emphasized.

O-115

CNS Tumours

INTEGRATED GENOMICS ELUCIDATES RELATIVE SPATIAL HOMOGENEITY OF PEDIATRIC BRAIN TUMORS

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Objectives

Comprehensive, genome-wide profiling and next-generation sequencing based studies have dramatically improved our understanding of pediatric brain tumor biology over the past decades. However, the vast majority of these studies are based on the assumption that single biopsies are representative for the entire primary tumor. Intratumor heterogeneity comprises a common phenomenon previously described in renal cell carcinoma, breast cancer, and glioblastoma multiforme. Highly disparate genetic profiles of spatially separated tumor areas within the same tumor may preclude development of personalized, molecularly targeted therapies based on single tumor biopsies.

Methods

To address this issue, we conducted multiregion whole exome sequencing, high-resolution DNA copy number analysis (Cytoscan HD) and DNA methylation profiling (Infinium HumanMethylation450 BeadChip) on over 25 distinct pediatric and adult brain tumors with a median of six spatially distant biopsies per tumor (range 4-9). Histological entities included ATRT (n=2), DIPG (n=2), ependymoma (n=1), glioblastoma (n=10), medulloblastoma (n=10), and medulloepithelioma (n=1). We assessed the degree of intratumor heterogeneity and subgroup affiliation using integrated genomics and unsupervised hierarchical clustering algorithms.

Results

Epigenetic signatures were highly similar from individual multiregion biopsies within a single tumor. However, we identified up to 250,000 CpG dinucleotides that were differentially methylated when comparing the intertumor heterogeneity of DNA methylation patterns even within disease subgroups. Further, pediatric brain tumors displayed highly similar focal and broad DNA copy number alterations unlike their adult counterparts. Multiregion sequencing further reinforced the relatively higher degree of intratumor homogeneity in pediatric brain tumors. Lastly, we showed that subgroup affiliation was stable in all multiregion biopsies from the same medulloblastoma.

Conclusions

Our results demonstrate that single biopsies are representative of the tumor genomics landscape and that subgroup affiliation of pediatric brain tumors is more stable than in their adult counterparts.

O-116

CNS Tumours

SPINAL MYXOPAPILLARY EPENDYMOMA EXHIBIT A 'WARBURG' PHENOTYPE

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Objectives

Myxopapillary spinal ependymomas are a distinct histological variant arising predominantly in the conus medullaris, cauda equina, or filum terminale. Despite a generally favorable prognosis, metastases, subarachnoid dissemination, and late recurrences have been reported. Currently, maximal safe resection is the only effective treatment for myxopapillary ependymoma. We characterized the genomic and transcriptional landscape of spinal ependymomas in an effort to delineate the genetic basis of this disease and identify new targets for therapy.

Methods

Gene expression profiling was performed on 35 spinal ependymomas using Affymetrix Gene 1.1ST microarrays, and on 16 spinal ependymomas using RNA seq. Copy number profiling was also performed on an overlapping cohort of 38 spinal ependymomas using Affymetrix SNP6.0 microarrays. Western blot analysis was used to confirm gene expression values. Functional validation experiments were performed on tumour lysate consisting of assays measuring pyruvate kinase M activity (PKM), hexokinase activity (HK), and lactate production.

Results

On a transcriptional level, we demonstrate that Grade II and myxopapillary spinal ependymomas are molecularly distinct. These findings are supported by subgroup-specific copy number alterations occurring in each histological variant. Pathway analysis revealed that myxopapillary ependymoma are characterized by metabolic networks, namely up-regulation of HIF-1a and its transcriptional targets. These findings were validated by western blot analysis demonstrating increased protein expression of HIF-1a, HK2, PDK1, and phosphorylation of PDHE 1a. Functional assays were performed on myxopapillary tumour lysates to demonstrate decreased PKM activity, increased HK activity, and elevated lactate production.

Conclusions

Our findings suggest that myxopapillary ependymoma may be driven by a Warburg metabolic phenotype, mediated by the HIF1a transcriptional network. The key enzymes promoting the Warburg phenotype: HK2, PKM2, and PDK are targetable by next-generation small molecule inhibitors/activators that inhibit glycolysis, and which should be tested in pre-clinical studies as therapy for myxopapillary ependymoma.

O-117

CNS Tumours

NEW INTRAOPERATIVE MONITORING OF CORTICOBULBAR MOTOR EVOKED POTENTIALS IN CHILDREN.

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Objectives

The motor function of cranial nerves (CN) can be continuously monitored by transcranial corticobulbar motor evoked potentials (CoMEPs) during neurosurgical interventions. While there are several publications of these new CoMEPs in adults, the feasibility and safety of CoMEPs in children has not yet been documented.

Methods

We included 13 consecutive procedures involving 12 patients (median age 2.5 y, range 1-15 y, 7 male) that were operated by the first author in 2013 and in whom CoMEPs were monitored. While most authors use a 50% reduction of CoMEP response amplitudes as a warning criterion, our approach was to keep the response amplitude constant by increasing the stimulation intensity and to establish a warning criterion based on the "threshold-level" method. For the facial nerve, a threshold increase greater than 20 mA for eliciting CoMEPs in the most reliable facial nerve target muscle was considered a prediction of reduced postoperative facial nerve function, and subsequently a warning was issued to the surgeon.

Results

Monitoring of CoMEPs was feasible in all 13 surgeries in at least one facial nerve target muscle. The mentalis muscle yielded the best result (89% of trials), followed by orbicularis oris (85%) and orbicularis oculi muscles (80%). The median stimulation threshold was initially 69 mA (range 40-100 mA) for CoMEPs and 60 mA (15-95 mA) for MEP of the thenar muscles. The initial CoMEP threshold exceeded the MEP threshold in 5/13 patients (median difference 5 mA). CoMEP deterioration showed specificity for HB deterioration of 88% CI [47-100%].

Conclusions

Intraoperative CoMEP monitoring is feasible and safe also in young children. We found no evidence that procedures and thresholds should differ from CoMEP in adults. CoMEP monitoring is a valid indicator of CN function in neurosurgery. It should be used as an adjunct to direct electrical CN stimulation and continuous EMG monitoring of CN target muscles.

O-118

CNS Tumours

REPORT FOR THE SIOP-CPT-2000 STUDY AND THE CURRENT SIOP-CPT REGISTRY

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Objectives

Analysis of clinico-pathological variables of patients with choroid plexus tumors (CPT) of all age groups and WHO grades recruited into an international registry and treatment outcomes according to risk-adapted treatment stratification.

Methods

The SIOP-CPT-2000 study (01/2000 - 03/2010) and the SIOP-CPT registry (04/2010 - 04/2014) have recruited 221 patients with reference reviewed CPT. A risk-adapted treatment algorithm stratified into an observational group for all non-metastatic classical plexus papilloma (CPP) and atypical plexus papilloma (APP), and a treatment group for all metastatic CPT, incompletely resected APP and all choroid plexus carcinoma (CPC). SIOP-CPT-2000 patients older than 3 years diagnosed with CPC received primary focal irradiation.

Results

Median age at diagnosis was 2.7/ 0.64/ 2.11 years for CPP/ APP/ CPC with equal gender distribution. Primary location for all CPT was the lateral ventricles without right/left preference. With increasing age, CPP localized more frequently to the IVth ventricle. CPC did not occur exclusively within the IIIrd ventricle. Primary metastasis were recognized in 10/ 14 / 20 % of all CPP/ APP/ CPC. Germline mutational analysis identified 8 patients with Li-Fraumeni syndrome. The median follow-up time for 130 SIOP-CPT-2000 study patient was 5.5 years. The 5-year overall survival / 5-year event-free survival was 100/ 97% for CPP (n=48), 96/ 85% for APP (n=37) and 50/ 38% for CPC (n=45). Extended follow up showed no difference between a carboplatin based regimen compared to a cyclophosphamide based regimen. The cumulative incidence for secondary neoplasm was comparable to infant brain tumor populations with different histologies. Nuclear accumulation of p53 showed no prognostic impact.

Conclusions

Adjuvant treatment improved outcome of high grade choroid plexus tumors. Carboplatin as well as cyclophosphamide based regimens are equally effective. WHO grade is the most significant prognostic marker.

Acknowledgement: Funded by the German Childhood Cancer Foundation (DKKS)

O-119

CNS Tumours

IS RE-VACCINATION UPON A NEW EVENT IN PATIENTS WITH HIGH-GRADE GLIOMA USEFUL?

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Objectives

Multimodal strategies are developed to treat patients with high grade glioma (HGG). Active specific immunotherapy rapidly emerges as a new treatment modality. We provide immunotherapy for adults with primary diagnosis of GBM (HGG-2006) and for children/adults with relapsed HGG (HGG-IMMUNO-2003). In this retrospective analysis, we questioned whether second immunotherapy upon a new event was useful in patients who already got immunotherapy for their disease.

Methods

35 patients were treated with two vaccination treatments, 12 adults (26-69y) with primary diagnosis of GBM and 23 patients (7-55y) with relapsed HGG at time of first immunotherapy. At both times, leukapheresis was performed and DCs were loaded with lysate of the newly resected tumor tissue.

Results

HGG-2006 patients treated with two immunotherapies had a median OS of 41.8m versus 14.8m in HGG-2006 patients (n=68) treated with one immunotherapy program. The age distribution of the former was younger than of the latter group. Similarly, HGG-IMMUNO-2003 patients treated with two immunotherapies had a median OS of 32m versus 11m in HGG-IMMUNO-2003 patients (n=163) with one immunotherapy program. The age of the former patient group was younger, and their HGG-IMMUNO-RPA risk profile was better. The time interval between the first and second leukapheresis was longer in the HGG-2006 than the HGG-IMMUNO-2003 patients. All second immunotherapy approaches were similar. There were less injections during second immunotherapy as compared to the first immunotherapy. The number of injections was similar to the numbers given to HGG-IMMUNO-2003 patients who got first vaccination at time of relapse. The OS calculated from the second leukapheresis in re-vaccinated patients was similar as the OS observed in HGG-IMMUNO-2003 patients treated for the first time at relapse. Second immunotherapy was feasible, and no extra vaccine-related toxicities were observed.

Conclusions

These retrospective results show that second immunotherapy is worth to be considered along the disease course of patients with HGG.

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CNS Tumours

ADULT SURVIVORS OF CHILDHOOD CNS TUMOURS: THEIR SELF-PERCEIVED MOST PROMINENT ILLNESS- AND TREATMENT-RELATED LATE EFFECTS, DIFFICULTY OF SEQUELAE, AND SURVEILLANCE NEEDS

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Objectives

As part of the longitudinal Swedish childhood CNS tumour LIFE study, this study aimed at identifying self-perceived most prominent late-effects (SPLEs) among very long-term survivors (VLTs), and the extent to which sequelae were experienced as disabling. SPLEs were analysed in relation to self-perceived needs of -, and current involvement in clinical follow-up.

Methods

The study targeted an entire cohort of 706 Swedish 24-46 years old (mean=32) VLTs diagnosed 1982-2001. SPLEs data were collected using a study-specific questionnaire in the second wave of data collection, while single predictor factor data emanate from prior wave 6 years earlier. SPLEs were in this study addressed in open-ended question format, and ratings of their difficulty using 5-point Likert-scale response format. Data were analysed quantitatively and qualitatively.

Results

Three hundred thirty, 65.7%, of 507 data-providing survivors, reported prevalence of one to several SPLEs. Sixteen identified categories of problems, experienced by ≥ 20 survivors, covered a range of SPLEs of medical, neurological, neurosensory, or neuropsychological origin. Most prevalent sequelae involved one or several of *vision, balance, endocrinopathy, fatigue, hearing, pain, memory, and seizures/epilepsy*. SPLEs were experienced as harmless by 7.4%; somewhat, clearly, very difficult by 33.4%, 28.5%, and 24.8% respectively; and completely disabling by 5.9%. Occurrence and severity varied with diagnosis age, gender, sub-diagnosis, and whether past cancer treatment included radiation therapy or not. Of 132 survivors with considerable to entirely disabling SPLEs. and who experienced need of surveillance/follow-up, 21% lacked access to such. As expected, health status 6 years earlier predicted SPLEs later in life.

Conclusions

A majority of CNS tumour VLTs experience late effects that intrude upon functioning and quality of survival. Open-ended enquiry reveals subjectively experienced prominent difficulties, and informs about their perceived manageability. Today, as many as 1 of 5 studied CNS tumour VLTs may lack required specialised surveillance in life-long follow-up.

O-121

New Drugs

AALL07P1: BORTEZOMIB WITH REINDUCTION CHEMOTHERAPY FOR FIRST RELAPSE PEDIATRIC ALL. A CHILDREN'S ONCOLOGY GROUP STUDY.

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Objectives

Bortezomib (bortez) is a reversible inhibitor of the 26S proteasome. Promising results were reported adding bortez to reinduction chemotherapy in patients (pts) with ALL in 2nd or later relapse (Messinger, Blood 2012). The primary objective of this study was to compare CR2 rates at the end of block 1 to historical control CR2 rates. Biology objectives included assessment of NF-κB and proteasome activity.

Methods

This phase 2 study of bortez with reinduction chemotherapy in 1st relapse pediatric ALL enrolled pts with either pre-B ALL, T-cell ALL or T cell lymphoblastic lymphoma (T-LL). This report summarizes results from 99 evaluable pre-B ALL pts ≤21 yrs old, either <18m (stratum 1) or 18-36m (stratum 2) from diagnosis, and 22 evaluable T-cell ALL patients. Initial therapy consisted of bortez (1.3 mg/m², days 1, 4, 8, and 11) with reinduction chemotherapy (vincristine, prednisone, PEG-asparaginase, doxorubicin). CR2 rates were determined at the end of the first 5-week therapy block. We compared CR2 to the historical control study AALL01P2.

Results

121 evaluable ALL pts were assessed. Toxicities included 18 Grade 3-4 hypotension, 8 Grade 3-4 typhilitis, 5 Grade 3-4 pancreatitis, 5 Grade 3 sensory/motor peripheral neuropathy, and 4 Grade 3-4 enterocolitis. There were 3 deaths due to infection. Although Grade 3-4 infections were not infrequent (54 infections in 44 patients in block 1 and 13 infections in block 2) there were no reports of respiratory distress syndrome or Grade 4 peripheral neuropathy. 63 of the 99 pre-B patients (27/45 (60%) in Stratum 1 and 36/54 (67%) in stratum 2) attained CR2 at the end of block I. 15/22 (68%) patients with T-cell ALL also achieved CR2. The study met its primary response objective.

Conclusions

The addition of bortezomib to ALL reinduction therapy appears quite effective and is worthy of further study in pediatric ALL. Clinical trial information: NCT00873093.

O-122

New Drugs

THERAPEUTIC EFFECTS OF ROMIDEPSIN, A HISTONE DEACETYLASE INHIBITOR (HDACI), ALONE AND IN COMBINATION WITH NATURAL KILLER CELLS AGAINST PEDIATRIC BURKITT LYMPHOMA

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Objectives

The outcome for children with Burkitt Lymphoma (BL) has improved significantly but for patients who relapse or progress, the prognosis is dismal due to chemo-radiotherapy resistance (Cairo, *J Clin Oncol*, 2012). Our group has successfully engineered expanded peripheral blood Natural Killer cells (exPBNK) cells with an anti-CD20 chimeric antigen receptor (CAR⁺ exPBNK) to target relapsed/resistant CD20⁺ BL (Chu & Cairo, *ASH*, 2013). Romidepsin, a histone deacetylase inhibitor, enhances NKG2D ligand expression on tumor cells (Chu & Cairo, *EMBT*, 2013). We investigated the anti-tumor effect and mechanisms of Romidepsin against BL; and the combination effect of Romidepsin with CAR⁺ exPBNK cells against CD20⁺ BL cells in NSG mice.

Methods

CD20⁺ BL cells were treated with 10ng/ml Romidepsin, provided by Celgene. Cell viability, MICA/B expression, cell cycle, and signal pathway changes were analyzed by flow cytometry. Raji-Luc or Raji-2R-Luc cells were injected into NSG mice. CAR⁺ exPBNK, Romidepsin or combination was given to each mouse once a week for 3 weeks. The cumulative luciferase signals and tumor size were measured with the IVIS-200 system and caliber.

Results

Romidepsin induced strong cell death in rituximab rsensitive Raji (p We further found MICA/B expression was significantly enhanced in Romidepsin treated BL cell lines (p⁺ exPBNK cells combined with Romidpesin significantly increased the survival of Raji-Luc xenografted NSG mice compared to the controls (p<0.01).

Conclusions

Romidepsin has dual-therapeutic effects in BL by inducing cell death, cell cycle arrest, and enhancing CAR⁺ exPBNK cytotoxicity against CD20⁺ BL.

O-123

New Drugs

CLOFARABINE IN COMBINATION WITH HIGH-DOSE CYTARABINE AND LIPOSOMAL DAUNORUBICIN IN PEDIATRIC AML: RESULTS OF A PHASE 1 COMBINATION STUDY BY THE ITCC CONSORTIUM

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Objectives

Relapsed/refractory pediatric AML has a poor prognosis despite salvage therapy including stem-cell transplantation. Chemotherapy using FLAG plus liposomal daunorubicine (FLAG-DNX) is currently considered the standard in 1st relapse in Europe. FLAG is based on potentiation of cytarabine (Ara-C) by fludarabine (Flu) by increasing Ara-CTP levels. Clofarabine (CLO) is a novel purine nucleoside analog, designed to have improved efficacy.

Methods

We initiated an ongoing phase 1B dose-escalation study using a '3x3 design' to define the optimal dose of CLO, replacing FLU in FLAG-DNX. Dosages consisted of Ara-C 2gr/m²/day (day 1-5), with escalation of DNX from 40, 60 to 80 mg/m²/day (day 1, 3 and 5), and CLO from 20, 30 to 40 mg/m²/day (day 1-5) in 5 dose-levels, without GCSF priming. At day 6 intrathecal Ara-C was administered. Serum and CSF were collected for pharmacokinetics (PK). CLO plasma and CSF concentrations were analyzed using LC-MS/MS.

Results

We report safety and PK data on all dose levels after accrual of 33 AML patients. Patients were treated at 5 dose-levels (DL). Updated results and DLTs will be presented at the meeting.

PK samples were available from 19 patients. At day 1 the median AUC was 28 ng/ml.mg.hr (range 6-401), with a mean T1/2 of 1.5 hrs. Day 1 and day 5 results were similar. CSF levels were not measurable in most patients and were 0.1-0.2 ng/ml.mg in the 3 patients with detectable levels.

Conclusions

The RP2D of CLO in a CLARA/DNX course in relapsed/refractory pediatric AML is 40 mg/m², excluding patients with evidence of prior subclinical aspergillus. There is no evidence for PK interaction between CLO and the other drugs. We are currently testing the safety of an augmented dose of DNX (80 mg/m²) in 1strelapse AML patients (n=4). Responses are centrally reviewed and will be disclosed at the meeting.

O-124

New Drugs

BLINATUMOMAB IN PEDIATRIC PATIENTS WITH RELAPSED/REFRACTORY (R/R) B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (BCP-ALL): A PHASE 1/2 STUDY

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Purpose/Objective:

Blinatumomab, a bispecific T-cell engaging (BiTE®) antibody, has demonstrated activity in adults with r/r ALL. In the phase 1 part of this phase 1/2 study, the optimal blinatumomab dose was evaluated in children with r/r BCP-ALL.

Materials and Methods:

Eligible patients (

Results:

41 patients received a median (range) of 2 (1 to 5) cycles. 83% of patients had refractory disease or relapses after hematopoietic stem cell transplantation (HSCT), 17% had relapses without prior HSCT. Dose-limiting adverse events (AEs) were grade 4 cytokine release syndrome (CRS) with gastrointestinal hemorrhage (15 µg/m²/day), 2 instances of CRS (grades 4 and 5; 30 µg/m²/day), and grade 5 respiratory failure (15→30 µg/m²/day). The MTD was 15 µg/m²/day. To mitigate CRS, stepwise dosing of 5 µg/m²/day for 7 days then 15 µg/m²/day was subsequently evaluated (18 patients). At this dose, 1 patient developed CRS (grade 3). Across all doses, the most common AEs regardless of causality included pyrexia (71%), headache (37%), and hypertension (32%). One patient permanently discontinued treatment due to a grade 3 seizure. Within the first 2 cycles, the overall remission rate was 37%; 30% achieved minimal residual disease (MRD) negativity. 5 and 9 patients achieved response by days 15 and 29, respectively. 8/15 responders received HSCT during CR (MRD-negative=7; MRD-positive=1); 7/15 did not (MRD-negative=5; MRD-positive=2).

Conclusions:

In phase 1 of this study, 15 µg/m²/day was established as the MTD. CRS was dose-limiting but could be ameliorated with stepwise dosing (5→15 µg/m²/day). 53% of responders underwent HSCT following blinatumomab treatment.

O-125

New Drugs

PHASE I STUDY OF THE CDK4/6 INHIBITOR LEE011 IN PATIENTS WITH MALIGNANT RHABDOID TUMORS OR NEUROBLASTOMA

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Objectives

The majority of malignant rhabdoid tumors (MRTs) have *SMARCB1* mutations and are dependent on cyclin D1 (*CCND1*) for genesis and survival. Genetic aberrations in *CCND1* and *CDK4* are frequent in neuroblastoma cell lines. LEE011, an orally bioavailable, selective inhibitor of CDK4/6, demonstrated tumor growth inhibition in MRT and neuroblastoma models. This multicenter, Phase I, dose-escalation study evaluated LEE011 in patients with MRT, neuroblastoma, or other cancers with documented cyclin D–CDK4/6–INK4a–Rb pathway aberrations.

Methods

Patients (aged 1–21 years) receive once-daily LEE011 for 21 days of 28-day cycles in a dose-escalation fashion using a Bayesian Logistic Regression Model with overdose control. Primary objective: maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) determination. Secondary objectives: safety, pharmacokinetics, efficacy. This study was approved by local institutional review boards/ethics committees and patients/guardians signed written informed consent.

Results

As of February 27, 2014, 20 patients (10 MRT [eight primary central nervous system (CNS) and two extra-CNS], nine neuroblastoma, and one *CDK4*-amplified alveolar rhabdomyosarcoma) have received LEE011: five at 280 mg/m²; nine at 350 mg/m²; six at 470 mg/m². Median age: 4.5 (range: 1–20) years. Two dose-limiting toxicities were reported: one Grade (G)3 fatigue at 280 mg/m²; one G4 thrombocytopenia at 470 mg/m². Study drug-related AEs (n=17) (all grade >20%, G3/4 [all]) included neutropenia (65%, 59%), leukopenia (53%, 24%), thrombocytopenia (29%, 24%), anemia (24%, 0), lymphopenia (24%, 12%), vomiting (24%, 0), fatigue (18%, 6%), and decreased appetite (12%, 6%). Preliminary pharmacokinetic data suggest exposure is similar to that in adults at 280 and 350 mg/m² and slightly higher at 470 mg/m². LEE011 demonstrates rapid absorption (1–4 hours; median T_{max}=2 hours). Currently, best response is stable disease.

Conclusions

LEE011 demonstrated an acceptable safety profile and dose-dependent pharmacokinetics. Enrollment continues to identify the MTD/RDE with expansion arms for patients with MRT or neuroblastoma at the RDE.

O-126

New Drugs

A PHASE I STUDY OF RACOTUMOMAB IN NEUROBLASTOMA AND OTHER REFRACTORY MALIGNANCIES

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Objectives

To evaluate the toxicity and maximum tolerated dose, and secondarily immunological response, of an anti-idiotypic vaccine targeting N-glycolylated gangliosides including N-glycolyl GM3 (NGcGM3): racotumomab, formerly known 1E10, as a candidate for immunotherapy.

Methods

A Phase I study enrolling children with relapsed or resistant neuroblastoma and other neuroectodermic tumors was carried out, due to the expression of NGcGM3 in those tumors. Dose was escalated into 3 levels (0.15 – 0.25 – 0.4 mg) of racotumomab administered intradermally. Each drug level included 3 patients receiving a total of 3 doses, every 14 days; with clinical, radiologic and laboratory evaluations at 30 and 60 days after the last dose was administered. A confirmation cohort was added to the higher dose level. Antibody response was assessed upon study entry and at 4-week intervals for at least 3 immunological determinations for each patient.

Results

14 patients were enrolled (10 with neuroblastoma, 1 with retinoblastoma, 1 with Wilms tumor and 2 with brainstem glioma). 3 patients were included in each dose-level and 4 in the confirmation cohort. One patient died of tumor progression before completing the 3 applications. The remaining patients completed the applications scheduled.

Racotumomab was well tolerated. The most common local side effects included grade 1 erythema, induration, and local mild pain at the injection site. Racotumomab elicited an antibody IgM and/or IgG response directed to NGcGM3 in 9 patients, and IgM against racotumomab in 11 of 13 evaluable patients. The maximum tolerated dose was not reached and no dose-limiting toxicity was seen. No antitumor activity was evident in any patient.

Conclusions

Racotumomab vaccination showed a favorable toxicity profile up to a dose of 0.4 mg, and most patients elicited an immune response. Its activity as immunotherapy for neuroblastoma will be tested in further clinical trials.

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Leukemia, MDS and Bone Marrow Transplantation

ETV6 MUTATIONS AND DELETIONS IN PEDIATRIC ACUTE MYELOID LEUKEMIA

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Objectives

The ETS-Variant gene 6 (*ETV6*) encodes a transcription factor that acts as transcriptional repressor required for hematopoiesis of all lineages. In pediatric and adult acute lymphoblastic leukemia (ALL), and adult acute myeloid leukemia (AML) *ETV6* mutations and deletions that lead to silencing of the *ETV6* gene have been described. However, the prevalence of such alterations in pediatric AML has not been fully addressed.

Methods

We aimed to determine whether *ETV6* mutations and deletions are recurrent by screening for mutations in exons 2-8 with direct sequencing and for deletions by multiplex ligation-dependent probe amplification, and analyzed outcome parameters.

Results

In a cohort of 275 pediatric AML patients with available gene-expression data (median age 9.6 years, median white blood cell count (WBC) $46.7 \times 10^9/L$, and 5-yr pOS $62 \pm 3\%$), we found 6 patients (2.2%) with mutations affecting the predicted amino acid sequence of *ETV6*. Three cases showed a heterozygous insertion resulting in a frame shift and shorter predicted amino acid length, while 3 had point mutations leading to an amino acid change. In addition, *ETV6* deletions were found in 4/257 (1.6%) patients. The median age of patients with an *ETV6* gene alteration was 11.3 years (4.0-15.3) and median WBC $15.1 \times 10^9/L$. The 5-yr pOS was $17 \pm 15\%$, 6/10 patients encountered a relapse and 1/10 died in complete remission, demonstrating poor clinical outcome. Other cytogenetic aberrations were *RUNX1/RUNX1T1* (n=3), *PML/RARA* (n=1), *MLL/AF6* (n=1) and one *NPM1*-mutant. Previously, functional *ETV6*-silencing in T-ALL demonstrated up-regulation of genes, such as *CLDN5* and *BIRC7*, and high expression of *BIRC7* has been associated with poor prognosis in acute leukemia. In patients with an *ETV6* mutation (n=6) or deletion (n=4) 13 and 38 genes, respectively, were significantly up-regulated, including *CLDN5* and *BIRC7*.

Conclusions

We conclude that *ETV6* mutations and deletions are rare but recurrent in pediatric AML and may associate with poor prognosis.

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**Leukemia, MDS and Bone Marrow Transplantation
PRODUCTION AFFECTING CYTOKINE GENE VARIANTS AS BIOMARKERS OF
POST ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION
COMPLICATIONS**

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Objectives

Complications of hematopoietic cell transplantation (HCT), mainly graft-vs-host disease (GVHD) and infections are substantial and are the leading causes of morbidity and mortality. Cytokines act as chief mediators/regulators of immune responses. Genetic control of cytokine production is evidenced by polymorphisms in cytokine gene regulatory regions resulting in low, moderate, or high cytokine production. Here, we investigated the impact of cytokine gene variants on allogeneic HCT outcomes.

Methods

A total of 240 adult and 55 pediatric allo-HCT donors and 50 healthy individuals were analyzed for 22 single nucleotide variants located in the regulatory and/or exonic regions of 13 cytokine or cytokine receptor genes. Genotyping was performed by sequence-specific primer based assay. PBMNCs from healthy individuals were stimulated with CMV lysate, CMV peptide and SEB to enumerate CMV specific immune response.

Results

Allo-HCT donors carrying low producing IL-10 genotypes have high incidence of both acute GVHD grades II-IV ($p=0.001$, HR=2.3), and chronic GVHD ($p=0.01$, HR=1.7). 28% vs 76% of HCT recipients developed significant GVHD when they received graft from donors carrying high vs. low IL-10 producing genotypes respectively ($p=0.01$, OR=8.167). Further, allogeneic HCT performed with donors carrying low producing IL-1R genotype showed high rates of CMV reactivation ($p=0.01$, HR=2.3), recurrent CMV infection ($p=0.001$, HR=3.9) and low counts of CMV-specific T cells.

Conclusions

Genetic predisposition to low IL-10 production and that to low production of IL-1R are strong predictors of GVHD and post HCT CMV complications respectively. These results implicate the importance of assessment of cytokine gene variants in developing new algorithm for improved allogeneic HCT donor selection.

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Leukemia, MDS and Bone Marrow Transplantation

OUTCOME OF CHILDHOOD ACUTE PROMYELOCYTIC LEUKEMIA(APML) TREATED WITH SEQUENTIAL ARSENIC TRIOXIDE(ATO) AND ALL TRANS RETINOIC ACID (ATRA) BASED THERAPY:A RETROSPECTIVE STUDY FROM A TERTIARY CARE CENTRE

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Objectives

To study the clinical profile and outcome of children treated with a novel protocol using sequential ATO and ATRA based chemotherapeutic regimen in APML.

Methods

Children <15 years of age with APML diagnosed between March-2009 and February-2014 were retrospectively analyzed. Patients received induction with ATO (8 weeks) along with oral prednisolone, etoposide and thioguanine (PET); consolidation with ATRA and anthracycline; followed by 4 monthly cycles of maintenance with ATO+PET/ four 3monthly cycles of ATRA (Total treatment duration 18months).

Results

Forty four patients were registered during this period (Median age-9years, range 2-14years, M:F-3:1). Presenting symptoms were fever (75%), mucosal bleeding (32%), cutaneous bleeding (32%) and CNS bleed (18%). 42% patients had WBC counts >10,000/mm³ and 33% had >25,000/mm³. As per Sanz risk stratification, 16% had low, 34% intermediate and 50% high risk disease. 7 patients were not evaluable (3 died before starting induction, 4 still on induction). Out of 37 evaluable patients who received induction, 4 expired (2 CNS bleed, 1 pulmonary bleed, 1 infection). Rest all (89.2%) achieved CR. During induction, 5 developed differentiation syndrome, 1 pulmonary bleed, 2 fungal pneumonia, 2 asymptomatic QT prolongation. Except for initial phase of induction, no patient required admission or blood/platelet support. Post consolidation, all except one achieved complete cytogenetic and molecular remission. At median follow up of 22.2 months (range:3-59months), 1 high risk patient relapsed, 1 patient in CR died at home of uncertain cause. The EFS is 86.5 % (HR:94.4%, IR:69.2%, LR:100%) with DFS of 94.6%(HR:94.4%, IR:92.3%, LR:100%).

Conclusions

Sequential use of both ATO and ATRA showed a favorable outcome with minimal toxicity in pediatric APML with minimal supportive care need. This novel protocol is able to achieve a very high rate of EFS in high risk patients. Bleeding rather than relapse continues to be important cause of treatment failure in APML.

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Leukemia, MDS and Bone Marrow Transplantation

GSTA1 HAPLOTYPES INFLUENCE CLEARANCE OF INTRAVENOUS BUSULFAN AND OCCURRENCE OF SINUSOIDAL OBSTRUCTIVE SYNDROME IN CHILDREN UNDERGOING HSCT ON BEHALF OF THE PDWP OF THE EBMTGROUP

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Objectives

Intravenous Busulfan (BU) based conditioning regimens are widely used in children undergoing hematopoietic stem cell transplantation (HSCT). Assessment and prediction of inter-individual differences in BU pharmacokinetics (PKs) are important since BU has narrow therapeutic window. BU is mainly metabolized by glutathione S-transferase alpha1 (GSTA1). We recently reported the relationship between GSTA1 haplotypes with first-dose BU PKs, and the relationship with HSCT outcomes in 69 children receiving myeloablative conditioning regimen in UHCSJ. To validate these observations further we have extended our analysis to include 135 children diagnosed with malignant and non-malignant conditions recruited at 5 different centres.

Methods

All patients received IV BU in 16 doses, with first dose decided based on age. BU plasma levels were measured by HPLC or LC-MS/MS methods and majority of the patients were dose-adjusted to have a steady state concentration of 600-900 ng/ml. Genotyping of GSTA1 promoter variants at -69, -513, -631 and -1142 loci and inferred haplotypes were analyzed, for their association with BU PKs and occurrence of sinusoidal obstructive syndrome (SOS).

Results

In accordance with its suggested functional role *GSTA1**A2 haplotype was associated with lower BU levels and higher BU clearance ($P \leq 0.02$), with apparent influence in female patients. Higher incidence of SOS was observed in *GSTA1**B haplotypes carriers ($P=0.02$), and this association was also potentiated in female patients ($P=0.003$).

Conclusions

These results confirm our prior observations and support the possibility to tailor the first BU dose according to *GSTA1* haplotype status. We also demonstrate the possibility of segregation of patients at higher risk for SOS development based on *GSTA1* haplotype status.

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Leukemia, MDS and Bone Marrow Transplantation

APPLICATION OF BONE MARROW (BM) AND PERIPHERAL BLOOD (PB) FOR MINIMAL RESIDUAL DISEASE (MRD) MONITORING IN INFANTS WITH MLL-REARRANGED ALL ENROLLED INTO MLL-BABY PROTOCOL

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Objectives

To estimate prognostic significance of MRD in BM and PB by qualitative detection of different *MLL* fusion gene transcripts (FGt) in infants with ALL treated by MLL-Baby protocol.

Methods

Fifty three infants (20 boys and 33 girls) and with defined *MLL* rearrangements were included in the current study. Median age was 5.3 months (range 0.03-11.80). MRD detection was performed from BM and PB samples by real-time PCR and nested RT-PCR with sensitivity non-less than 1E-04. MRD-negativity was defined as absence of FGt in the both assays. Median of follow-up period in the observed group was 5.2 years. TPs for MRD assessment were as follows: day 15 of remission induction (time point (TP) 1), at the end of remission induction (TP2), after each course of ATRA administration (TP3-TP9).

Results

We estimated 142 paired BM/PB samples. Among them 79 samples were double positive, 41 were double negative. Thus concordance between MRD results in BM and PB samples achieved 84.5%. All discrepant results (22 samples, 15.5%) were BM-positive/PB-negative. MRD-positivity at TP4 in BM led to unfavorable outcome. EFS was significantly lower in MRD-positive group in comparison to MRD-negative one (9.9±6.1% vs 75.9±8.0%, p=0.001). MRD-positivity at this TP in BM was the only significant factor in the diagnostic model where initial risk factors (age at diagnosis, initial WBC count, immunophenotype, CNS disease, presence of *MLL-AF4*) were combined to response criteria (number of blast cells at day 8) (Table). We could not find any TP when MRD data obtained from PB samples had prognostic values.

Parameters	Patients	Events	Univariate analysis	p	Multivariate analysis	p
			Hazard ratio (95% CI)		Hazard ratio (95% CI)	
Age (mo)						
≥6 mo	22	8	Reference	0.059	Reference	0.513
<6 mo.	31	19	2.179 (0.949-5.005)		1.393 (0.515-3.765)	
Immunophenotype						
BI-ALL	36	16	0.746 (0.346-1.610)	0.623	1.611 (0.405-6.416)	0.499
BII-ALL	8	7	2.136 (0.899-5.077)	0.079	1.225 (0.274-5.469)	0.790
BIII-ALL	9	4	0.703 (0.242-2.041)	0.514	1 (-)	-
MLL-AF4						
Absence	28	16	Reference	0.685	Reference	0.529
Presence	25	11	0.853 (0.396-1.840)		0.752 (0.311-1.821)	
Initial WBC count						
<100*10 ⁹ /L	29	11	Reference	0.019	Reference	0.995
≥100*10 ⁹ /L	24	16	2.443 (1.129-5.285)		0.996 (0.338-2.934)	
Initial CNS disease						
Absence	33	12	Reference	0.004	Reference	0.071
Presence	19	15	2.995 (1.382-6.493)		2.187 (0.936-5.114)	
Absolute blast cell on day 8 of dexamethasone administration						
<1000	46	21	Reference	0.096	Reference	0.993
≥1000	7	6	2.131 (0.856-5.304)		0.996 (0.364-2.722)	
MRD-positivity at TP4 in BM						
Absence	31	7	Reference	0.001	Reference	0.001
Presence	22	20	7.181 (3.002-17.177)		7.326 (2.378-22.565)	

Conclusions

Despite high qualitative concordance rate between BM and PB samples we could not show prognostic significance of MRD monitoring by FGt detection in PB. Univariate and multivariate analysis revealed that MRD-positivity at TP4 in BM was significant and independent prognostic factor of unfavorable outcome.

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Leukemia, MDS and Bone Marrow Transplantation
GENETIC AND METABOLIC DETERMINANTS OF METHOTREXATE INDUCED
MUCOSITIS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

Methotrexate (MTX) is an important and effective chemotherapeutic drug in the treatment of pediatric acute lymphoblastic leukemia (ALL). However MTX can induce toxicity, which can lead to amendments of treatment and subsequent impaired survival. The aim of this study was to identify metabolic and genetic determinants of MTX toxicity.

Methods

In this prospective study, 134 Dutch pediatric ALL patients were treated with four high dosages MTX (HD-MTX: 5 g/m²) every other week according to the DCOG-ALL10 protocol. Toxicity of previous courses was prospectively scored before each HD-MTX course and a National Cancer Institute (NCI) grade ≥ 3 was considered clinically relevant toxicity. Plasma MTX levels were measured at 24 and 48 hours after each HD-MTX infusion. Erythrocyte folate, plasma folate and plasma homocysteine levels were determined at the start of protocol M. Seventeen single nucleotide polymorphisms (SNPs) in 7 candidate genes in the MTX pathway were analyzed.

Results

Mucositis occurred in 20% of the patients, skin toxicity in 7%, diarrhea in 3%, and neurotoxicity in 3%. Hospital admissions were necessary in 8% of the patients in between MTX courses. Mucositis was not associated with plasma MTX, plasma folate or plasma homocysteine levels. Patients with mucositis had higher baseline levels of erythrocyte folate (median 1.2 $\mu\text{mol/L}$ vs. 1.4 $\mu\text{mol/L}$, $p < 0.008$). Wildtype rs7317112 in the *ABCC4* gene was the only SNP associated with a higher frequency of mucositis (AA (39%) vs. AG/GG (15%), $p = 0.016$).

Conclusions

Only a higher baseline erythrocyte folate and the wild-type variant of rs7317112 SNP in *ABCC4* were determinants of mucositis in pediatric ALL during MTX-HD treatment. In contrast, plasma MTX and plasma folate were unrelated to toxicity.

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**Pulmonary Manifestations of Paediatric Solid Tumors
PROGNOSIS IMPACT OF REMAINING LUNG NODULES AFTER
METASTASECTOMY IN OSTEOSARCOMA PATIENTS: ARE THEY RESPONSIBLE
FOR RECURRENCE?**

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Objectives

Aim of the study: Survival of patients having a pulmonary metastatic osteosarcoma is improved by the complete removal of all metastases. Due to the dramatic increase of CT-scan quality over the years allowing the detection of millimetric nodules unable to be found at surgery, we aimed to determine if the remaining nodules has an impact on recurrence.

Methods:

We retrospectively compared all lung CT scans performed from diagnosis to first relapse to the surgical and pathological reports in 24 patients treated for an osteosarcoma with a high-dose methotrexate based chemotherapy (OS2006 protocol) and operated on for lung nodules from 2007 to 2012.

Main results:

Three patients were excluded, 2 because of countless nodules and one because of tuberous sclerosis at pathology. Among the 21 patients finally included, 12 were classified as metastatic at diagnosis and 9 had doubtful nodules. With a median follow-up of 35 months from diagnosis [range, 10-61], 5 patients relapsed and 3 experienced a progression. Among 210 nodules (median 6 per patient [1-52]) described at diagnosis, 165 remained after neoadjuvant chemotherapy and 37 new nodules were detected. Among these 202 nodules, 130 (64%) were found at surgery and 111 proved to be lung metastases either viable (n=54) or necrotic (n=57) at pathological analysis. 48 additional nodules were removed (18 viable and 22 necrotic metastases). Among the 72 nodules not found at surgery, 37 were still present at the end of treatment (EOT) of which only 2 (5%) were involved in a relapse (9 nodules described) and 2 (5%) in a progression (13 nodules described).

Conclusion:

The lung nodules not found at surgery and still remaining on the CT scan at EOT did not seem to be responsible for recurrence in pulmonary metastatic osteosarcoma patients.

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Pulmonary Manifestations of Paediatric Solid Tumors

CLAMSHELL THORACOTOMY: A PLAUSIBLE ALTERNATIVE FOR BILATERAL PULMONARY METASTASECTOMY IN PEDIATRIC PATIENTS WITH OSTEOSARCOMA

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Objectives

Osteosarcoma is the most common malignant bone tumor in children and adolescents. Up to 70% of patients will eventually develop metastatic disease. Lung is the most frequent site. Techniques described for bilateral metastasectomy include staged posterolateral thoracotomy and median sternotomy.

We present our experience for bilateral pulmonary metastasectomy in pediatric patients with osteosarcoma, using the “clamshell” thoracotomy. We describe indications, advantages and disadvantages.

Methods

During a 25-years review, out of 297 cases of osteosarcoma, 69 cases of bilateral lung metastasectomy were identified. 43 underwent staged posterolateral thoracotomy, 10 had a median sternotomy, and 16 cases underwent “clamshell” thoracotomy.

Results

There were seven boys and nine girls, with a median age of 11 years. Most common primary site was distal femur; most common tumor type was osteoblastic. 69% of patients had limb-salvage. Most frequent time of presentation of pulmonary metastases was during follow up (50%).

We preserved the sternum (synchronous bilateral anterior thoracotomy) in five out of the 16 cases.

Five patients required reoperation for local recurrence.

Surgical time ranged from 2 to 6 hours. Average blood loss was 250 ml. Chest tubes were removed on postoperative day two. Hospital length of stay was 5 days.

Thoracotomy identified more lesions than CT in 70% of cases.

There was no perioperative mortality, and surgical complications were minimal (three cases of postoperative pneumothorax requiring 24 extra hours of pleural drainage). All lesions were removed with histological confirmation.

Chemotherapy was initiated 7 to 10 days postoperatively.

Conclusions

Clamshell thoracotomy is a safe and feasible alternative for bilateral metastasectomy in pediatric patients with osteosarcoma. Procedure is well tolerated, with minimal postoperative pain, allowing adequate simultaneous exploration of both lungs, including posterior-basal segments, decreasing the time of recovery needed for chemotherapy. Re-do thoracotomies via this approach are easily performed. Anterior chest-wall lesions are technically difficult.

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Pulmonary Manifestations of Paediatric Solid Tumors

SURGERY PLAYS A KEY ROLE IN THE TREATMENT OF PULMONARY RELAPSES FROM WILMS TUMORS: DATA FROM SIOP 93-01/GPOH AND SIOP 2001/GPOH

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Objectives

To evaluate the outcome of children suffering from pulmonary Wilms tumor relapses registered within the multicenter trials SIOP 93-01/GPOH and SIOP 2001/GPOH of the Society of Pediatric Oncology and Hematology (GPOH).

Methods

Data of children with pulmonary Wilms tumor relapses were retrospectively analysed with regard to patients' characteristics, as well as oncological and surgical outcome.

Results

In both study trials there were 87 children with nephroblastoma relapses in the lung.

Histology revealed intermediate risk in 62 and high risk in 25 patients. Relapses were singular (<6) in 59 and multiple (>6) in 25 patients (no data in 3). Location was unilateral in 54 and bilateral in 28 cases (no data in 5). Primary lung metastases were initially present in 28 patients, whereas in 59 patients there were no primary lung metastases. All but 4 patients had received neoadjuvant chemotherapy during first line treatment, Tumor nephrectomy was performed as first line local treatment of primary tumors in 84 patients, partial nephrectomy in 4 patients. Median time to pulmonary relapse was 5 months (0-75). Local treatment of pulmonary relapses (surgery, irradiation or both) was performed in 70 patients, in 64 of them, surgery was part of the local treatment. Overall survival was 56/87 patients (64.4%).

Conclusions

The vast majority of children with pulmonary relapses undergo surgery for local treatment. Survival is relevantly inferior compared to children without relapses. A aggressive approach seems justified in order to treat affected patients.

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Pulmonary Manifestations of Paediatric Solid Tumors
SURVIVAL WITH LUNG METASTASES IN PEDIATRIC SOLID TUMORS - A
SYSTEMATIC REVIEW

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Objectives

Metastatic lung lesions from pediatric solid tumors are treated using multimodal therapy and survival is reported to be improving. We performed a systematic review of the literature to robustly analyse survival outcomes for these children with disseminated disease linked with their primary tumor sub-group(s) and the role of surgical metastectomy.

Methods

Studies were identified using Medline (1950-), Embase (1980-) and Cochrane database(s) using the key relevant search terms. Literature reviews, case reports (<3 patients) and adult studies (age >18 years) were excluded. Data were extracted independently following paper selection by at least 2 study authors. Overall survival (OS) and event-free survival (EFS) was assessed for the different primary tumors.

Results

The original search retrieved 2,080 articles. Following application of exclusion criteria and removing duplicate data - 34 studies (1,643 patients) were included for final review. Published studies covered the era(s) 1967 - 2013. The most common primary tumor disseminating to lung was osteosarcoma (n= 535) followed by Wilm's tumour (n=435). Overall patient survival was 36% (CI 26% - 48%), 55% (CI 39%-71%), 32% (CI 22%-44%) for osteosarcoma, Wilms' tumor and Ewing's sarcoma respectively. Surgical metastasectomy was performed in 1153 /1643 (71%) patients linked to cancer therapy programmes to achieve 'cure'. Insufficient high quality data was available to address and answer the real therapeutic benefit(s) of surgical metastasectomy vs chemotherapy or radiotherapy in patients with pulmonary metastases.

Conclusions

Surgical lung metastectomy is well-established oncological practice. This review found no individual case series or subgroup(s) of pediatric cases which were exclusively managed without considering the potential role for operative metastectomy. The true value of surgery in management of patients with advanced pulmonary metastases cannot be fully established currently. Examination of the published world literature has allowed us though to summarise and benchmark outcomes for subgroups of patients / tumour types with pulmonary metastases.

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Sarcoma

LOCAL CONTROL FOR DIFFUSE INTRABDOMINAL AND PELVIC RHABDOMYOSARCOMA: RESULTS OF A PHASE 1-2 STUDY OF CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

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Objectives

Diffuse and recurrent intrabdominal and pelvic rhabdomyosarcoma are rare forms of RMS. Instead of a localized mass, RMS can be multiple and present as sarcomatosis, in the abdominal/pelvic cavity. This presentation can be secondary to tumor rupture or 'de novo'. The incidence sarcomatosis in rhabdomyosarcoma is unknown, but of approximately 250 RMS cases per year in the USA, 10-15 are abdominal/pelvic, non genito-urinary cases.

Methods

We performed cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) with curative intent, as part of neoadjuvant and adjuvant chemotherapy, as a phase 1 and then a phase 2 trial. RMS patients were a subset of a larger cohort of patients with other sarcoma histologies. Patients included had RMS that was multifocal in the abdominal cavity and/ or recurrent post radiation. All patients had imaging characteristics consistent with surgically resectable disease. Cisplatin was used at 100mg/M2 and 150mg/M2 continuously for 90 minutes intra-operatively after surgical resection.

Results

There were 8 patients aged 2 to 16 years, who underwent 9 cytoreductive surgery and HIPEC procedures. Three of eight, 37%, of patients had successful local control of their abdominal disease for greater than one year. Two of eight, 25%, of patients are alive without disease, at 21 and 34 months. Five of eight, 62%, had a complete resection prior to HIPEC. All patients with an incomplete resection recurred at less than 3 months from surgery. Dose limiting toxicity was grade 3 or higher elevation in creatinine. One patient required chronic dialysis. There were 2/9, 22%, major postoperative complications including high grade bowel obstruction and wound infection with skin separation.

Conclusions

At a dose of 100mg/M2 Cisplatin, HIPEC is safe in children with RMS sarcomatosis. Complete or partial response was seen in 37% of patients with RMS and sarcomatosis. Alternative intraperitoneal chemotherapy is needed for cisplatin insensitive patients.

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Sarcoma

EVALUATING THE NECESSITY FOR SURGERY AS LOCAL THERAPY IN RHABDOMYOSARCOMA OF THE BLADDER AND PROSTATE: 14 YEAR EXPERIENCE AT A TERTIARY CARE CENTRE

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Objectives

To assess whether surgical resection is essential for good outcomes in children with rhabdomyosarcoma (RMS) of the bladder and/or prostate (BP).

Methods

The records of children treated for RMS-BP from 1999 through 2013 were analysed. Outcomes in terms of 2-year overall survival(OS) and event free survival(EFS) were analysed according to the age, presence of metastases and local therapy given (resection vs no resection). Events included death, recurrence and progression. Multimodal chemotherapy (Vincristine+Actinomycin+Cyclophosphamide), external beam radiotherapy(RT) was used in all children.

Results

Of the 41 children with RMS-BP included for analysis, 20(48.8%) were older than 24 months at presentation, of whom 9(45%) had events including 3 deaths(15%) giving an OS of 53.6 %(95CI 0.61,0.95) and EFS of 53.7 %(95CI 0.43,0.95). The EFS was significantly better($p=0.038$) than those < 24 months of age. Ten of the 41(24.4%) had metastasis. Five(50%) had events including two deaths giving an OS of 26.8 %(95CI 0.44,0.95) and EFS of 26.8 %(95CI 0.17,0.76). The OS($p=0.896$) and EFS($p=0.148$) were not significantly different for those without metastasis. Thirty-four of the 41(83%) received neoadjuvant chemotherapy and all received adjuvant chemotherapy and RT. Only 9(22%) had surgical resection(6 upfront) as a part of the local therapy. Of these 9, there were no deaths, 2 events and 5(55.5%) achieved complete remission (CR) giving an EFS of 75%(95CI 0.52,17.1). Among the 32(74%) who were not operated upon, 16(50%) had events including 8(25%) deaths and 9(28%) achieved CR giving an OS of 78%(95CI 0.22,7.19) and an EFS of 50%(95CI 0.05,0.94).

Conclusions

Though 28% achieved CR without resection, the chances of achieving it were three times greater in those undergoing surgery (upfront or after neoadjuvant chemotherapy). The OS($p=0.102$) and EFS($p=0.301$) were not different in the two groups. These results lead us to question the need for aggressive surgical excision for patients with RMS-BP.

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Sarcoma

HIGH DOSE RATE BRACHYTHERAPY IN SUCCESSFUL TREATMENT OF CHILDHOOD LOWER URINARY TRACT MALIGNANCIES

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Objectives

Iridium-192-based low dose rate brachytherapy (BT) has been shown to reduce long term morbidity after treatment for bladder-prostate rhabdomyosarcoma (BP-RMS).^{1,2}

Aiming at minimized long term morbidity from radical surgery we developed and introduced high dose rate brachytherapy (HDR-BT) using Iridium-192 in multi-modal treatment of childhood lower urinary tract malignancies.

Methods

6 children, (4 boys), aged 1-10 years, diagnosed with BP-RMS (n=5) and malignant triton tumour in the bladder (MTT, n=1) were treated with HDR-BT at the Karolinska University Hospital 2004-2013. All patients were pre-treated according to CWS protocols. Surgery was limited to placement of BT-catheters in 4 out of 6 patients that had a tumour diameter less than 5 cm after induction chemotherapy. Blind ending brachytherapy catheters were placed at intervals of 10 mm to cover the clinical target volume with a margin of 5-10 mm in all directions. A dose-planning CT-scan was performed during the same anaesthesia and HDR-BT was given twice daily during the first five postoperative days (HDR Micro-Selectron, Nucletron, The Netherlands). The dose per fraction was 3.0-3.3 Gy to a total dose of 18-39 Gy. Most treatments were performed under mild sedation.

Results

All 5 children treated for primary tumours (4 BP-RMS, 1 MTT) are alive with no evidence of disease after 12-120 months. The child receiving HDR-BT as part of salvage treatment for recurrent BP-RMS died. All patients alive have retained their bladder function. Detailed urological follow-up including voiding patterns, upper urinary tract ultrasonography, kidney function and erectile function is ongoing.

Conclusions

We report the use of HDR-BT on a widely available instrument platform to reduce the need for radical surgery and potential long-term morbidity. The clinical results are promising and warrant further investigation.

1 Martelli H et al. J Ped Surg. 2009

2 Jenney M et al. Pediatr Blood Cancer 2014

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Sarcoma

REDUCING LONGITUDINAL BONY RESECTION MARGINS IN LIMB-SPARING SURGERY FOR EXTREMITY OSTEOSARCOMA DOES NOT IMPACT ONCOLOGIC OUTCOMES

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Objectives

Bony resection margins in limb-sparing surgery for osteosarcoma should be sufficiently wide while maximizing preservation of native bone. However the optimal distance of this margin is not well established. This study investigated the effect of decreasing bony resection margins, and the association of other surgicopathological factors, with oncologic outcomes in these patients.

Methods

Retrospective review of children and adolescents with newly diagnosed osteosarcoma enrolled on 4 consecutive institutional trials (1986–2012), where the preoperatively-planned longitudinal bony resection margins for limb-sparing surgeries were serially decreased from 5 to 1.5 cm. The association between bony resection margins and other surgicopathological factors with local recurrence-free survival (LRFS), event-free survival (EFS), and overall survival (OS) was determined.

Results

One hundred eighty-one limb-sparing surgeries were performed on 173 patients. Planned and actual resection margins did not correlate with LRFS, EFS, and OS; that is, serial reduction of planned bony resection margins from 5 to 1.5 cm did not adversely affect survival outcomes. At median 5.8 years' follow-up, there were 18 (9.9%) local recurrences, 41 (22.6%) distant recurrences, and 6 (3.3%) concurrent local and distant recurrences. Fifty-one (29.5%) patients died from their disease. On multivariable Cox regression analysis, metastatic disease at diagnosis was independently associated with decreased LRFS, EFS, and OS ($P=0.002$, 0.005 and <0.0001 , respectively). Post-chemotherapy tumor necrosis $\leq 90\%$ was independently associated with decreased OS and EFS ($P=0.022$ and 0.001 , respectively). Earlier years of treatment and pathologic fractures were independently associated with decreased OS only ($P=0.018$, and 0.008 , respectively), and previous cancer history and male gender were associated with decreased EFS only ($P=0.043$ and 0.023 , respectively).

Conclusions

In limb-sparing surgery for osteosarcoma in children and adolescents, reducing longitudinal bony resection margins to 1.5 cm does not increase the risk of local recurrence or adverse survival outcomes. Established prognostic factors continue to be relevant in this group of patients.

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Sarcoma

LYMPH NODE SAMPLING IN PEDIATRIC EXTREMITY SOFT TISSUE SARCOMAS: RISK-ADJUSTED SURVIVAL OUTCOMES

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Objectives

Extremity rhabdomyosarcoma (RMS) and some subtypes of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) commonly involve regional lymph nodes. We sought to determine the effect of lymph node sampling (LNS) on survival for pediatric extremity soft tissue sarcomas (STS).

Methods

The SEER registry (1973-2010) was analyzed for all patients <20 years of age with extremity STS. Multivariate and propensity-score matched analyses were performed to obtain risk-adjusted assessments of survival.

Results

Overall, 1,554 patients were identified with an overall age-adjusted incidence of 0.31 per 100,000 persons and a significant annual increase of 0.95% ($p < 0.05$) over the study period. Patients were most commonly male (53%), age ≥ 10 years (72%), and white (78%). Most were diagnosed with localized disease (64%), lower extremity (63%), originating from muscle (24% NRSTS/19% RMS) or fibrous tissues (18%), and with undifferentiated/anaplastic grade IV (34%). Most RMS were alveolar type (69%). The majority of patients had surgery (89%) but only 40% had radiotherapy. LNS was performed in 46% of RMS and 11% of NRSTS patients. Overall, 20-year disease specific survival was 69%, and 46% for RMS, but higher for age 5-9 years (77%), localized disease (80%), arm (76%), and NRSTS adipose (96%), fibrous (92%), and vascular (80%) types (all $p < 0.05$). There was no survival advantage for LNS by stage, grade, histology type, or site for RMS or NRSTS. Multivariate analysis revealed poorly differentiated (OR=2.916), undifferentiated/anaplastic grade (OR=3.236), and nerve tissue type (OR=8.211) as significant independent prognostic indicators of mortality, while localized (OR=0.133) and regional disease (OR=0.215) as significant independent prognostic indicators of decreased mortality (all, $p < 0.01$). Propensity score matched analyses revealed that LNS was associated with improved overall survival for RMS (73% vs 51%, $p = 0.006$) but not for synovial sarcoma.

Conclusions

Analysis of SEER with propensity score matching demonstrates a survival advantage with LNS for pediatric extremity RMS.

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Surgical Techniques

RETROPERITONEOSCOPIC ADRENALECTOMY FOR ADRENAL TUMOR IN CHILDREN

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Objectives

To report the authors' results of retroperitoneoscopic adrenalectomy (RA) for adrenal tumor in children.

Methods

Medical records of all patients undergoing RA for adrenal tumor at our center from December, 2009 to December, 2013 were reviewed. Only relatively small adrenal tumors with well defined border, without encasement of the great vessels and without lymph node involvement on CT scan were selected for RA. A lateral retroperitoneal approach was used in all cases.

Results

19 patients were identified, 8 girls and 11 boys, with a median age of 5 years (range: 1 to 14 years). Tumors were on the left side in 4 cases, on the right – in 15, with a median size of 4.5 cm (range: 3.0 to 9.0 cm). Three ports were used in 15 cases and just 4 cases required additional fourth port. RA was successful in 18 cases (94.7%) with minimal blood loss. The median operative time was 110 minutes (range: 70 to 220 minutes). Conversion to open surgery was needed in a case of 9 cm pheochromocytoma due to bleeding. There was no perioperative death or major complication. Most patients resumed oral feeding in the same day after the operation. Pathology study showed ganglioneuroma in 6 cases (31.6%), pheochromocytoma in 5 cases (26.3%) ganglioneuroblastoma in 4 cases (21.0%) and neuroblastoma with favorable histology in 4 cases (21.0%). At a median follow up of 31 months, all patients were alive and disease free.

Conclusions

RA for pediatric adrenal tumor is feasible and safe in carefully selected cases. This technique can give good results not only for benign tumors but also for some malignant tumors, including neuroblastomas with favorable histology.

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Surgical Techniques

THORACOSCOPIC ASSISTED RESECTION OF PEDIATRIC CHEST WALL TUMORS

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Objectives

was to evaluate the role of thoracoscopy in facilitating resection of pediatric chest wall Tumors without rib spreading ,and how it could decrease number of resected ribs without compromising the margin .

Methods

This was a retrospective study which included 14 cases (rib Ewing sarcoma 12 cases, rabdomyosarcoma chest wall one case and rib chondrosarcoma one case) treated by surgical resection.

Results

The average age was 9.1 years .Neoadjuvant chemotherapy was given in all cases of Ewing sarcoma. The procedure started by thoracoscopic assessment in 10 cases. It could identify all margins in 7 cases so we made the incision directly around the lesion and resection was done without rib spreading. Thoracoscopic assessment failed to identify one or more of the margins in 3 cases(tumor arise from the 2nd rib in one case ,2 cases the tumor was attached to the diaphragm) , thoracoscopy was not attempted in 4 cases due to large tumor diameter or massive adhesions .Resection included 1,2,3 and 4 ribs in (5,3,4 and 2 cases) respectively. Primary closure was feasible in 7 cases and rib transposition was done in one case. Reconstruction by prolene mesh covered by muscle flap was done in 6 cases. Margins were negative in all except one case

Conclusions

Pediatric chest wall tumors are rare .Thoracoscopic assisted resection helps to accurately choose the site of incision, and in some cases avoids rib spreading and decreases the number of ribs resected.

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Surgical Techniques

LAPAROSCOPIC RETROPERITONEAL LYMPH NODE DISSECTION FOR PARATESTICULAR RHABDOMYOSARCOMA IN CHILDREN

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Objectives

Paratesticular rhabdomyosarcomas usually present with an enlarging painless scrotal mass. A majority of patients will have clinical stage 1 disease. The most common sites of metastases are the retroperitoneum and lungs. Patients with retroperitoneal metastases should undergo a modified unilateral nerve-sparing RPLND (Retroperitoneal lymph node dissection). The increased use of minimally invasive surgery has spread to RPLND. We report on our experience with Laparoscopic-RPLND in adolescents.

Methods

Children with Paratesticular rhabdomyosarcomas presenting to us formed the study group. Children underwent detailed evaluation and imaging. The surgical procedure of laparoscopic RPLND involved placement of three ports, one 10 mm periumbilical camera port and two 5 mm ports (one midline below the xiphoid and one midline above the pubis). The colon was medialised by incising along the white line of Toldt from the spleen up to the sigmoid colon exposing the common iliac vessels bifurcation, the testicular vessels and the ureter. First, the spermatic cord was dissected out and taken down to the point of the previous orchiectomy. The ureter was dissected out from the nearby vessels to avoid ureteral injury. The peri-aortic tissue was then split to begin the dissection of the peri-aortic lymph nodes. Dissection was carried out from the renal vessels down to the bifurcation of the aorta. The common iliac, pericaval and interaortocaval lymph nodes were dissected out.

Results

During the study period Jan 2013 to Dec 2013, three children with a mean age of 10.3 years underwent laparoscopic RPLND. The mean operative time was 363.3 mins and the mean blood loss was 40 cc. There were no major intra/postoperative complications. The mean hospital stay was 50 hrs.

Conclusions

The increased use of minimally invasive surgery has spread to RPLND. Laparoscopic RPLND for high-risk pediatric patients with PTRMS is a safe diagnostic and therapeutic procedure with the benefit of rapid convalescence, enabling early commencement of adjuvant chemotherapy.

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Surgical Techniques

ENDOSURGERY IN THE DIAGNOSIS OF ONCOLOGY IN CHILDREN

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Objectives

To summarize and analyze the experience of use in the diagnosis of endosurgery neoplastic diseases in children.

Methods

From 2007 to 2012, performed 161 diagnostic operations in 153 patients. Of them diagnostic thoracoscopy – 44, diagnostic laparoscopy - 63, thoracoscopic lung resections for the differential diagnosis of cancer with an infectious process – 53 operations and one-stage laparoscopy and thoracoscopy - 1 operation . The age of patients ranged from 2 months to 19 years (median 12.6 years)

Average time during laparoscopic operations was - 62min., thoracoscopic - 54 min. The mean blood loss during laparoscopy 61ml at thoracoscopy - 104ml. Intraoperative complications appeared in 5 cases out of 161 operations . In 3 cases there was bleeding from the tumor, the superior vena cava injury and wound duodenum 1 case . In 4 of 5 cases required conversions . In one case, bleeding from the tumor site was eliminated without resorting to conversion. In 8 cases identified postoperative complications.

Surgical complications in 4 registrars patients: 2 cases eventration omentum through an incision in periumphalic region, two cases pneumothorax; nonsurgical complications also occurred in 4 patients: two children, pneumonia, and one case of acute bronchitis and chickenpox.

Results

During two surgeries material for histological examination was not obtained , which required in one case re endosurgery operation and suddenly open surgery. In other cases, the material obtained for morphological examination. Use of narcotic analgesics (fentanyl , promedol) was needed during surgery and during the postoperative period first day . All patients received prophylactic antibiotic therapy. Average number of hospital days was - 4 ± 2 days.

Conclusions

Thoracoscopy and laparoscopy allows you to perform a biopsy of tumors of the chest and abdominal cavity , retroperitoneal and pelvic cavity , and given the minimal invasiveness , short postoperative period and rapid recovery after such an operation may start special treatment as soon as possible after surgery.

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Surgical Techniques

SAFETY AND DIAGNOSTIC ACCURACY OF TISSUE BIOPSIES IN CHILDREN WITH CANCER

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Objectives

Tissue biopsies are frequently used in pediatric cancer and may be increasingly employed for research purposes, yet information on their associated risks and diagnostic yield is lacking. This study sought to evaluate the safety and diagnostic accuracy of tissue biopsies in children with cancer.

Methods

With IRB approval, all surgical or percutaneous biopsies performed in children with a suspected or established diagnosis of cancer from January 2003 to December 2012 were retrospectively reviewed. Patient, disease, and procedural factors were correlated with diagnostic accuracy and incidence of complications using logistic regression analysis.

Results

One thousand seventy-three biopsies were performed in 808 patients. Median age at procedure was 12.7 (range: 0–33.7) years, and median body mass index (BMI) was 19.0 (range: 10.1–61.1). Of 1023 biopsies that had at least 30-days' postoperative follow-up, 69 (6.7%) had complications. Using Common Terminology Criteria for Adverse Events, 35 were minor (Grade 1–2) and 34 were major (Grade 3–4) adverse events. No deaths occurred that were procedural-related. The most common major adverse events were blood transfusions of >10cc/kg (24 cases) and infections requiring intravenous antibiotics or debridement (6 cases). Nine hundred sixty-two (90%) biopsies provided definitive histologic diagnoses, and 111 (10%) yielded unconfirmatory or non-diagnostic results; 150 were biopsies of a previously-biopsied site. Using multivariable analysis, thoracic sites ($P<0.0001$), decreased age at procedure ($P=0.052$), increased BMI ($P=0.005$), and decreased hematocrit ($P=0.0005$) were associated with an increased risk of complications. Musculoskeletal sites ($P=0.0077$), incisional biopsies ($P=0.0025$), increased white blood cell count ($P=0.0181$), a non-malignant histology result ($P<0.0001$), a malignant primary diagnosis ($P=0.0232$), and method of performing biopsy ($P<0.0001$) were associated with a non-diagnostic histologic result.

Conclusions

Tumor biopsies in children with cancer are associated with a low incidence of complications and a high rate of diagnostic accuracy. Predictive factors identified for these adverse outcomes may aid preoperative counseling and risk assessment.

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Surgical Techniques

BILATERAL ANTERIOR STERNOTHORACOTOMY (CLAMSHELL INCISION) IS A SUITABLE ALTERNATIVE FOR BILATERAL LUNG SARCOMA METASTASIS RESECTION IN CHILDREN

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Objectives

The aim of our study was to assess the postoperative course of bilateral anterior sternothoracotomy (BAT) in children with sarcoma lung metastases, in a curative care perspective.

Methods

We reviewed the records of 7 patients under 18 years old, who underwent surgical procedures for sarcoma metastasis to the lung between 2000 and 2012. We compared the postoperative course of the BAT group to that of patients who underwent unilateral posterolateral thoracotomies (PLT) for the same etiology.

Results

Of 17 surgical procedures, there were 7 BAT and 10 unilateral PLT. Mean ages at the time of the procedures were 12.9 +/- 5.4 years old for BAT, and 17.4 +/- 1.9 years old for PLT. Mean operative time was 173 +/- 37 minutes in the BAT group, and 145 +/- 39 minutes in the PLT group (p=0.19). Patients received epidural analgesia in all cases for a mean time of 3.8 +/- 1.3 days in the BAT group, and 3.21 +/- 4 days in the PLT group (p=0.36). Chest tubes were removed after 3.6 +/- 1.3 days in the BAT group, and 3 +/- 1.2 days in the PLT group (p=0.69). Total hospital stay was 7.7 +/- 6.6 days in the BAT group, and 7 +/- 1.2 days in the PLT group (p=0.72).

Conclusions

In our experience, BAT seems suitable and shows similar outcomes to PLT for sarcoma metastasis resection. The BAT procedure allows the manual exploration of both lungs during a single surgical intervention, and so to reduce the delay of further therapies.

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PBC-Session: Best of IPSO

IMPROVEMENTS IN THE TREATMENT OF PATIENTS SUFFERING FROM EMBRYONAL BLADDER-PROSTATE-RHABDOMYOSARCOMA – A COMPARISON BETWEEN THE CWS-96 AND CWS 2002-P TRIALS

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Objectives

Modern treatment of bladder/prostate rhabdomyosarcoma (BPRMS) is aimed to improve survival, to reduce therapy intensity as well as to increase bladder preservation rates.

The aim of the study was to compare treatment results of patients suffering from BPRMS treated within the CWS-2002P trial with the precursor trial CWS-96.

Methods

A total number of 119 children with non-metastasized embryonal BPRMS treated within CWS-96 (n=69) and -2002P (n=50) trials were analyzed. Fourteen patients were excluded (CWS-2002P: n=8, CWS-96: n=6). Patients received 3 cycles of neoadjuvant chemotherapy (CWS-96: VAIA/CEVAIE, CWS-2002P: VAIA/I²VA). At week 9, reassessment was carried out. Depending on tumor size, age, and response, local therapy consisting of radiotherapy and/or surgery was initiated. After local control, adjuvant systemic therapy was continued.

Results

Patients' age ranged from 0 to 16 years in both trials. Median follow up was 59 (CWS-2002P) and 64 months (CWS-96). The 5-year-OS and -ES for the whole group were higher in CWS-2002P than in CWS-96 (5-y-OS CWS-2002P: 84.5%±6; CWS-96: 76.3%±5.6; 5-y-ES CWS-2002P: 79.9%±6.4; CWS-96: 69.8%±6.2). One third of the patients received radiotherapy in both trials. Successful local control was feasible using radiotherapy and/or surgery and the outcomes for different local control approaches were comparable. The bladder preservation rates were matchable (67% (CWS-2002P) / 73% (CWS-96)).

Conclusions

Despite reduction of chemotherapy burden, the outcome of patients suffering from BPRMS treated within the CWS-2002P trial regarding OS and ES was obviously better than in the precursor trial CWS-96. Although there was no difference in individual local control rates, the improved outcome is caused by the fact that the number of prognostic unfavourable incomplete resections with salvage radiotherapy was significantly lower in CWS-2002P than in CWS-96. Novel concepts will be required in the future to improve bladder preservation rates.

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PBC-Session: Best of IPSO

WILMS TUMOUR NOT RESPONDING TO PREOPERATIVE CHEMOTHERAPY

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Objectives

In majority of patients with nephroblastoma (WT), preoperative chemotherapy decreases tumour volume. Risk of the intraoperative tumour rupture and stage of the disease become lower. In some, however, tumour volume does not decrease or even increases. Aim of this review was to describe surgical, clinical and pathological characteristics of WT not responding to preoperative chemotherapy.

Methods

Of 1774 patients (SIOP9301), 220 (12%) with unilateral or metastatic WT evidenced stable (31) or increasing volume (189) of their tumours under preoperative chemotherapy (106/boys, 114/girls, age range 6-187 months, median=33); 209 had localised tumours, 11 – metastatic. Abdominal stages were I/108 (49%), II/57(26%), III/39(18%), IV/3(1%) missing 13(6%). Pathology was of low risk in 14 (6%), intermediate risk in 161 (73%) and high risk in 45 (20%). The stage III rate, the intraoperative tumour rupture rate and the pathology groups in non-responders and the remaining patients were compared.

Results

The stage III rates in non-responders (18%) and remaining patients (11%) were not different ($p=0.105$), intraoperative tumour ruptures were more frequent in non-responders (8% vs. 2%, $p=0.00006$). Pathology of low and intermediate risk was less frequent in non-responders (respectively: 6% vs. 11%, $p=0.0387$ and 73% vs. 85%, $p=0.00001$). The stromal predominant subtype, however, was more frequent in non-responders (15% vs. 8%, $p=0.0005$), whereas the rates of blastemal predominant subtype were not different (10% vs. 7% $p=0.193$). High risk pathology was more frequent in non-responders (20% vs. 3%, $p=0.00000$). Outcomes: 78% of non-responders with localized tumour and 8/11 metastatic cases are in 1st CR; 87% of non-responders and 9/11 metastatic patients are alive (60 months).

Conclusions

Patients with WT non-responding to preoperative chemotherapy have higher rates of high risk pathology variants and the stromal predominant subtype of intermediate risk and are at elevated risk of tumour rupture. Outcome remains acceptable.

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PBC-Session: Best of IPSO

WILMS TUMOUR WITH INTRAVASCULAR EXTENSION - TIME TO REFLECT AND RESECT. A REPORT FROM SIOP 2001

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Objectives

Preoperative chemotherapy is recommended for children with Wilms tumour with intravascular extension. Extended chemotherapy may improve resectability, but increase tumour adherence to vascular endothelium, precluding complete resection. To evaluate the optimal length of preoperative treatment we report a review of patients with tumour thrombus treated in the SIOP 2001 study.

Methods

Patients with Wilms tumour (WT) and thrombus were identified from the SIOP 2001 study. Preoperative chemotherapy with Vincristine/Actinomycin D was recommended for all patients. Overall (OS) and event free (EFS) survival, tumour regression, completeness of resection, use of cardiopulmonary bypass (CPB) and cavectomy were analysed for those patients receiving standard preoperative chemotherapy (4 courses over 4 weeks) versus extended treatment (more than 4 courses).

Results

Of 4500 registered patients 166 had thrombus. Pre-treatment tumour extent was cardiac in 31, caval in 120 and renal vein in 15. 97% received chemotherapy; details were available for 139 of which 65 received standard treatment (StC); 65 extended treatment (EC). Tumour regression was observed in 20% StC and 25% EC; complete resection achieved in 70% and 73% respectively; cavectomy was required in 20% and 28% (n.s.). Survival was significantly higher in those receiving StC than EC (OS 95% vs 82%, $p=0.025$; EFS 88% vs 72%, $p=0.047$), though there were more high-risk tumours in the EC group (18% vs 5% StC). Of 30 patients with intracardiac extension, 9 received StC and 12 EC. Slightly more tumour regression into the vena cava was observed in the EC group (58% vs 50%); with reduced CPB (33% StC 17% EC); but without improved survival.

Conclusions

Extended preoperative chemotherapy confers no added benefit in those with intracaval thrombus. For those with intracardiac extension, the current data is inadequate to guide the value of extended treatment, but improved tumour regression into the cava may permit resection without bypass.

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PBC-Session: Best of IPSO

ADRENOCORTICAL CARCINOMA IN CHILDREN: A REVIEW OF THE NATIONAL CANCER DATABASE

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Objectives

Adrenocortical carcinoma (ACC) rarely occur in children. Prior studies suggest that ACC in children may represent a different pathologic entity when compared to adults. The purpose of this study was to compare the survival trends of children with that of adults with ACC.

Methods

Utilizing data from the National Cancer Data Base (NCDB), we analyzed all patients, adults (≥ 18 years of age) and children (< 18 years of age), with ACC from 1998 to 2011. Kaplan-Meier and logistic regression models were used to analyze trends and factors associated with improved survival.

Results

A total of 2,886 patients with a primary ACC were identified (2,765 adults, 121 children). Factors that significantly ($p < 0.05$) affected survival include ethnicity, tumor grade, regional lymph node status, extent of surgery at primary site, surgical margins, and age. Patients with ACC < 18 years of age had a significantly superior 5-year overall-survival (OS), 64% (95% CI 53-74%), compared to those ≥ 18 years of age, 32% (95% CI 30-34%; $p < 0.0001$). Improved 5-year OS in the younger age group remained significant when stratified by tumor size > 5 cm and positive lymph node status ($p < 0.0001$, $p = 0.002$, respectively). In patients where complete resection was achieved, younger patients had better 5-year OS than older patients (82% [95%CI 66-91%] vs 48% [95% CI 44-51%]).

Conclusions

ACC patients < 18 years of age had a better 5-year OS compared to older adults, a finding that persisted in a subgroup with complete resection. These data support that ACC in children behaves as a different pathologic entity from that observed in adults.

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Germ Cell Tumours / Rare Tumours

PREDICTORS OF OUTCOME IN PEDIATRIC HEPATOCELLULAR CARCINOMA: A REVIEW OF THE NATIONAL CANCER DATA BASE

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Objectives

To examine demographic characteristics and factors associated with survival in children with hepatocellular carcinoma (HCC).

Methods

The National Cancer Data Base was queried for pediatric patients (<18 years) with HCC of all subtypes diagnosed between 1998 and 2011. We examined demographic, diagnostic, and treatment variables to identify factors associated with survival using log-rank comparisons of Kaplan-Meier survival curves. We also compared the variables of pediatric and adult patients with HCC.

Results

Of 110,438 total patients with HCC, 309 (0.280%) were less than 18 years old. Pediatric patients had an average age of 14.7 years, and better 5-year overall survival (OS) than adult patients (30.9% vs. 14.8%; $p < 0.001$). In the pediatric cohort, the children with fibrolamellar HCC comprised 32.7% of the cases, were older than 7 years, and had better OS than patients with non-fibrolamellar HCC (46.5% vs. 21.3%; $p < 0.001$). White children had better OS than black children and those of other racial groups (36.5% vs. 16.7% vs. 8.11%; $p < 0.001$). Additionally, improved OS was observed in children with negative lymph nodes (69.2% vs. 25.70%; $p < 0.020$), in those who underwent some type of lymph node sampling or resection (58.3% vs. 17.8%; $p < 0.001$), and in those with negative margins after resection (57.2% vs. 23.8%; $p = 0.002$). There were 148 resections: 47 wedge/segmentectomies, 44 anatomic hepatectomies, 18 extended hepatectomies, and 39 transplants. The OS for each type of procedure was 73.1%, 51.0%, 25.0%, and 34.0%, respectively. In children, neither size of primary tumor nor treatment with chemotherapy was associated with improved OS.

Conclusions

Histologic subtype, race, lymph node resection and status, and complete resection of primary tumor were the most significant predictors of survival for pediatric HCC.

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Germ Cell Tumours / Rare Tumours

PROGNOSTIC IMPLICATIONS OF MULIFOCALITY IN HEPATOBLASTOMA

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Objectives

To evaluate the impact of multifocalilty in hepatoblastoma outcome

Methods

The analysis included 52 patients treated between March 2006 and February 2014. Tumors characteristics like the lobe affected, unifocal or multifocal disease, extrahepatic extension, involvement of portal vein or the hepatic veins and presence of metastases were recorded. Serum alfa-fetoprotien levels were measured in all patients. The tumors were assigned PRETEXT group and risk categories as per SIOPEL system in retrospect. All patients, except one, received induction chemotherapy (cisplatin, doxorubicin or cisplatin, vincristine and 5-fluoruracil). Right or left hepatectomy were performed in 27 patients, extended resection in 13 and non-anatomical resection in 9 patients. Left lateral sectorectomy, median hepatectomy and enucleation were performed in one each. Parenchymal cut margins were negative in 48 patients.

Results

The median age was 15 months (range, 11-138 months) with 36 boys and 16 girls. There was no postoperative mortality and complications occurred in 5 patients (biliary fistula=3, wound infection=1 and intestinal obstruction=1). The projected 5-year overall and relapse-free survival were 88% and 70% respectively. Disease relapsed in 11 patients (7 within 18 months) at local site (7) or in the lungs (4). Multifocality was significant prognostic factor for both overall and event free survival ($p<0.05$).

Conclusions

Multifocal hepatoblastoma are associated with increased risk of disease relapse and death.

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Germ Cell Tumours / Rare Tumours

SINGLE CENTRE REVIEW OF HEPATOBLASTOMA OVER 20 YEARS IN NEW ZEALAND

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Objectives

Hepatoblastoma (HB) is a rare childhood malignancy for which surgical resection remains the only chance of cure. The aim of this study was to review the outcome of all children that underwent surgical resection or liver transplantation (LT) for HB at a single centre in New Zealand

Methods

The patients were identified retrospectively from 1992 to 2014. Data included patient demographics, associated conditions, PRETEXT staging with CT scanning , histology, treatment and outcome

Results

22 children aged from 1.8 to 74 months (median 15.8) with a male to female ratio of 12:10 were identified.

13 were European (59 %) , 4 Asian and 1 indigenous Maori. Two patients had Familial adenomatous polyposis and one patient each had neurofibromatosis and Beckwith-Wiederman Syndrome. The majority were PRETEXT II(32% n=7) with 2 in I, 5 in III and 5 in IV. Staging was not available in 3 patients. Six (27%) had lung metastasis at diagnosis, one of whom had tumour involving diaphragm and IVC. All except one patient with a small tumour were treated with neoadjuvant chemotherapy according to SIOPEL protocol. 18 patients underwent R0 hepatic resection and 4 patient LT. The most common histological type was epithelial (61%) followed by mixed type(39%). One patient developed intrahepatic recurrence post resection and was treated with LT

Conclusions

At a mean follow up of 104 months (3-253) five patients developed recurrence. Two with pulmonary and one with cerebral metastases that were resected with no evidence of recurrence after 25 and 204 months respectively , the other 3 died. 19 patients remain alive and well with 1 and 5 year overall and event free survival of 91/86% and 91/85% respectively

This is one of the largest single centre reports of HB with survival rates exceeding multicentre reviews

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Germ Cell Tumours / Rare Tumours

MALIGNANT HEMOPERITONEUM IN CHILDREN: A SINGLE INSTITUTION EXPERIENCE

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Objectives

We present our experience with malignant hemoperitoneum in children.

Tumors may produce hemoperitoneum after spontaneous or chemotherapy-induced rupture. Some present as acute abdomen, diagnosis being made at surgery.

Tumors at risk include: neuroblastoma, Wilms, hepatoblastoma, and ovarian tumors.

Methods

We retrospectively reviewed 10 cases of malignant hemoperitoneum between 2004 and 2010.

Results

Five boys and five girls (two to 16 years), underwent surgery for malignant hemoperitoneum.

Diagnoses included ovarian germ cell tumor (oGCT), followed by Wilms tumor (WT) and hepatoblastoma (HB), then neuroblastoma (NB), ovarian leukemic infiltrate, and rhabdomyosarcoma of the urachus (uRMS).

Seven had history of malignancy, three more presented as acute abdomen, the diagnosis being made at laparotomy.

Most underwent primary tumor resection, while two (NB and HB) underwent damage-control surgery alone.

Free peritoneal blood found at surgery was 300 to 1,500 ml. All required intensive care after surgery.

Five patients are alive without evidence of disease. One with WT and four with oGCT.

Five children did not survive. Three (WT, NB and HB) died from multiple organ failure 72 hours after the event. The patient with RMS died from disease progression. One with HB died later of multiple organ failure, not related to the hemoperitoneum.

Conclusions

Delayed cancer diagnosis is common in developing countries. 30% of our patients presented with acute abdomen, the tumor being incidentally found at laparotomy.

Not all patients present hemodynamic instability. Signs include abdominal mass/distension, compartment syndrome, and hematocrit drop.

CT-scan is ideal for diagnosis. However, in unstable patients, bedside ultrasound identifies the mass/free fluid, and guides a diagnostic paracentesis.

Malignant hemoperitoneum is a serious complication in pediatric cancer patients, which entails a dismal prognosis with elevated mortality rate. A high index of suspicion for a timely diagnosis cannot be over-emphasized.

Management should be individualized according to tumor characteristics and patient status.

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Germ Cell Tumours / Rare Tumours

MANAGING OVARIAN MASSES IN CHILDREN – WHEN IS OVARIAN SPARING SURGERY APPROPRIATE?

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Objectives

Ovarian sparing surgery in children presenting with an ovarian mass is controversial. We aimed to report preoperative findings that may be predictive of the safety of this approach.

Methods

Retrospective review of all children (0-16 years) presenting with an ovarian mass from January 2006 to December 2013. Operative approach was at the discretion of the operating surgeon. Ovarian sparing surgery was performed with gynaecological expertise present.

Results

Fifty six children were treated during the study period (51 benign, 1 borderline and 4 malignant). Forty two oophorectomies were performed and fourteen ovarian sparing procedures (all benign). Of the oophorectomies, thirty seven (92%) had a benign histology, of which nineteen (51%) had histologically viable ovarian tissue.

All malignant tumours had large mass size (mean 21.4cm \pm 5.4[SD]), positive tumour markers (BHCG, Ca125 or AFP) and mainly solid elements on preoperative ultrasound scan. Benign masses were smaller (mean 9.9cm \pm 7.1cm [SD]). 31 of these had preoperative tumour markers taken, 9 of whom were positive (29%). Appearance on USS was cystic in (64%), mixed (27%) or solid (9%). Of the benign masses with predominantly solid elements all underwent oophorectomy; two had torsed ovarian cysts (no viable ovarian tissue in either); two were considered for ovarian sparing surgery but due to suspicious intraoperative appearances oophorectomy was performed.

Conclusions

In our experience ovarian sparing surgery (performed by a surgeon with appropriate expertise) in children presenting with ovarian masses is safe and effective. Combining preoperative findings may be helpful in selecting those for ovarian-preserving surgery. Masses that were <15cm in diameter, primarily cystic and had negative tumour markers were all benign. Viable ovarian tissue was frequently seen in benign masses and therefore consideration of ovarian sparing surgery in patients with these three preoperative findings is desirable.

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Germ Cell Tumours / Rare Tumours

SINGLE TROCAR LAPAROSCOPIC ASSISTED SURGERY FOR BENIGN OVARIAN CYST IN CHILDREN

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Objectives

To report our technique and results of single trocar laparoscopic assisted surgery (STLAS) for benign ovarian cyst (BOC) in children

Methods

Medical records of patients with diagnosis BOC undergoing STLAS at our center from February, 2009 to February, 2014 were reviewed. For the STLAS, a 10 mm umbilical trocar was placed and a 10 mm camera with engrafted 5 mm working channel was used. The ovarian cystic wall was grasped and brought to the umbilical site and then the cystic fluid was aspirated outside the peritoneal cavity. The cyst then was brought out of abdomen via the umbilical incision and excision of the cyst was performed extracorporally, sparing ovarian tissue when possible. When delivery of the cyst to the umbilical site was impossible due to short adnexal pedicle, the cyst was delivered out of the abdomen via a minimal transversal suprapubic incision after fluid aspiration and cystic removal was performed as described.

Results

30 patients were identified, with median age of 4 years (range: 8 days - 15 years). The median size of the cyst was 7.0 cm (range: 3 - 13cm). In 16 cases (53.3%) the cyst was mature teratoma, in 10 cases (33.3%) – simple cyst and in 4 cases (13.3%) – dermoid cyst. In 25 patients (83.3%) the cyst was excised via the umbilical incision and in 5- via the suprapubic incision. Sparing of the ovarian tissue was performed in 27 cases (90%). The mean operative time was 48±15.3 minutes. There was no perioperative complication. The mean postoperative hospital stay was 1.8±0.6 days. At a median follow up of 24 months, all patients were in good health, without recurrence. The postoperative cosmesis was excellent.

Conclusions

STLAS is feasible, safe, with excellent cosmesis and could be a viable approach in minimally invasive management of BOC in children.

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Germ Cell Tumours / Rare Tumours

POSTERIOR SAGITTAL APPROACH FOR SACROCOCCYGEAL TERATOMAS – AN EXCELLENT ALTERNATIVE

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Objectives

Chevron shaped buttock incision which is the standard surgical approach for sacrococcygeal teratomas has a major disadvantage due to an ugly scar and deformed buttocks which persist throughout life. Modification in the surgical approach through a posterior sagittal incision in the midline natal cleft provides an excellent cosmetic result, almost non-noticeable scar and no buttock deformity.

Methods

A prospective descriptive study was performed between March 2001 till December 2013. All patients with sacrococcygeal teratomas presenting in the neonatal age group or later who were operated through a posterior sagittal approach by a single surgeon were included in the study. The pre-operative features of the tumor, the difficulties faced during surgery with this approach and the post-operative outcome were analysed.

Results

19 sacrococcygeal teratomas (8 boys, 11 girls) were operated through midline posterior sagittal approach. Majority (16/19) presented in the neonatal period, whereas 3/19 presented at 1-3 years of age. The sizes of the tumor varied from 5.5 to 13 cms in horizontal dimensions of which 9 were type 1, 7 were type 2, 3 of type 3 as per Altman's classification. Excision of the tumor with the posterior sagittal incision was done with ease in all except in type 3 tumors wherein a slight lateral or superior extension of the incision was needed for adequate exposure. Complete excision including coccygectomy was done in all. Wound healed well in all except 3 patients having superficial wound gapes which healed spontaneously.

Conclusions

As compared to the chevron incision, the posterior sagittal approach requires meticulous midline dissection and raising of the flaps on both sides without damaging the external anal sphincter and the surrounding structures. With slight extension of the incision even the presacral component could be completely excised. Cosmetic results were excellent in all without any deformity of the buttocks.

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Germ Cell Tumours / Rare Tumours

GASTROINTESTINAL STROMAL TUMOR IN CHILDREN: A CLINICAL-PATHOLOGICAL REPORT FROM THE ITALIAN PEDIATRIC RARE TUMOR PROJECT (TREP)

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Objectives

Gastrointestinal stromal tumours (GISTs) are the most important group of mesenchymal smooth muscle neoplasms that can arise anywhere within the gastrointestinal tract. However, their incidence during childhood, is about 0.02 cases per 1 million per year. All tumors of mesenchymal origin that express the membrane protein kit (CD117) or which have a mutation in platelet-derived-growth factor a (PDGFRA) should be considered as GISTs. Purpose of this study is to define the clinical-pathological characteristics of GISTs in patients recruited in the study Italian TREP.

Methods

All patients enrolled in this study were less than 16 years old at the diagnosis. Staging and follow-up workup included the following investigations: digestive endoscopy, magnetic resonance imaging (MRI), and, in some cases, computed tomography (CT). Samples of tumour tissue were also stained with the antibodies against KIT and PDGFRAa. Histomorphologically, GISTs were subtyped according to Fletcher et al. into three categories: spindle cell type, epithelioid type, or mixed type.

Results

Nine patients (5 male and 4 female) with GIST were enrolled in this study. Tumour was located in the stomach in 8 patients and 50 cm proximal to the ileocecal valve in 1. The most common symptom in gastric GIST was the anemia, associated with bleeding; patient with jejunal GIST complained abdominal pain. All patients underwent sparing surgery. One patient with gastric GIST required afterward a radical gastrectomy because of a local recurrence. All patients are alive at the most recent follow-up, although 3 patients are currently undergoing chemotherapy with Sunitinib because of hepatic/peritoneal metastases before a second look surgery.

Conclusions

Currently, there are no international guideline-concordant treatment for GIST during childhood. However, it is important to remember that in children with a GIST the 5-year probability of survival is 90%, therefore sparing surgery should be considered even in cases of multifocal disease or local nodal metastases.

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Germ Cell Tumours / Rare Tumours

INCIDENCE AND OUTCOMES OF PEDIATRIC EXTREMITY MELANOMA: A PROPENSITY SCORE MATCHED SEER STUDY

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Objectives

There is a paucity of literature on the treatment of melanoma in children with surgical management often extrapolated from the adult experience. We sought to determine the incidence, surgical treatment, and outcomes of extremity melanoma in pediatric patients.

Methods

The SEER registry was analyzed for all patients <20 years of age with extremity melanoma between 1973 and 2010. Multivariate and propensity-score matched analyses were performed to identify independent predictors of survival.

Results

Overall, 917 patients were identified with an overall age-adjusted incidence of 0.2 per 100,000 persons/year, with an annual percent change of 0.96 ($p < 0.05$). Patients were most commonly female (66%), age 15-19 years (72%), and white (91%). Most were diagnosed with localized disease (77%), lower extremity (54%), melanoma-NOS (52%), superficial spreading (33%), and nodular histology (7%). Surgical procedures included wide local excision (50%), excisional biopsy (32%), surgery-NOS (14%), major amputation (0.2%), sentinel lymph node biopsy (SLNB) (15%), and lymphadenectomy (LA) (28%). SLNB/LA was performed in 32% of patients with localized disease and 95% with regional disease. Overall, 20-year disease specific mortality was 7% with lower survival for males (89%), regional (79%) and distant disease (36%), nodular histology (69%), and upper extremity (90%) (all $p < 0.05$). For regional and distant disease there was no survival advantage for SLNB or LA vs no sampling. Multivariate analysis revealed localized disease (OR 5.247), lower extremity site (OR 2.145) as significant independent prognostic indicators of survival, while distant disease (OR 0.249), and nodular histology (OR 0.338) were indicators of poor survival (all $p < 0.02$). Propensity-score matched analysis found no differences in survival rates between SLNB or LA vs no sampling for localized and regional disease.

Conclusions

Multivariate and propensity score matched analysis of pediatric extremity melanoma in SEER demonstrates no survival advantage between children undergoing sampling procedures or no sampling for localized/regional disease.

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Germ Cell Tumours / Rare Tumours

THE ASSESSMENT OF QUALITY OF SURGICAL TREATMENT IN CHILDREN WITH AGGRESSIVE FIBROMATOSIS - THE STUDY OF 50 PATIENTS

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Objectives

Aggressive fibromatosis (AF) is locally destructive proliferative process with marked tendency to recur.

The Aim of the study was to assess the risk factors for failure of the surgical treatment in children with AF.

Methods

Between 1981-2014, 50 children (median age 8,43 yrs) with AF were treated in centres cooperating within Polish Paediatric Solid Tumours Study Group. Clinical data regarding localisation of tumour and treatment modalities (resections: wide-R0, marginal-R1, incomplete-R2) were retrospectively evaluated and correlated with the results of treatment (complete remission-CR, stable disease-SD, progressive disease-PD, occurrence of the relapse).

Results

25/50 patients (pts) had R0 resection, 13 R1, 8 R2. Cht was used in 21 and XRT in 6 cases. After a median follow up of 33 months 31/50 pts had CR, 14 SD, 5 PD. Relapses developed in 17/50. 24/25 pts achieved CR after R0 resection, 7/13 after R1, 0/8 after R2 ($p < 0,0001$). All 38pts after R0 and R1 resections entered CR or SD vs 4/8 pts after R2 entered SD ($p = 0,00043$). 7/13 pts had CR and 6 SD after R1 resection vs 4 SD and 4 PD after R2 ($p = 0,00446$). 26/36 pts without symptoms of mutilation achieved CR vs 5/14 ($p = 0,0441$). Rates of relapses by quality of resection were as follow R0-8/25, R1-6/13, R2-3/8 ($p = 0,692$). Resections R0 and R1 were more likely in extremity and trunk (32/35 vs 6/11; $p = 0,0127$), however localisation of tumour did not have influence on the outcome ($p = 0,480$) and the occurrence of relapse ($p = 0,220$).

Conclusions

The importance of the radical surgical margin (R0) seems not clear. Patients after R1 resections can also achieve good outcomes. Mutilating surgery does not improve outcome. The achievement of SD should not be classified as the negative treatment result. Extremities and trunk seem to be favourable sites regarding possibility of R0 and R1 resection.

O-162

Miscellaneous

RESECTABILITY FOR STAGE IA LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA

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Objectives

Outcomes for children with Hodgkin lymphoma (HL) are excellent, but short and long term toxicities may be significant. Lymphocyte predominant Hodgkin lymphoma (LPHL) is a subtype of HL that typically presents with localized peripheral disease. A recent Children's Oncology Group (COG) study, AHOD03P1, demonstrated excellent outcomes for LPHL stage IA, single node disease treated by surgery alone. The purpose of this analysis was to assess the feasibility of extending surgery only treatment to all children with stage IA LPHL.

Methods

Initial imaging for patients enrolled on COG AHOD03P1 with stage I disease >1 lymph node was reviewed independently by two pediatric surgical oncologists for disease location, extent of nodal involvement, and resectability. Concordance between the surgeons was compared, and reasons for unresectability were noted.

Results

Forty-seven patients were identified. There were 36 males (77%) and 11 females (23%). Median age was 12.3 years (range 4.4 to 20.7 years). Eleven cases were not evaluable due to insufficient imaging available for review. Of the 36 cases that were evaluated, involved nodal locations included submandibular (1), inguinal/iliac (5), and cervical (30). Mean number of nodes requiring resection was 5 (range 1-15). Thirty-four cases (94%) were felt to be resectable by at least one of the surgeons. Surgeon agreement on resectability was 81% (29/36). The resectability opinion differed between surgeons in 5 cervical and 2 iliac cases. Reasons for unresectability and disagreement included morbidity due to extent of the anticipated operation, and proximity to vital structures. Surgeon agreement on type of operation required occurred in 97% of cases.

Conclusions

The technical feasibility of surgery for children with stage I LPHL is high. However, this approach to the treatment of stage 1 LPHL should not be considered the standard of care and must be studied within the context of a clinical trial.

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Miscellaneous

LONG-TERM PHYSIOLOGIC AND ONCOLOGIC OUTCOMES OF INFERIOR VENA CAVA (IVC) THROMBOSIS IN MALIGNANT ABDOMINAL SOLID TUMORS IN CHILDREN

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Objectives

To evaluate the physiologic and oncologic outcomes of IVC thrombosis in children with abdominal malignancies, in order to better understand the long-term risks and benefits of multimodal interventions employed in their management.

Methods

Retrospective review of 15 children with malignant IVC tumor thrombosis treated between January 1996 and December 2011. Extent of tumor thrombus was classified according to Hinman levels I-III. Completeness of thrombus resection and caval patency on follow-up imaging was evaluated. For 12 patients with Wilms tumor, disease characteristics, treatment, and oncologic and physiologic outcomes were correlated with overall survival (O.S.).

Results

Twelve patients had Wilms tumor, 2 had hepatoblastoma, and 1 had adrenocortical carcinoma. Thirteen (87%) patients received neoadjuvant chemotherapy, which reduced the Hinman level in 2 patients. Six (40%) patients had complete thrombus resection, 7 (47%) had partial resection, 1 (7%) had no resection, and in 1 (7%) patient the extent of resection was unknown. On follow-up imaging, 8 (53%) patients' IVCs were patent, 6 (40%) had residual thrombus, and 1 (6.7%) was surgically interrupted. On follow-up imaging, all 6 patients with complete thrombus resection and 2 of 8 patients with partial or no thrombus resection had patent IVCs. These 2 patients both received additional boosts of adjuvant IVC radiation. Only 3 (20%) patients had perioperative complications and 2 (13%) patients experienced transient effects related to IVC occlusion. Among Wilms tumor patients, O.S. was associated with histologic subtype ($P=0.096$) and IVC patency on follow-up imaging ($P=0.027$, Log-rank test).

Conclusions

In children with malignant IVC thrombosis, complete resection of the thrombus is associated with maintenance of long-term caval patency. Adjuvant radiation may be effective in clearing residual IVC thrombus. Complete clearance of malignant IVC tumor thrombus in Wilms tumor may confer a survival benefit. Independent of the surgical management of the thrombus, few perioperative and long-term physiologic complications were encountered.

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Miscellaneous

ONCOLOGICAL AND FUNCTIONAL OUTCOME WITH MULTIMODALITY MANAGEMENT OF MALIGNANT PEDIATRIC MUSCULOSKELETAL TUMORS OF THE PELVIS AT A TERTIARY CANCER CENTER IN INDIA

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Objectives

To evaluate the morbidity, functional outcome, and oncologic results in pediatric patients with malignant tumors of the pelvis treated with surgical resection as part of their multimodality treatment.

Methods:

From Nov. 2000 to Dec 2009, 30 patients with pelvic tumors had undergone surgical excision. The medical records, imaging, oncological and functional status were reviewed. There were 20 males and 10 females, mean age 13 years, range 2 to 18 years. The diagnosis included Ewing's sarcoma in 22, Osteogenic sarcoma in 4, chondrosarcoma in 2 and synovial sarcoma of bone in 2 cases.

Results:

Eighteen resections included the acetabulum and 12 did not. Two of 30 patients had involved margins. Of the 26 patients in whom histologic response to chemotherapy was assessed, 19 patients showed a good response to chemotherapy and seven were poor responders. Five patients with Ewing sarcoma had postoperative radio-therapy (four poor responders and one good responder with a very large soft tissue component). Two patients died because of chemotherapy complications at 6 and 4 months, respectively. One patient had an intra-operative urethral injury, two had wound dehiscence that required secondary suturing, and three had infection. One patient had progressive painless ankylosis of hip. Twenty-seven patients were available for follow-up. Follow-up ranged from 4 to 158 months (mean 48 months). Nineteen patients are currently alive. There were two local recurrences. The overall survival was 68% at 5 years. The Musculoskeletal Tumor Society Score ranged from 22 to 29.

Conclusion:

Surgery in malignant pelvic tumors is extremely challenging and requires utmost surgical planning and its careful execution. It provides good local control and oncologic outcomes with acceptable function in these patients.

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Free Paper Session 1: Supportive Care: What Can Nurses Do?

AN EVALUATION OF THE PEDIATRIC ONCOLOGY NUTRITION SCREENING TOOL

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Objectives

The Pediatric Oncology Nutrition Screening (PONS) tool is proposed as a method of assessment of nutritional risk in children with cancer. The aim of this study was to assess the validity of the PONS Tool for determining current nutritional status in children with cancer.

Methods

Validity of the PONS tool was tested in children being treated for cancer at the Queensland Children's Cancer Centre. The PONS tool was performed for each subject and involved 5 questions relating to cancer type, therapy and side effects, oral intake, weight loss and a measure of body size. To represent current nutritional status; body mass index (BMI), mid upper arm circumference (MUAC), triceps skinfold and percent fat (%fat) from the Bodpod®, were measured in each child.

Results

A total of 59 inpatients and outpatients (n=34 liquid cancers) were assessed between 5.4 and 17.1 years. Using the PONS Tool cut-offs, 36% of population were classed as low nutritional risk, 34% as moderate risk and 30% as high nutritional risk. The PONS tool was strongly correlated ($p < 0.01$) with weight Z score ($r = -0.62$), BMI Z score ($r = -0.68$), triceps skinfold ($r = -0.34$), MUAC ($r = -0.43$) and %fat ($r = -0.44$). The mean weight Z score (-1.1), BMI Z score (-1.4) and MUAC (18.5cm) of the high risk group was significantly ($p < 0.05$) lower than the moderate and low risk group. The %fat of the high risk group (25.2%) was significantly lower ($p < 0.05$) than the low risk group (35.3%).

Conclusions

The PONS tool identifies current nutritional status in children undergoing treatment for cancer and significant nutritional differences are evident between the groups classified by PONS as low, moderate and high risk. The next steps in the evaluation involve assessing the concurrent and predictive validity of the tool, and assessing the feasibility, reliability and applicability in international sites.

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Free Paper Session 1: Supportive Care: What Can Nurses Do?

THE IMPACT OF NUTRITIONAL STATUS ON HEALTH-RELATED QUALITY OF LIFE IN CHILDREN TREATED FOR CANCER

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Objectives

Malnutrition in childhood cancer patients has been associated with lower levels of health related quality of life (HRQL). However, this association has never actually been tested. Therefore, we aimed to assess the impact of nutritional status on HRQL in children treated for cancer.

Methods

In 104 children, aged 2-18 years and diagnosed with hematological, solid, or brain malignancies, nutritional status and HRQL were assessed at diagnosis and at 3, 6, and 12 months using the child- and parent-report versions of the PedsQL 4.0 Generic Core scale and the PedsQL 3.0 Cancer Module. Scores on both scales range from 0-100.

Results

Undernourished children (BMI or FFM<-2SDS) reported significantly lower PedsQL scores compared with well-nourished children on the domains physical functioning (-13.3), social functioning (-7.0), cancer summary scale (-5.9), and nausea (-14.7). Overnourished children (BMI or FM>2SDS) reported lower scores on emotional (-8.0) and cognitive functioning (-9.2) and on the cancer summary scale (-6.6); whereas parent-report scores were lower on social functioning (-7.5). Weight loss (>0.5 SDS) was associated with lower scores on physical functioning (-13.9 child-report and -10.7 parent-report), emotional (-7.4) and social functioning (-6.0) (child-report), pain (-11.6), and nausea (-7.8) (parent-report). Parents reported worse social functioning and more pain in children with weight gain (>0.5 SDS).

Conclusions

Undernutrition and weight loss were associated with worse physical and social functioning; whereas overnutrition and weight gain affected the emotional and social domain of HRQL. These findings stress the importance of adequate nutritional care during treatment. Measures that improve nutritional status will contribute to enhanced health outcomes in children treated for cancer.

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Free Paper Session 1: Supportive Care: What Can Nurses Do?

PEDIATRIC ONCOLOGY NURSES INVESTIGATE SOCIALIZATION CHALLENGES RELATED TO NUTRITION: A SOUTH AFRICAN STUDY

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Objectives

The effect of cancer and treatment modalities affect and compromise nutrition intake, but socialization has an even greater impact on individuals and society in general. When taken in a well-planned balanced meal, nutrition is beneficial for preventing and reducing cancer and treatment side effects, while providing wellness and preventing cancer-related malnutrition and obesity. The benefits of nutrition are only achievable if nurses have insight into the importance of environmental socialization for patients and its effect on proper nutrition. We highlight how socialization impacts on a patient and family's interpretation of nutrition in terms of lifestyle, culture, norms, beliefs, religion, age, gender and education. We emphasize that simple changes in diet interpretation, availability, preparation and provision can increase the benefits of nutritional intake and improve the patient's quality of life regardless of their socio-economic status.

Methods

A prospective observational and cross-sectional survey of 32 parents (30f-2m) and 78 children ages 3-19 [3-6(15); 7-12(39), 13-19(28;15f-13m)] was performed on a day-to-day basis and twice a week on clinic days for three months. The subjects signed written informed consent. The survey included questions on the environment, attitude, presentation and serving of meals while on therapy for cancer. Verification of cultural-socio-economic background was done in relation to food preference, attitude, eating times, hospital and home environment, and served portions especially for teenagers even when at home.

Results

Compliance with nutritional recommendations was found to be the main problem due to diverse social issues and ignorance. Patients' nutritional intake remained compromised when they were introduced to new eating habits while on treatment for cancer that went against their food socialization norms.

Conclusions

Despite socialization challenges, nurses must provide children, adolescents and their parents/guardians with nutritional information that is appropriate for all levels of cultural-socio-economic status so that adequate nutrition remains a cornerstone for improving chances of recovery throughout treatment.

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Free Paper Session 1: Supportive Care: What Can Nurses Do?

DECISION MAKING IN CHILDREN WITH CANCER: IT'S NOT ABOUT MAKING "BIG" TREATMENT DECISIONS

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Objectives

Informed by the control preferences construct, we developed the Child and Adolescent Decision Involvement Scale (CADIS) for use in children and adolescents with cancer. Cognitive interviews were undertaken to ascertain content validity of the new instrument before initiating large scale psychometric evaluation. Interview techniques provoked in-depth discussion of what being involved in their treatment decisions meant to child and adolescent participants, which focused on access to information along with decision involvement. We conducted additional analyses to better understand how children perceived the interchange between information and decision involvement.

Methods

Twenty children and adolescents (9-17 years) with cancer participated in audio-recorded cognitive interviews. We asked participants to recount their previous treatment decision making (TDM) experiences and to interpret the CADIS statements. We employed constant comparative analysis of verbatim interview transcripts to generate codes and descriptive statements using Atlas.ti.

Results

A majority of participants aligned the five CADIS statements according to Degner's original Control Preference Scale metrics. Participants interpreted the statements using both their personal and theoretical TDM experiences. Children recognized their limited authority/ability for making "big" treatment decisions. They described how being part of TDM helped them gain disease and treatment knowledge, understand why decisions are made and to know what to expect. Children discussed how they had information needs that were both independent of and necessary for TDM. Children also had unique information about themselves that they wanted to contribute to TDM. Children described a larger role for their involvement in "small" supportive care decisions. A few participants of all ages related a desire for limited information and decision involvement.

Conclusions

Child descriptions of their TDM role did not follow a traditional shared decision making paradigm. Additional research is needed to understand TDM from the child's perspective before intervention research can be initiated.

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Free Paper Session 1: Supportive Care: What Can Nurses Do?

IT'S THE ONLY THING HE ENJOYS ABOUT THE WHOLE (HOSPITAL)

EXPERIENCE: EXPERIENCE OF MASSAGE THERAPY WHEN RECEIVING CANCER THERAPIES

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Objectives

While the use of complementary and alternative (CAM) therapies in children with cancer has been reported (as high as 84%) there are few systematic accounts of families experiences, let alone proper investigations of their impact on pain and symptom relief and quality of life. This study was occasioned following identification of a therapies room and the introduction of a Complementary Therapy Nurse Specialist in a children's cancer unit. Our aim was to capture the child's experience of receiving massage alongside conventional cancer therapy and to examine its impact on child and family.

Methods

All children, young people (4-12 years) and their parents, as well as parents of infants (under 4 years) admitted to a large tertiary centre in the UK and accessing the service during the period of recruitment were approached. Participatory research methods, such as symptom sorting cards, were used alongside scales to measure sleep and pain with children. Qualitative content analysis was used to detail 28 stories of children's experiences, and 22 accounts from parents, of their reflections on their child's experience.

Results

Children's and parents' descriptions of the experience were only positive. Massage helped with a range of symptoms including pain, and anxiety. It also provided a safe space for children to relax, think about something else and enjoy calming thoughts. Children spoke about the 'special room' and clearly for many the nurse specialist had taken on an important role in their care. Head massages were particularly popular with some children, helping them with headaches and sleep. In the majority of cases where scales were completed there was indication of perceived improvement.

Conclusions

This presentation will focus on these accounts that suggest massage has a place in the care for children with cancer. Further research is needed to assess specific impact and outcomes in different populations (e.g. children receiving palliative care).

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Free Paper Session 1: Supportive Care: What Can Nurses Do?

COMPLEMENTARY ALTERNATIVE MEDICINE USED FOR THE MANAGEMENT OF FATIGUE AND PSYCHOLOGICAL STRESS IN PEDIATRIC ONCOLOGY POPULATION

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Background: Cancer-related fatigue (CRF) has been described as the most stressful and prevalent symptom in pediatric oncology patients, occurring in 35.6% to 93% of cases. Psychological stress generated during hospitalization can negatively influence the immune system through neuroendocrine and behavioral pathways. For these patients, other modalities of treatment such as the Complementary Alternative Medicine (CAM) can be necessary. Scientific evidence supports the use of CAM for the management these symptoms in adults with cancer, however, the pediatric oncology population studies are still scarce.

Purpose: To identify and analyze scientific evidence about the use of CAM for the management of fatigue and psychological stress in pediatric oncology population.

Material and Methods: We conducted an integrative literature review in which eight databases were accessed for the search: PubMed, Web of Science, CINAHL, LILACS, EMBASE, SCOPUS, PsycINFO and Cochrane Library. Full-text articles were included, studies in English, Spanish or Portuguese published in the last 14 years (2000 until 2013). Controlled and uncontrolled descriptors, as well as its synonyms, were crossed for location of the articles, for example: 'fatigue; cancer-related fatigue; cancer/neoplasm; stress, psychological; child; adolescent; complementary alternative medicine and non-pharmacological interventions'. Two researchers independently analyzed the studies. Initially, 273 articles were found. After the exclusion of duplicate articles and of those that did not match inclusion criteria, and after full reading, we obtained a final sample of nine articles.

Results: The nine studies were grouped into five themes: physical exercises, therapeutic touch, music therapy, massage therapy and nursing interventions & health education. Among the nine studies, six (66.6%) showed a significant p value for CRF and/or psychological stress, evidencing that after the use of CAM there was a decrease in symptoms.

Conclusions: The use of CAM can improve symptoms of CRF and psychological stress in pediatric oncology population.

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Free Paper Session 2: Education and Collaboration in Nursing Practice
BASELINE STANDARDS FOR PROVIDING PAEDIATRIC ONCOLOGY NURSING
CARE IN LOW AND MIDDLE INCOME COUNTRIES: POSITION STATEMENT OF
THE SIOP PODC NURSING GROUP

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Objectives

Paediatric oncology nurses in low and middle-income countries (LMICs) lack education, resources, support and adequate staffing needed to provide quality care. This is a major impediment for any childhood cancer program and contributes to the low survival rates in LMICs, where most childhood cancers occur.

At the 2011 Congress of the International Society of Pediatric Oncology (SIOP), the Nursing Working Group was established as one of 12 new working groups within the Pediatric Oncology in Developing Countries (PODC) structure. The group partners with and advocates for nurses and healthcare teams worldwide to improve paediatric oncology in LMICs. One of our first goals as a group was to develop a position statement regarding baseline standards for providing paediatric oncology nursing care in LMICs.

Methods

In 2013, the SIOP Nursing Working Group, representing 23 countries, collaborated to develop a position statement on baseline nursing standards needed to safely implement quality pediatric oncology nursing care.

Results

Six baseline standards were developed and included recommendations for staffing plans based on patient acuity, paediatric oncology orientation programme, continuing education and training, acknowledgement of nurses as core members of the multidisciplinary team, available resources for safe care, and evidence-based nursing policies and procedures to guide delivery of care.

Conclusions

These baseline standards represent what is needed to provide the minimum level of quality care; however, they are rarely met in LMICs, even in those programs supported by a twinning partnership with a high-income country. This is an international issue that needs addressing in order to improve the survival rate of children with cancer in LMICs. These standards can serve as a critical tool for allocating much needed nursing resources.

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Free Paper Session 2: Education and Collaboration in Nursing Practice
DELIVERING CULTURAL COMPETENT NURSING CARE: A GLOBAL PERSPECTIVE

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Objectives

Pediatric oncology nurses must develop cultural competency to care for children of varying backgrounds. Cultural competency includes self-awareness, knowledge about different cultures, languages, values and beliefs. The purpose of this study was to explore nurses' delivery of culturally competent care in both high income countries (HIC) and low/middle income countries (LMIC).

Methods

A brief web-based survey on cultural competence was developed, focusing on nurses' attitudes, practices and challenges. In March 2014, nurses from both LMIC and HIC who care for children with cancer received emailed invitations to complete the survey with multiple choice and open-ended questions.

Results

Data from 66 surveys were analyzed. Nurses from 12 LMIC comprised 26% of respondents; the remainder included nurses from 9 HIC. Commonly identified challenges included language barriers, obtaining information about specific cultures and developing trusting relationships. Nurses shared successful strategies to deliver culturally competent care (e.g., recognizing non-verbal cues, listening, being respectful and non-judgmental, consulting with knowledgeable staff members, using humor), as well as desired resources (e.g., increased access to interpreters, written information for patients/parents, accessible online/written resources). Prior education in cultural competency differed between the groups. Only 24% of the nurses from LMIC received prior cultural training, compared to 71% of the nurses from HIC ($p=0.001$). Overall, 86% of the nurses stated that more education was needed to develop cultural competence (100% among LMIC nurses). Lectures, written modules and videos were the top formats identified.

Conclusions

Nurses from LMIC and HIC viewed cultural competency as vital to their practice and felt that exposure to other cultures provides opportunities for individual and professional growth. In addition, they gain new perspectives on life and show increased sensitivity in nurse/patient relationships. Survey results will guide the development of resources and educational programs to support nurses. A written teaching module is proposed for implementation in LMIC and HIC.

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Free Paper Session 2: Education and Collaboration in Nursing Practice
INTERNATIONAL PEDIATRIC ONCOLOGY NURSING PARTNERSHIPS ARE
COMPLEX: AN OVERALL HISTORY AND A NORWEGIAN/US AND ETHIOPIAN
EXAMPLE

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Objectives

To describe the complexity of international pediatric oncology nursing partnerships between a high-resource country and a low-resource country by reviewing the history of twinnings and using specific examples from an on-going collaboration in Ethiopia.

Methods

Review the history of pediatric oncology twinnings starting in the late 1980s when nurses from Italy collaborated with nurses in Nicaragua. Early St. Jude Children's Research Hospital's International Outreach Program and World Child Cancer twinnings will be included. Provide examples of local (low-resource partner) nursing training, equipment purchases, and travel for nurses from local partner sites to attend international conferences within the context of the larger twinning agenda. Review early models of didactic and clinical teaching such as short-term nursing trainings (1-2 weeks), distance learning, and specific curriculum materials/strategies that have been utilized in the past.

Results

How nurses' collaborations and training are operationalized in low-resource country settings is complex. The role of a nurse in many of these countries may be understood as entirely distinct from the nurse's role in high-resource countries. How nursing practice is defined and constricted by local hospital administration regulations can dramatically impact visiting nurses' ability to provide up-to-date specialized training. Local nurses' and community perceptions of the hazards of working with children with cancer and chemotherapy complicate educational efforts.

Conclusions

An understanding of the history of international pediatric oncology nursing twinning programs reveals the challenges of nursing training and collaborations in countries with low resources. Cultural, language, and educational differences are identified that complicate collaboration, notwithstanding the local nurses', experience, knowledge and strengths. A current twinning in Ethiopia that includes nurses from the US and Norway is highlighted to provide specific examples of the complexity of partnering with and providing 'training' programs for pediatric oncology nursing specialization in a low-resource country.

O-174

Free Paper Session 2: Education and Collaboration in Nursing Practice
NURSING CARE PRIORITIES OVER TIME IN A NEW PEDIATRIC ONCOLOGY UNIT
IN A RESOURCE-LIMITED AFRICAN COUNTRY

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Purpose:

Describe nursing care priorities over time in a setting with limited resources on Ethiopia's newly opened (April 2013) only dedicated ward for childhood cancer.

Materials and Methods:

The 26-bed unit has 14 non-rotating nurses and about 257 children on treatment. Approximately 95% of patients receive free care because they are officially recognized as living in extreme poverty; most have no/little education. Generally, children arrive at the hospital with advanced cancer; survival is <5%.

Results:

The ward has newly dedicated pediatric oncology nurses who are learning to manage complex disease and social issues. Advancements have been made in the scope of nursing care since two newly graduated pharmacists on the ward mix some chemotherapy and a newly graduated volunteer psychologist provides play therapy thus assuming some non-nursing tasks. New outpatient housing from a Mother Teresa House has reduced nursing attention to this family support issue. Teaching pediatric nurses about cancer care from other government hospitals has begun.

Conclusions:

Remaining challenges: nursing concerns about side effects of preparing chemotherapy, high death rate, low staffing, and lack of parent teaching about the child's disease, infection control and side effects of chemotherapy. Families' extreme poverty is reflected in low levels of personal hygiene and exposure to health care and education. Families arriving from remote areas often speak dialects that local hospital personnel do not understand, thus compounding the challenge of family teaching. The nurses must use critical thinking skills, including their knowledge of multiple Ethiopian cultures and practices, to strive for safe and supportive care for the children and their families. This presentation highlights how the nurses continually prioritize their care over time in this public hospital with severely limited resources, and in a setting of significant professional hierarchy where nursing does not always have a strong voice.

Document not received

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**Free Paper Session 2: Education and Collaboration in Nursing Practice
ESTABLISHING PEDIATRIC ONCOLOGY NURSING EDUCATION DEPARTMENT AT
CHILDREN CANCER HOSPITAL, PAKISTAN**

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Objectives

Developing countries are far behind in sub-specialty care such as pediatric oncology where 80% of children with cancer live. Pakistan is a developing country with total population of 180 million. Nursing in Pakistan like other profession is also in transition phase with emerging new sub-specialties there is a dire need for education and training programs in all areas.

Methods

Keeping in sight the identified need for educational/training programs for nurses children cancer hospital initiated Pediatric Oncology Nursing Education Department (PONED). The Department developed three major programs for nurses over the period of four years with two courses already successfully running and one to start in September 2014. Pediatric Oncology Technician Course is a diploma certification one year course for young adults interested in health care career. Secondly a short course for Registered Nurses already working in pediatric oncology setup is offered twice a year it is a two weeks certification course designed to enhance knowledge and practice. Thirdly a one year post RN diploma first ever in Pakistan to be started in September 2014 with focus on creating sub-specialty case management nurses.

Results

We now have a first ever fully operational pediatric oncology nursing education department with courses registered with licensure bodies that is technician course with Sindh medical faculty and RN diploma with Pakistan nursing counsel. Have completed 4 cycle of technician course with 25 successful nurse technician and 6 courses for RN with 82 trained nurses from all over Pakistan

Conclusions

Children Cancer Hospital has taken the lead in professional training of Pediatric Oncology Nursing with vision to create centre of excellence in Pediatric Oncology. This can be a model for other health care institutes looking after childhood cancer.

O-176

**Free Paper Session 3: The challenges of the professional role
A SWEDISH PERSPECTIVE ON CARING SCIENCE RESEARCH IN PAEDIATRIC
ONCOLOGY: A LITERATURE REVIEW**

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Objectives

The body of research-based knowledge in paediatric caring sciences has been increasing thanks to a dramatic improvement in outcomes related to research and advances in treatment.

The aim of this review was investigate the content of published studies in paediatric oncology related to caring sciences.

Methods

A systematic literature review of 137 published articles on paediatric oncology related to caring science in Sweden was performed.

Results

The result shows that most of the studies were descriptive or comparative studies with a quantitative design. Most of them had parents in focus, and only 22% had focus on the child. Most of the studies investigated wellbeing, using questionnaires or interviews. The result, as stated in the articles, demonstrated that the child's disease has affected the wellbeing of all people coming in contact with the child, in both positives and negative ways. Also the child's disease causes distress related to physical, psychological, existential and social aspects. Several mediating factors for the experience of distress and wellbeing were found, as; disease and treatment severity, gender, time since diagnose, and the use of internal and external support. Frequent reported health promoting aspects were: family togetherness, coping strategies and engaging in activities and normal life, as well as quality of care; as emotional support, information and family participation in care. Suggestions for clinical implications, stated in the articles, were often described in a diffuse manner making translation into clinical practice difficult. However, some areas of clinical implications could be identified and described.

Conclusions

To reflect the child's perspective in paediatric oncology requires that future researchers take on the challenge of including children. The biggest challenge for the future would be to make a shift from explorative studies to intervention studies. There is an urgent need to transform research results into clinical practice.

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**Free Paper Session 3: The challenges of the professional role
AN EXPLORATION OF NURSES' VIEWS REGARDING PROFESSIONAL
BOUNDARIES WHEN CARING FOR A CHILD OR YOUNG PERSON AND THEIR
FAMILIES WITH A LIFE THREATENING CONDITION**

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Objectives

Professional boundaries (PB's) are central for the establishment of therapeutic relationships. Tensions exist between the balance of involvement that is beneficial in the therapeutic relationship, to one that is too close and potentially destructive. This challenge is one that is of common occurrence in nursing, where prolonged involvement, caring, and intimacy form the basis from which nursing care is delivered. This presentation reports on the findings from a small exploratory study conducted to uncover experienced nurses' views of PB's when caring for a child or young person with a life threatening condition.

Methods

Conducted in a large teaching hospital within the south of England. Semi-structured interviews were undertaken with six experienced nurses caring for a child or young person and their families with a life threatening condition. Content analysis was utilized to extrapolate meaning from the transcribed interviews.

Results

Knowledge and understanding of PB's and awareness of meaning was good yet PB's are a routine concern. Management of PB's are currently insufficient for nurses working in this area of practice. Strategies are required to improve awareness and support nurses. Support from senior staff could help to reduce the incidence and consequence of boundary crossing and violations.

Conclusions

The study suggests that the determination of PB's within a professional yet therapeutic relationship is one of the most significant challenges for nurses caring for a child or young person. Because of the levels of intensity, and the emotive nature of working with a child or young person with a life threatening condition the study suggests that the crossing or violation of PB's should be considered as an occupational hazard that must be given due attention. The motive that drives boundary crossing and violations, and the governance that is placed to determine such behavior is important. Further research is required to understand such behavior to develop improved coping techniques.

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**Free Paper Session 3: The challenges of the professional role
BALANCING BETWEEN COMPASSION AND PROFESSIONALISM –
INTERPRETERS EXPERIENCES OF CHILDHOOD CANCER CARE**

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Objectives

Linguistic and cultural diversity is an integral part of our society, and so even in childhood cancer care. Children with cancer and their families not sharing a common language with health care staff are in a fragile and vulnerable situation. The purpose of this paper is to describe interpreters' experiences of interpreting in childhood cancer care in a paediatric cancer care unit at Astrid Lindgren Children's Hospital, Sweden.

Methods

Ten (n=10) interpreters with interpreting experience in childhood cancer care were interviewed in individual semi-structured interviews. Data from the interviews were analysed using qualitative content analysis.

Results

The analysis of the data resulted in the sub-theme reported in this paper: *Balancing between compassion and professionalism*. Interpreters strive constantly to keep a balance between their empathy and compassion, and to perform their task professionally. This balance is sometimes complex to keep because of the difficult circumstances their clients face. The interpreters will handle this balance by "*sparing them my tears*" while, feeling compassion. There is a basic desire to help from a humane perspective, but also since they are countrymen with the same cultural background. In particularly vulnerable situations, interpreters sometimes step outside their professional role e.g. in terms of neutrality, to become, in their view, a fellow human instead.

Conclusions

Interpreters are struggling to be the "neutral party" their professional code of conduct requires in the relation to the families. Interpreters explicitated two phenomena of struggle. First, emotional involvement (children suffering from cancer). Secondly, striving for a meeting point of understanding, this requires commitment beyond interpreters' obligation of neutrality. Establishing a meeting point of understanding requires explanation of both context and cultural aspects. You cannot only "translate" words. Creating a meeting point of understanding and opening up multi-dimensional understanding requires creation of a relationship between the parties.

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Free Paper Session 3: The challenges of the professional role

CREATING A TAXONOMY OF TEENAGE AND YOUNG ADULT CANCER CARE IN ENGLAND THROUGH A MAPPING STUDY

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Objectives

Cancer services for teenagers and young adults in England are currently organised around 13 Principal Treatment Centres. We know that place of care, in terms of both disease and age appropriate specialist settings, is increasingly acknowledged as impacting on outcome. The objectives of this study were to undertake a mapping exercise of the 13 Principal Treatment Centres and develop a national taxonomy of care.

Methods

Our study combined observations, a review of annual reports, interviews with young people, family members, and healthcare professionals, and an activity with young people modelled after the Mosaic approach in 11 of the centres. The main purpose of the interviews was to document different views on care. Each interview transcript was analysed for content and organized in a framework to facilitate data management. Each framework was then summarized into a list of components of care. This list was then grouped in three broader categories created through thematic analysis of the list and which included: staff, environment of care, and activities. The information included in these categories was then used to develop the taxonomy of care in England.

Results

The analysis of the interview transcripts revealed shared perceptions of care in England, despite the wide diversity of models of specialised services currently in operation and the different contexts of care. Even though we found some differences in perceptions of care, all three groups agreed that the overall goal of teenage and young adult care is an individualized and specialised service which is made possible by: caring and supportive staff, an environment that feels like home, and age-appropriate activities.

Conclusions

The taxonomy allowed us to highlight the most important components of care in England. This taxonomy could be useful for other countries currently developing and shaping their own teenage and young adult services.

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Free Papers: Nurses and Psycho-Oncology Group

UNDERSTANDING BODY IMAGE, SEXUALITY, DATING, FRIENDSHIPS, AND FERTILITY IN ADOLESCENTS WITH CANCER FROM AN ADOLESCENT AND PARENT PERSPECTIVE

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Objectives

To assess: (1) the impact of cancer and its treatment on adolescents' body image, dating relationships, sexuality, as well as fertility from the perspective of adolescents and their parents, (2) the information needs of adolescents and parents regarding these issues, and (3) whether an Internet-based intervention is an appropriate tool for addressing these needs.

Methods

Twenty adolescents (12-18 years) either under cancer treatment or in remission and 20 parents were recruited from one pediatric tertiary care center. Participants completed demographic and medical history (adolescents only) questionnaires. Semi-structured interviews and participant observation were the primary data collection methods. All interviews were audio-recorded and transcribed. Transcribed data were entered into NVivo 10.0 and independently coded according to the study objectives by two trained analysts. Codes were organized into categories that reflected emerging themes. Discrepancies in coding were resolved through third-party discussion.

Results

Analysis revealed main themes for adolescents and parents around the impact of cancer on: (a) body image (i.e., hair loss, scarring, weight loss/gain, amputation), (b) dating relationships (i.e., relationships 'put to the test', [sexual] relationship readiness), (c) friendships (i.e., social isolation, needed support networks), and (d) fertility (i.e., lack of knowledge). For parents specifically, a change in family and work dynamics was noted. Parents and adolescents generally thought a web-based resource would be beneficial, and especially endorsed the notion of an interactive and engaging site. The anonymity and privacy of a website were cited as main advantages of the medium.

Conclusions

Findings from this study highlight the specific body image-, relationship- and sexuality-issues facing adolescents with cancer. Information gleaned from this study will inform the creation and evaluation of a developmentally appropriate online program for adolescents, parents and healthcare providers. This online program will provide information related to body image, relationships and fertility to ultimately improve the psychosocial health of adolescents with cancer.

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Free Papers: Nurses and Psycho-Oncology Group

THE CREATIVE BOX: A PATIENT CENTERED COMMUNICATION TOOL FOR USE IN ADOLESCENTS AND YOUNG ADULTS WITH CANCER

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Objectives

There is a growing recognition that taking care of adolescents and young adults (AYAs) is distinctive from that of children or adults.

A study has been conducted to explore the personal views of AYAs with cancer in order to get insight in their perspectives during treatment and survivorship.

The integration of study results in a patient centered tool in order to enhance the communication with the AYA and the multidisciplinary team was a secondary objective.

Methods

A qualitative study based on the principles of Grounded Theory was conducted. Twenty four adolescents aged 15 to 25 years were interviewed. Interviews were transcribed and coded using NVIVO 7. Constant comparison was used to analyse the data.

Datacollection and –analyse took place in a cyclic process

Results

From the AYAs' perspective, cancer is something temporarily passing their life-path. The diagnosis is a shock but their coping strategies are focused on preserving identity and guarding normal life. Three phases were identified: cancer freezes life – maintaining normal life is hard and cancer changed their life forever. The AYA is the director in his treatment and customized information, social network, contact with friends, ... are key aspects in AYA care.

A creative AYAbbox has been developed to meet these specific needs and to enhance the communication with the AYA. The box belongs to the AYA and contains a booklet with revealing stories of AYAs' experiences, postcards, a unique AYA tag, stickers mentioning feelings or concerns, cards with information or instructions and smart aids in communication with their relatives and professional caregivers.

Conclusions

The results are translated in a practical and meaningful tool, based on the experiences of the AYAs, inspiring caregivers on our pediatric ward to provide patient centered care in accordance to the specific preferences and wishes of the AYA.

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Free Papers: Nurses and Psycho-Oncology Group

THE DEVELOPMENT OF AN ONLINE PSYCHOLOGICAL SUPPORT INTERVENTION FOR TEENAGERS AND YOUNG ADULTS (TYA).

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Objectives

Findings by the Bristol On Target programme identified 55% TYA received no psychological support after a diagnosis of cancer and showed a significant gap between patient need and availability of information/advice on specific issues. This highlighted a need for accessible information on common psychological problems and for coping strategies/self-management tools. Using a co-creation approach, patients were asked to engage in the development of content, design and functionality of an online psychological/emotional support website.

Methods

Patients and professionals worked collaboratively through a variety of techniques including design studio events, co-design sessions, focus groups, 1:2:1 meetings and email correspondence. Engagement with both patients and professionals allowed the prioritisation and development of content, with a focus on self-management approaches to common psychological distress areas (anxiety, body image, low mood and anger). A series of events were held which brought together patients, healthcare professionals and website developers to establish and refine the required functionality and agree aspects of design for the site.

Results

The creation of a prototype website produced a tangible product for evaluation by the co-creation team, and formed the basis of the specification to develop the final product. The process ensured that the intervention has been built in a way that represents how TYA have asked for psychological support to be delivered, and what will engage them in the content. The format is multi-media based and TYA appropriate in its approach and content, and includes an interactive wellbeing tracker and the ability for user customisation.

Conclusions

The ability to engage and fully integrate the patient into service development, demonstrates the ability for TYA to work with healthcare professionals to design and deliver complex interventions. Further evaluation will confirm acceptability of a product created using this approach to increase availability of psychological support to TYA at times of immediate need.

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Free Papers: Nurses and Psycho-Oncology Group
USABILITY TESTING OF AN ONLINE SELF-MANAGEMENT PROGRAM FOR
ADOLESCENTS WITH CANCER

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Objectives

This study utilized a user-centered design approach to develop a bilingual (English and French) "Teens Taking Charge: Managing Cancer Online" Internet-based cancer self-management program that is acceptable, understandable and easy to navigate for adolescents and their parents.

Methods

Iterative cycles of qualitative usability testing involving user observation were used to refine the intervention. English- (Cycle 1: n=6, Cycle 2: n=6) and French-speaking (Cycle 1: n=6, Cycle 2: n=4) 12-18 year olds with cancer and one of their parents were recruited from two pediatric tertiary care centers. A brief intervention demonstration was provided. Participants used the website while "thinking aloud" about issues encountered with the interface and content, while a trained observer recorded difficulties and navigation errors. Participants then answered open-ended questions addressing their experience and recommendations for website improvement. Audio-recorded data were transcribed verbatim. French interviews were transcribed into English by a bilingual transcriptionist. Content analysis of transcripts and observer field-notes captured emergent themes related to intervention usability.

Results

French and English adolescents, as well as parents provided similar feedback on needed intervention changes. Overall, participants liked the website aesthetics and content. Both groups rated intervention content as appropriate, credible, and relevant to their cancer experiences. Usability issues identified after Cycle 1 of English and French testing related to (1) aesthetics (i.e., recommendation to eliminate 'blank-spaces' on pages), (2) navigation tools, and (3) English to French translation. Changes were made and no new issues were identified following the second phase of either French or English testing.

Conclusions

The multifaceted usability approach utilized provided insight into how Internet-based self-management programs can be made amenable to adolescents with cancer. Next steps will include feasibility testing before ultimately testing intervention effectiveness in a multicenter randomized controlled trial. It is expected that an acceptable, trusted and cultural competent intervention will improve health outcomes for adolescents with cancer.

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Free Papers: Nurses and Psycho-Oncology Group

IMPROVING QUALITY OF LIFE OF SIBLINGS OF CHILDREN WITH CANCER AFTER PARTICIPATION IN A PSYCHOSOCIAL GROUP INTERVENTION: A RANDOMIZED CONTROLLED TRIAL

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Background:

The social and emotional needs and overall quality of life (QOL) of siblings of children with cancer are often ignored. Systematic research assessing psychosocial interventions designed *exclusively* for siblings of children with cancer is rare.

Objective:

To determine if participating in *Siblings Coping Together* (SCT), a manualized group intervention (Experimental Group, EG), improves siblings' QOL relative to an Attention Control Group (CG).

Methods:

This study employed a multi-site randomized controlled trial (RCT) design with repeated measures. Inclusion criteria: Siblings, ages 7 to 16 years, of patients at least three months from diagnosis. Both groups completed 8 two-hour weekly group sessions and three assessments (pre-, T1; immediate post-intervention, T2; and three months later, T3). In the **EG**, sessions were designed around a theme, following the SCT plan of educational, social, and therapeutic problem-solving activities through games and crafts; **CG** sessions focused only on the social component through games and crafts. Outcome measures included parent proxy and self-reported QOL (PedsQL4.0). Analyses: Repeated-measures ANOVAs with partial eta-squared as indices of effect size. Institutional approval was obtained and participants signed consent forms.

Results

Preliminary analyses were based on completed data for 53 siblings at T1 and T2 and 26 at all 3 assessments. *Parent Report.* At T3, significant group by time interactions suggested improved *total* PedsQL ($\eta^2=0.18$) and *school functioning* ($\eta^2=0.26$) in the EG compared to the CG over time. Both groups improved *emotional* PedsQL over time ($\eta^2=0.25$) with greater scores in the EG ($n=0.21$). *Self-Report.* There were some trends suggesting general improvements in siblings' *total* PedsQL scores ($\eta^2=0.20$), and greater improvement in EG's PedsQL scores compared to the CG in *school functioning* ($\eta^2=0.14$) and *feelings* ($\eta^2=0.19$).

Conclusions

Preliminary findings suggest the manualized group intervention is an effective program, resulting in major improvements in emotional and school related quality of life in siblings of children with cancer.

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Free Papers: Nurses and Psycho-Oncology Group

PSYCHOSOCIAL HEALTH-RELATED QUALITY OF LIFE IN A COHORT OF CHILDHOOD CANCER SURVIVORS: IMPLICATIONS FOR SURVIVORSHIP CARE

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Objectives

As part of a larger study characterizing transfusion-derived iron deposition among childhood cancer survivors (CCS), health-related quality of life (HRQOL) constructs including psychosocial health, physical health, and fatigue were assessed.

Methods

Design: single institution cross-sectional cohort study. Participants and parents/guardians completed validated patient-/parent-reported outcomes (PRO) measures in English or Spanish. The primary outcome variable was psychosocial HRQOL.

Results

Participants completed the PedsQL™ 4.0 Generic Core Scale (70 CCS/63 parents) and PedsQL™ Multidimensional Fatigue Scale (71 CCS/63 parents). CCS rated their overall HRQOL as good, although there were subsets (ranging from 13% to 17%) with scores indicating at-risk status for diminished HRQOL. CCS endorsed more fatigue symptoms on every scale than did healthy children, with cognitive fatigue most often reported. Sex, age at study evaluation, duration of follow up, tumor resection, cumulative red blood cell transfusion volume, physical health, and fatigue were considered in a multivariate analysis of psychosocial HRQOL. In the final reduced multivariate model, higher psychosocial HRQOL was associated with older age at evaluation ($p=0.0003$), better physical health ($p<0.0001$), and fewer fatigue symptoms ($p<0.0001$). There was a statistically significant positive correlation between patient self-report and parent proxy report on all aspects of HRQOL and fatigue, although cross-informant variance was noted in ratings of individual items on study measures.

Conclusions

Findings underscore the clinical value of systematically assessing HRQOL, fatigue/other symptoms using validated PRO measures during survivorship care, with both patient and parent as informants whenever possible/applicable. HRQOL assessment may identify symptoms and risk factors that may not otherwise be elicited, and can be used to guide personalized interventions to mitigate adverse psychosocial effects of the cancer experience to improve long-range HRQOL.

Acknowledgements: St. Baldrick's, Concern, ThinkCure, Oncology Nursing, and DAISY Foundations; and Grant Number UL1TR000130, CHLA, National Center for Advancing Translational Sciences at the National Institutes of Health.

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Free Paper Session 5: Improving practice through evidence and evaluation
AN EVIDENCE-BASED PRACTICE PROGRAM WITHIN THE CHILDREN'S
ONCOLOGY GROUP NURSING DISCIPLINE

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Objectives

Evidence-based practice (EBP) is an increasingly important component of nursing care, especially within pediatric oncology where nurses administer intense therapies. Despite the significance of EBP, much of nursing care lacks evidence based recommendations. In an effort to promote EBP, nursing leaders within the Children's Oncology Group (COG) Nursing Discipline developed a mentorship program to train pediatric oncology nurses on the EBP process. The program was launched in 2012 and to date, has completed four EBP projects. This presentation provides an overview of the EBP mentorship program and highlights the projects.

Methods

The focus for each EBP project was solicited from nursing discussions regarding nursing practice care variations for pediatric oncology patients. Interested groups of nurses applied for the mentorship program, through a formal call sent out to the COG membership. One team was selected in 2012 and three teams were selected in 2013. These teams received didactic information and individual mentorship on the EBP process that included developing a focused question, performing a comprehensive literature search, summarizing and evaluating evidence, creating recommendation statements, and disseminating the information.

Results

All teams completed the EBP process and provided positive feedback on the program. The 2012 team identified physical activity recommendations for childhood cancer survivors with a single kidney. The 2013 teams identified fertility preservation recommendations for childhood cancer patients, prevention and treatment recommendations for post-lumbar puncture headaches in pediatric patients, and hydration recommendations to prevent bladder toxicity in patients receiving cyclophosphamide.

Conclusions

Pediatric oncology nurses are interested in developing EBP recommendations for the pediatric oncology population. A structured mentorship program of didactic information along with guidance of EBP skill application is a successful process. Future COG nursing EBP projects are planned.

Acknowledgement: This project was supported by the National Cancer Institute - Children's Oncology Group Chair's Grant (U10 CA098543).

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Free Paper Session 5: Improving practice through evidence and evaluation
WHAT CAN SERVICE DESIGN DO FOR THE PEDIATRIC RADIOTHERAPY EXPERIENCE?

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Objectives

While radiotherapy is considered a non-invasive treatment for cancer, it can be both stressful and challenging for children to endure, and often requires the use of sedation or general anesthesia which are both costly and have negative side effects. Procedures aimed at reducing distress for both parents and children are important for the child's coping and health during radiotherapy. This research project investigates the benefits of using service design to create supportive pediatric radiotherapy experiences for children ages 2-12, focusing on decreasing fear and anxiety through preparation.

Methods

Service design methods were employed to research the pediatric patient experience in three radiotherapy clinics in Sweden in a controlled study. Observational fieldwork, as well as interviews with care staff, pediatric patients and their parents about the current radiotherapy experience were conducted. This material was analyzed using service design mapping techniques, and used to identify opportunity areas for designing a new pediatric patient journey focusing on preparation.

Results

The final result is a preparation kit comprised of digital and physical elements that uses visual storytelling and play therapy as a way to introduce radiotherapy to younger pediatric patients before the start of treatment. These preparatory materials are directly connected to the treatment experience at the clinic through different tangible touch points. The service involves both designed materials as well as minor changes in clinical routines to ensure the consistency and cohesiveness of the information provided to the child and parents, and has been implemented within the three participating clinics, and is currently undergoing evaluation.

Conclusions

Service design is a useful approach for studying the pediatric patient experience and creating new services aimed at properly preparing and supporting young pediatric patients and their parents throughout the radiotherapy treatment experience.

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Free Paper Session 5: Improving practice through evidence and evaluation
EFFORTS OF CHEMOTHERAPY ERROR REDUCTION BY COMPUTERIZED
PEDIATRIC CHEMOTHERAPY ORDER ENTRY SYSTEM.

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Objectives

Chemotherapy medication error occurred in a pediatric cancer unit. Chemotherapy administration is a high risk process because of high toxicity and low therapeutic index. While analyzing the causes, a number of near miss cases related to chemotherapy order errors were discovered which had not been reported. We organized multidisciplinary team to work out a feasible solution.

Methods

Computerized pediatric chemotherapy order entry system (CPCOES) was designed by one pediatric hemato-oncologist, clinical nurse specialist, pharmacist and one computerized system developer from March to August 2012. CPCOES was gradually applied to prescribe patient's chemotherapy orders from September 2012. We collected data of prescribing and administration errors from January to October 2012 at a pediatric cancer unit and surveyed doctors and nurses satisfaction before and after the system application.

Results

Total of 14 diagnosis, 135 protocol sheets were set. Three months after CPCOES was put into practice, the monthly average of chemotherapy order errors dramatically decreased by 67% (from 22 to 7.3 cases). The levels of doctors and nurses' satisfaction increased in terms of perceived ease and reduced time consumption for entering and verifying the orders. It also increased the levels of total process satisfaction of doctors and nurses administering chemotherapeutic treatments.

Conclusions

Prospective, CPCOES helped minimize chemotherapy order errors and promote patient safety. Absolutely preventing chemotherapy errors is impossible, but we should take an effort to reduce chemotherapy errors if possible by multi-disciplinary team approach.

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Free Paper Session 5: Improving practice through evidence and evaluation
EFFECTIVE PREVENTION AND MANAGEMENT OF TUMOR LYSIS SYNDROME:
THE IMPORTANT CONTRIBUTIONS OF ONCOLOGY NURSES

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Objectives

At present there is no published guideline that describes the corresponding nursing interventions for the prevention and management of tumor lysis syndrome. This study has aimed to identify appropriate nursing management procedures for the prevention and treatment of tumor lysis syndrome, in line with the currently available evidence-based medical guidelines in the literature.

Methods

A systematic approach was used to identify relevant studies. The reference materials collected included reviews, reports, guidelines, journal articles, randomized controlled trials, studies and conference reviews. The search results were then limited to publications from the past 10 years (Jan. 2004–Jan. 2014) for which the full texts were available.

Results

Based on the comprehensive literature review, the treatment algorithm for the prevention of tumor lysis syndrome from both the medical and nursing perspectives have been established. In particular, the study highlights the importance of oncology nurses in contributing to the prevention and management of tumor lysis syndrome, which has been commonly overlooked in the existing literature. Moreover, this study provides oncology nurses with the most up-to-date information on the prevalence, pathophysiology and the prevention and treatment interventions for tumor lysis syndrome. This information is crucial for delivering appropriate, high quality care to improve patient outcomes. Most importantly, this study describes a multidisciplinary approach that involves the collaboration of both medical healthcare professionals and oncology nurses in the prevention and treatment of tumor lysis syndrome.

Conclusions

This study has addressed a gap in the literature by describing nursing management in accordance with the currently available evidence-based medical guidelines for risk identification, prevention and treatment of tumor lysis syndrome.

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Free Paper Session 5: Improving practice through evidence and evaluation
PHYSICAL ACTIVITY AND FATIGUE IN CHILDREN WITH CANCER

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Objectives

Children with cancer identify fatigue as a pervasive, distressing symptom. Fatigue increases during the corticosteroid pulse given during acute lymphocytic leukemia (ALL) maintenance. We explored the feasibility of the FitBit®, an inexpensive device that measures steps and motion, in an activity and fatigue-prevention program. Data uploads to the internet allowing real time access. Aims were: 1. To evaluate if children, who have a step/day goal and receive daily Fitbit® coaching for 2 weeks before a maintenance steroid pulse, have increased steps, 2. To determine the relationship between steps/day pre-pulse and fatigue after the pulse.

Methods

Participants included 17 children in ALL maintenance, age 6- 15, who were receiving a steroid pulse and had a home internet access. The Child Fatigue Scale was administered at baseline, after 2 weeks /before the steroid pulse, and after 5 days of steroids. Participants wore the FitBit® for 3 days pre-intervention, to establish a baseline of steps/day. A tailored weekly step goal was then set by phone with the child and parent. Daily e-mails with FitBit® screen shots were sent with encouraging feedback. During the steroid pulse, participants determined their own level of activity while still wearing the FitBit®.

Results

There was a significant increase in steps/day from week 1 ($10,282 \pm 2773$) to 2 (10945 ± 2903) ($p < .001$) and a decrease in fatigue. A significant correlation ($r = -.60$, $p = .02$) was identified between the steps/day during week 2 and fatigue during the steroid pulse with more steps associated with lower fatigue.

Conclusions

The intervention was feasible and effective in this small sample. The mean steps/day each time period (week 1, 2, and during steroids) was over 10,000; an important finding that demonstrates that children with ALL are able to reach the recommended 10,000 steps/day.

Funding: St. Baldrick's Foundation

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**Free Paper Session 5: Improving practice through evidence and evaluation
PEDIATRIC PALLIATIVE CARE IN CHILDHOOD CANCER PATIENTS:USING
FUDAN'S MODEL TO IMPLEMENTATION IN CHINA**

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Objectives

Many children with childhood cancer in China could not benefit from pediatric palliative care. One national barrier is that we don't have the Medicare hospice reimbursement regulation. In response to the critical need to provide palliative care earlier for these kinds of children, Hematology/Oncology Division of Children's Hospital of Fudan University develop and implement an model of pediatric palliative care in Shanghai, China. Our objective was to describe Chinese experiences in designing, implementing the model.

Methods

Surveys were conducted with parents and staffs firstly. Then, according to the results of the surveys, we constructed the Fudan model of pediatric palliative care in developing area of China, which included multidisciplinary working team and a comprehensive intervention protocol. In the team there were nurse, pediatric oncologist, psychologist, therapist, hospital social worker and volunteer. The protocol contained three sessions: hospital, home and community. In these three sessions, we met children's and family members' needs, supported their emotional and financial difficulty.

Results

From July 2013 to February 2014, 62children have been enrolled in the program. Approximately 72% of parents report they are satisfied with the program and 85% of parents would recommend the program.

Conclusions

Fudan's model is the first in the nation to provide Hospital-Home-Community model of pediatric palliative care from the point of diagnosis onwards. Lessons learned from Fudan's experiences will help guide other city in China.

O-192

Free Paper Session 6: Supporting children and families through treatment and beyond

DEPRESSIVE SYMPTOMS IN CHILDREN DURING HEMATOPOIETIC STEM CELL TRANSPLANT RECOVERY

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Objectives

Depressive symptoms such as anxiety and sadness have been reported among pediatric patients prior to and during hematopoietic stem cell transplant (HSCT) hospitalization. These symptoms occur less frequently at one year post HSCT; however, little is known about their prevalence during the immediate months following HSCT hospitalization. This study describes depressive symptom scores as reported by pediatric patients during the first 6 months post HSCT and evaluates the association between the scores and quality of life (QOL).

Methods

A repeated measures design was used to evaluate depressive symptoms and QOL among 23 children and adolescents during HSCT recovery. Demographic and transplant information was obtained from the medical record and patients completed questionnaires monthly for a total of six months post HSCT. Depressive symptoms were measured with the Children's Depression Inventory 2 questionnaire and QOL was measured with the Peds Quality of Life Cancer Module.

Results

Although no significant difference, total depressive symptom mean scores fluctuated over time with the highest score at 1 month and the lowest at 4 months post HSCT. The emotional problem subscale mean scores steadily declined during the first 4 months post HSCT then increased at months 5 and 6. The functional problem subscale mean scores had minor fluctuations over time with the highest score noted at 3 months and the lowest at 4 months post HSCT. Depressive symptom scores were statistically associated with QOL ratings at months 1, 2, and 3 following HSCT.

Conclusions

Pediatric patients experience depressive symptoms throughout HSCT recovery that may be affecting their QOL. Nurses should perform routine assessments for depressive symptoms so that appropriate interventions can be promptly initiated.

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Free Paper Session 6: Supporting children and families through treatment and beyond

STUDY ON RELATIONSHIP BETWEEN CHINESE CHILDREN'S QUALITY OF LIFE AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION AND PARENTING COPING

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Objectives

The aims of this study were to assess relationship between quality of life in children after hematopoietic stem cell transplantation (HSCT) and parenting coping.

Methods

A cross-sectional descriptive study was designed using Pediatric Quality of Life Inventory™ 4.0 Generic Core Scale (PedsQL4.0) and Coping Health Invention for Parents (CHIP). All 78 children from the outpatient clinic in Beijing Children's Hospital between December 12, 2011 and March 2, 2013 were recruited. 2 were lost to follow-up and 43 were admitted to inpatient ward. Final sample included 33 patients and 33 parents. Parents were asked to complete CHIP, children age 5 years and over completed age appropriate PedsQL™4.0; for 2~4 year's children, parent proxy-report was used. Independent sample t-test and spearman correlation were performed.

Results

The median age of children was 5 years (range 2-16 years), the median post-transplant period was 15.5 months (range 3-53 months). 11 were fathers aged 28-43 years and 22 were mothers aged 27-49 years. The physical function scores were 62.51 ± 26.88 , the emotional function scores were 71.25 ± 17.73 ; the social function scores were 83.44 ± 14.67 ; the school function scores were 59.39 ± 20.89 ; the overall total scores were 69.44 ± 16.15 (table1). Coping scores of mothers was relatively higher than fathers, the list from most helpful to least helpful in CHIP was: family coping style, medical coping style and support coping style (table2). Spearman correlation coefficients revealed statistically significant positive correlations between children's physical, emotional function and parenting support coping style ($r = 0.41$, $p = 0.02$; $r = 0.31$, $p = 0.03$), between children's social function and parenting family coping style ($r = 0.42$, $p = 0.01$). No significant difference was found between parenting medical coping style and children's quality of life ($p > 0.05$) (table3).

Table1 Scores of PedsQL™4.0 (n = 33)

Scale	Mean \pm SD
Physical function	62.51 \pm 26.88
Emotional function	71.25 \pm 17.73
Social function	83.44 \pm 14.67
School function	59.39 \pm 20.89
Total	69.44 \pm 16.15

Table 2 Descriptive Statistics of CHIP (n = 33)

Scale	Father(Mean \pm SD)	Mother(Mean \pm SD)	Helpfulness ratings
family coping style	46.00 \pm 9.22	46.15 \pm 9.17	most helpful
support coping style	23.00 \pm 3.79*	33.10 \pm 11.61*	least helpful
medical coping style	16.86 \pm 6.07	18.20 \pm 5.16	moderate helpful
CHIP Overall Score	87.86 \pm 16.39	97.45 \pm 22.58	

Notes: (1) Independent sample *t* test was used; (2) **p* < 0.05 father vs. mother

Table 3 Relationship between quality of life in children and parenting coping

Scales		family coping style	support coping style	medical coping style
physical function	r	0.16	0.41	0.01
	P	0.21	0.02*	0.49
emotional function	r	0.03	0.31	0.07
	P	0.44	0.03*	0.36
social function	r	0.42	0.08	0.03
	P	0.01*	0.35	0.44
school function	r	0.01	0.07	0.23
	P	0.48	0.39	0.17

Notes: (1) Spearman correlation was used; (2) **p* < 0.05

Conclusions

Quality of life in Chinese children after HSCT was low, Chinese mothers coped well than fathers, parents maintaining family integration, social support and self-esteem could increase children's quality of life.

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Free Paper Session 6: Supporting children and families through treatment and beyond

PARENTS' EXPERIENCE OF THEIR HEALTHY CHILDREN'S PARTICIPATION IN E-HEALTH SUPPORT WHEN A CHILD IN THE FAMILY HAS CANCER

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Objectives

The aim of this study was to investigate parents' experience of their healthy children's participation in e-health support when a child in the family has cancer.

Methods

A qualitative descriptive method was employed in this interview study. Parents from families with a child with cancer and healthy siblings were individually interviewed about their experience of their healthy child's participation in a person-centered support intervention combining education, learning and reflection. The sick child was newly diagnosed with cancer and had been receiving treatment for a maximum of 1 month. The data were collected during spring 2012. Seven parents participated in the study, 5 mothers and 2 fathers in 5 families with 14 healthy children. The interviews were conducted more in the form of a conversation between the interviewer and parent. A qualitative content analysis was used to draw a systematic conclusion from the text and to extract its message.

Results

The result comprises 3 preliminary themes. The parents perceived that: 1) 'The healthy child via his/her contact could think and form an opinion through asking questions and receiving answers'; 2) 'The healthy child was acknowledged and involved during the intervention'; and 3) 'The child became calmer and more hopeful'. The parents felt unburdened as professionals in healthcare provided their healthy children with professional information about the sick child's cancer and also support in understanding and managing their own reactions.

Conclusions

These results allow for a better understanding of the parents' experiences of the situation of their healthy children. The study also indicates that a person centred nursing intervention using e-health in order to help the families may ease family burden.

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Free Paper Session 6: Supporting children and families through treatment and beyond

SURVIVING THE INCOMPREHENSIBLE - PARENTS' LIVED EXPERIENCES OF LOSING A CHILD TO CANCER

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Objectives

The aim of the study was to illuminate parents' lived experience of losing a child to cancer

Methods

This study is part of a longitudinal research project about family members' experiences of living with childhood cancer within the family. Seventeen families with a child diagnosed with cancer were followed during their child's cancer trajectory. Seven of these families lost their child to cancer, of these, three families participated in this study. Interviews were performed with three mothers and three fathers either at one, two or seven years after the child's death. The interviews were analyzed utilizing a hermeneutical phenomenological approach.

Results

Preliminary results: The essential theme was identified as "Surviving the incomprehensible". In relation to the essential theme, four related themes emerged "Wanting to keep the child, but not to see it suffer", "Wanting to protect the dead child and keep its spirit alive", "Feeling vulnerable and empty" and "Trying to see the light".

Conclusions

For staff, it is important to offer more than one meeting with the parents after the child's death, to be able to identify those in need for extensive support. To enable the contact, the responsibility should lie on the staff, not the parents. The preliminary results suggest that the parents need one contact close to the child's death and then one or two more contacts after a year or more.

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Free Paper Session 6: Supporting children and families through treatment and beyond

IMPACT OF SOCIAL SUPPORT ON BEREAVED SIBLINGS' ANXIETY: A NATIONWIDE FOLLOW-UP

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Objectives

To assess adolescent and young adult siblings' perception of social support prior to and following the loss of their brother or sister to cancer, two to nine years earlier, and their anxiety at follow-up.

Methods

In 2009 a nationwide, long-term follow-up study in Sweden was implemented, using an anonymous study-specific questionnaire. Adolescent and young adult siblings who at the age of 12 to 25 years of age lost a brother or sister to cancer between January 1, 2000 and January 1, 2007 and lived in Sweden were invited, 174 (73 %) bereaved siblings participated. The Hospital Anxiety and Depression scale (HADS) was used to measure self-assessed anxiety, relative risks (RR) with 95 % confidence interval (CI) were calculated to show the proportion reporting anxiety within dichotomized groups of bereaved siblings. Written informed consent was obtained.

Results

Siblings had a higher risk of anxiety if they perceived their need for social support was unsatisfied during their brother or sisters last month before death, RR=3.6 (1.8-7.3), time after death, RR=2.9 (1.5-5.6) and at follow-up, RR=3.8 (2.0-7.2). Furthermore, a higher risk for anxiety was shown for siblings if they did not perceive that their parents and neighbours cared for them after their brother or sisters' death RR=2.7 (1.3-5.5), RR=5.4 (1.3-21.9) respectively.

Conclusions

Bereaved siblings had a greater probability to report self-assessed anxiety if they perceived that their need for social support was not satisfied prior to and following death. Information from both nurses and other health-care professionals to families about the impact of social support may contribute to lessen the siblings' risk of anxiety.

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Free Paper Session 1

NOTHING ABOUT YOU WITHOUT YOU!: PARENTS' AND PATIENTS' VIEWS ON CLINICAL TRIALS AND BIO-BANKS. RESULTS FROM THE EU-FP7 ENCCA PROJECT AND LESSONS FOR THE FUTURE?

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Objectives

In the ethics work-package (WP18) of the "European Network for Cancer Research in Children and Adolescents (ENCCA)", parents, patients and survivors had the possibility to identify main expectations and concerns about ethical issues in paediatric oncology research, especially on clinical trials and bio-banks.

Methods

Two literature reviews on clinical trials and bio-banks ensured to address the relevant ethical issues. The literature review was followed by collecting the views of stakeholders (professionals, parents' and patients' representatives). Due to this process it was possible to characterise areas of agreement and discrepancies between the stakeholders.

Results

On one hand the views of the stakeholders were collected in two workshops on the topic "Are my tissue-samples available for research? Who knows, who cares?". Parents' and survivors' representatives of the European branch of the International Confederation of Childhood Cancer Parent Organizations (ICCCPO) and young people from the Young Person's Advisory Group (YPAG) at Birmingham Children's Hospital expressed their expectations and concerns about samples and data in paediatric cancer bio-banks. On the other hand, views about clinical trials, the consent procedure and the decision-making process were given by a questionnaire with the topic "Nothing about you without you". The expertise on paediatric cancer research, gained by the parents' and patients' representatives - based on their personal experiences and their activities in national and international levels – was central in the ethical consultation process.

Conclusions

Ethical deliberation does not preclude disagreements between professionals and parents and patients or within these groups. Discrepancies as well as agreements are clues about ways to improve research practices. Therefore, the feedback of parents, patients and survivors is highly appreciated in the definition of ENCCA guidelines on confidentiality in bio-banks and in ENCCA guidelines on clinical trials. Potential for development of long-term interactions is openly discussed.

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Free Paper Session 1

QUALITY CARE, RESEARCH AND IMPACT (QCRI) AT CANKIDS...KIDSCAN – ANOTHER DIMENSION TO CHILDHOOD CANCER SUPPORT AND ADVOCACY GROUPS

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Objectives

Through its presence in 34 centres, Cankids...Kidscan provide awareness, advocacy and patient support to over 13,000 children with cancer every year in India. Our national footprint naturally lends us to participating in research with/without partnering national and international individuals and/or institutions. At the same time any initiatives to assess and improve quality of care have the potential to create a larger impact.

The QCRI team was formed in April 2013 and the idea was to bring together under one umbrella all projects/studies which were being done in Cankids to evaluate service, assess impact and conduct research. The role of the team is to initiate such new projects when appropriate, provide input in ongoing projects and act as a focal point for such activities. The plan has been to put mechanisms into place to deliver the above desired output by setting up a team, holding regular meetings, monitoring progress and eventually assessing performance.

Current **quality care improvement initiatives** include

1. Immunisation for children with cancer – survey of practice in India; developing and disseminating guidelines; patient support for implementation
2. Fertility preservation and support for children with cancer – pilot fertility clinic for survivors; developing and disseminating fertility preservation guidelines.
3. Nutritional support of children with cancer - develop algorithms for nutritional assessment and interventions appropriate for the local setting; patient support for implementation

Current **research projects** include

1. Pilot study of cost of illness in children with cancer
2. Patient Navigation and Tracking to Reduce Abandonment of Treatment in Children with Cancer (PANTRACC) in India – Pilot to start
3. Incidence of cancer in children and young adults in India
4. Multi-centre study on delays in diagnosis and treatment of children with cancer in India – Protocol under development.

Methods

NA

Results

NA

Conclusions

NA

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Free Paper Session 1

WHEN TRAGEDY INSPIRES HOPE: A PARENTS' CALL TO ACTION TO CREATE AND IMPLEMENT A PSYCHOSOCIAL STANDARD OF CARE FOR CHILDHOOD CANCER

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Objectives

The Mattie Miracle Cancer Foundation will share their experiences with childhood cancer and their mission to create a national standard of psychosocial care. The importance of assembling a multidisciplinary team of professionals, the challenges of operating a large initiative, and the complexities of implementation will be discussed.

Methods

An oral presentation with Power Point slides will discuss:

- 1) the history of the project,
- 2) the nature of our multidisciplinary team of leaders and how such a team was assembled,
- 3) the methodology used to establish a standard of care, and
- 4) an update on where the project currently stands

Results

N/A

Conclusions

N/A

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Free Paper Session 1

CLOSING THE GAP: BUILDING A FRAMEWORK FOR OPTIMAL ORGANIZATION OF PEDIATRIC PALLIATIVE CARE WITH INPUT FROM EXPERTS AND PARENTS

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Objectives

To create a national framework for optimal organization of pediatric palliative care using the 'Idea Factory' method with input from professionals and parents. Recommendations on organization of pediatric palliative care are important for high quality palliative care.

Methods

We extracted recommendations on the optimal organization of pediatric palliative care from selected (inter)national guidelines categorized in prioritized topics. We sent this information to the participants of a work conference. The Idea Factory is a method to create intensive knowledge exchange about an important theme, to generate good ideas on how to take the theme forward and to create energy and support to implement the best ideas generated. During the conference the participants discussed in small teams their own ideas and a jury in pediatric palliative care scored these ideas using five predefined criteria. After the work conference, the expert panel reduplicated, discussed and prioritized these ideas and defined a final set of recommendations.

Results

We identified eight guidelines focusing on the organization of pediatric palliative care for extracting recommendations. General practitioners, pediatricians, pharmacists, nurses from different care settings, students, psychologists, remedial educationalists, chaplains, social workers, policy staff/managers, healthcare insurers, and parents participated in the working conference. The interactive session and written and verbal commentary rounds resulted in a list of 49 high-quality care recommendations for the organization of pediatric palliative care based on input of professionals and parents.

Conclusions

This study defines a unique set of recommendations for a national framework on the organization of optimal pediatric palliative care, based on literature and creative ideas of experts, including parents. The final set of recommendations provides a basis for improvement programs regarding the organization of pediatric palliative care.

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Free Paper Session 2

THE OPACC PARENT INTERVENTION GROUP AND PARENT LIAISON PROGRAM AT THE HOSPITAL FOR SICK CHILDREN

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Objectives

Parents play a crucial role in the care of a child with a cancer diagnosis. Social isolation, fear, and anxiety are realities for families of children admitted to a pediatric oncology ward. The need for a social network and a support community for families of children with a cancer diagnosis is significant (Richards et al, 1986). Peer navigation helps to normalize the experience for those embarking on a similar journey (Boyle-Bride et al, 2013).

Methods

Ontario Parents Advocating for Children with Cancer (OPACC's) mission is to educate, advocate, support, and enable families of children with cancer. Collaborating with The Hospital for Sick Children (HSC), OPACC identified a gap and piloted co-facilitated parent support groups and a dual track peer-to-peer support initiative. Survey results from 2009 suggested 72% of parents wanted a co-facilitated parent support group (i.e. two facilitators, one a member of the psychosocial team and the other a parent of a child treated at HSC), while as many as 70% of parents wanted peer support groups. In response, OPACC engaged in a collaborative initiative with HSC to offer co-facilitating parent intervention groups since 2010. The Parent Intervention Group and Parent Drop-in Group create a safe and supportive environment for parents to connect and provide peer-to-peer support. The Parent Liaison Program began in a volunteer capacity in 1997 and has been active as a member of the Haematology/Oncology Program at HSC since its inception. The OPACC-funded Parent Liaison program has evolved to two Parent Liaison positions at the hospital.

Results

Consistent offering of these programs and participation validate a need is being met by these initiatives, having a positive impact overall for family-centred care.

Conclusions

The OPACC Parent Intervention Group and Parent Liaison Program have bridged a gap and facilitated a social network for families facing a pediatric cancer diagnosis.

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Free Paper Session 2

CORPORATE SOCIAL RESPONSIBILITY (CSR) OR OPPORTUNITY

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Objectives

MAHAK as a successful humanitarian NGO in Iran is often the target of CSR outlays by private sector corporations. Although thankful, it believes this relationship should move away from a linear giver-taker one to a circular synergic one. Viewing this as part of its core responsibilities, MAHAK has embarked on a path of re-defining and expanding the parameters of traditional CSR approaches to include all societal actors including the non-profit and civil society sectors of society. In this vein, it has developed internal and external CSR models and applicable programs, which are fully customizable for International humanitarian societies and organizations. Stemming from the conviction that all actors have a social responsibility toward those impacted by their activities, the extent of this responsibility can be delineated in the two spheres of external and internal to the organization. Hosting two related International symposia and moving toward paperless operations are vivid examples for each sphere.

This approach has the potential of shifting CSR from a one-way, cost-based obligation to a win-win synergic opportunity with emphasis on instilling the sense of responsibility as a core cultural belief. Even though MAHAK's core activity fulfills its expected social responsibility, it should by no means relieve it from doing a lot more in the way of minimizing its carbon footprint, promoting civil society culture, addressing the needs of its stakeholders, and acting as a role-model and/or twinning partner for alike institutions in incipient stages of growth. Such undertakings not only provide opportunities for partners and other societal actors, the circular logic of the benefits through reciprocated opportunities, enhanced reputation, and demonstrated capability and effectiveness support a paradigm shift from the notion of 'social responsibility' to 'social opportunity'.

Moreover, we all have an additional responsibility to share such ideas and perspectives with others in forums such as ICCCPO.

Methods

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Results

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Conclusions

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Free Paper Session 2

ENGAGING THE YOUTH IN A NATIONAL AWARENESS CAMPAIGN FOR YOUTH AND GENERAL PUBLIC IN LEBANON

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Objectives

Although childhood cancer is highly curable, cancer remains the leading cause of disease-related deaths among children in several countries. Awareness campaigns are extremely needed in our country

Methods

In order to raise awareness against cancer in an interactive way, a nationwide poster competition with the theme: "A Healthy Environment and a Balanced Lifestyle for a Cancer Free World" was launched by CHANCE association in collaboration with the Ministry of Environment, among all professional media companies, universities and schools. Eighteen universities were visited over a period of 3 months by our team who delivered awareness lectures on site.

Results

129 entries were obtained (101 from students in 10 major universities and 28 from professionals), in addition to numerous entries from middle and high school students from 20 public and private schools. A jury was composed of several well-known public figures in the country.

Posters were judged according to their power in conveying the message. The top 10 posters were selected and prizes were then awarded personally by the Lebanese Minister of Environment and CHANCE team

All the posters were exposed in the capital Beirut Waterfront for general public viewing. Beautiful posters with powerful messages were viewed live by hundreds of people and seen on TV by thousands on several national and regional television stations.

Conclusions

This nationwide campaign was highly effective and achieved the goal of raising awareness against cancer among the youth in the schools and the universities and in the general public. Such initiatives are rare in the Middle East and should be widely encouraged due to their immediate impact.

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Free Paper Session 3

IMPROVEMENT IN POLICIES FOR CHILDHOOD CANCER

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Objectives

1. Outline of revised policies;

Ministry of Labor and Welfare of Japan (the “Ministry”) has proposed revisions in the policies concerning childhood cancer through i) launching the Second Five-Year Master Plan for Anti-Cancer Measures (the “Plan”), and ii) revising the existing Aid Program for Chronic Diseases in Childhood (the “Program”).

As for the Plan, childhood cancer is categorically described for the first time in it, and also 15 hospitals in 7 regions across Japan are designated as regional center for childhood cancer treatment. The Plan also calls for the establishment of networks in each region consisting hospitals having expertise in childhood cancer. In addition, two national hospitals have been nominated to jointly perform indispensable functions to lead the networks, to govern the management of childhood cancer registry system, and others.

As for the Program, since its inception in 1974, medical expenses for the designated diseases including childhood cancer are fully subsidized by the governments as the Act for Special Measures which is subject to annual budget allocation. The Ministry has now proposed to revise the Program to the extent of i) transforming the Program to a full-fledged stable measure not to be affected by annual budget condition, and ii) significantly broadening the diseases being covered. However, while these revisions address certain key issues, there are negative changes such as introduction of burden share depending on the level of income etc. leaving certain issues yet to be resolved.

2. Purpose for Presentation;

Sharing detailed information on recent revisions in major policies concerning childhood cancer in Japan as above, including the rolls of parents organizations in the process will surely provide fellow parents organizations in ICCCP with certain ideas useful for them in advocating the improvement of the policies in their country.

Methods

NA

Results

NA

Conclusions

Refer to purpose

O-205

Free Paper Session 3

BARRIERS AND HOPE TO PEDIATRIC CANCER DRUG DEVELOPMENT FROM THE FDA AND EMA PERSPECTIVE

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Objectives

Overview of childhood cancer drug development including barriers as well as hopeful incentives. Presentation will include the perspective from the FDA as well as information on collaboration with the EMA and will highlight directions that both agencies are taking to help promote pediatric oncology drug development.

Methods Oral Presentation.

Results NA

Conclusions NA

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Free Paper Session 1

POOR OUTCOME OF BRAIN TUMOR IN A DEVELOPING COUNTRY: EXPERIENCE OF A TERTIARY CARE CHILDREN CANCER HOSPITAL IN PAKISTAN

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Objectives

To study the clinico-pathological features and the survival of brain tumors in a Pediatric cancer referral centre in Karachi.

Methods

Retrospective chart review of children with brain tumors at Children Cancer Hospital (CCH) from 1997-2013. Data collected on demographics age, sex, location of residence, primary site, morphology, investigations, timing of interventions, treatment modalities and outcome.

Results

231/3315(7%) of all registered patients were diagnosed with brain tumors. Male to female ratio was 11:9 with a mean age of 7 years(0.1-19). 45% of patients were from karachi and remaining were from distant areas of Pakistan. Mean duration of first symptom to the presentation was 6 months. MRI was the first diagnostic modality in only 40% of the cases. Average interval from first scan until any surgical intervention was 30 days. Posterior fossa was the commonest site in 40% of patients. Gliomas(31%), medulloblastoma(21%) and Ependymoma(13%) were the three most common tumors.

129/231 (56%) either visited once or abandoned treatment. 50/231 received only palliative treatment mostly radiotherapy. Only 50/231(23%) treated with curative intent. 79(34%) of this cohort had tumor resection(STR or GTR), remaining were either inoperable or only had shunt surgery for hydrocephalus. Immediate post-operative scans were performed in only 40 (17.3%). Chemotherapy and radiotherapy were given as per protocol. Only 24/52 (46%) actively treated patients are alive with a mean follow up at 3 years. For whole cohort of 231 patients, survival is only 10%.

Conclusions

The outcome of brain tumors in our group is very dismal. Delays in suspecting, diagnosing and intervention lead to poor outcome. Poor socio-economic status, distance from treating centres and low literacy rates among parents might be the cause of high rate of abandonment in children with brain tumors.

O-207

Free Paper Session 1

SURVIVAL IN METASTATIC NEUROBLASTOMA WITH NON-AVAILABILITY OF STANDARD TREATMENT OPTIONS IN PODC SETTINGS

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Objectives

The standard treatment options in metastatic/advanced Neuroblastoma are chemotherapy, surgery, stem cell transplant, radiation therapy, isotretinoin, anti-GD2 antibody, interleukin-2/GM CSF. In RCN (resource challenged nations) set-ups all of the standard treatment options are not feasible. The survival rates in such situations with judicious use of chemotherapy, surgery, radiation therapy and isotretinoin are presented herewith.

Methods

Retrospective case cohort study was conducted wherein data of all children with metastatic Neuroblastoma was collected from January 2001 to December 2013. The treatment details and survival rates were analysed.

Results

Forty-three children (26 boys, 17 girls) presented with metastatic Neuroblastoma in the departments of pediatric oncology and pediatric surgery over a period of 12 years. 5/43 abandoned therapy. Upfront chemotherapy was given to all patients after confirmation of diagnosis with CT-Guided biopsy. 26/38 received CECA (Cis-platin, Etoposide, Cyclophosphamide, Adriamycin), whereas others received OPC/OJEC regime (Oncovarin, Cis-platin, Etoposide, Cyclophosphamide/Oncovarin, Carboplatin, Etoposide, Cyclophosphamide). All, except 9 patients(29/38) underwent surgical intervention of which incomplete excision and residual tumor was present in 14/29. Isotretinoin was given to 13/38 patients. 17/29(58.6%) patients died due to uncontrolled disease spread. 40% of the surviving 41.4% children are on some form of treatment and show non-functional residual lesions at the primary site.

Conclusions

With long-term and diligent management with the available resources for treatment of metastatic Neuroblastoma, the survival rate is about 41.4%. In spite of residual disease (majority being non-functional), the children remain well. Regular follow-up and immediate intervention is planned for these children in case of disease spread. Loco-regional control along with long term systemic therapy helps in controlling the tumor spread to a great extent.

O-208

Free Paper Session 1

KAPOSI SARCOMA IN HIV-INFECTED CHILDREN: A NOVEL CLINICAL STAGING CLASSIFICATION DETERMINES RISK STRATIFICATION

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Objectives

Kaposi sarcoma (KS) is the most common HIV-associated malignancy in Africa. Pediatric KS is distinct from adult disease. We aimed to evaluate the clinical characteristics of pediatric KS.

Methods

We retrospectively analyzed 53 HIV+ children with KS between 8/2010 – 9/2012 in Lilongwe, Malawi. Diagnosis was biopsy-confirmed in 24.5%. Local 1st-line chemotherapy included bleomycin and vincristine. HAART was based on local protocol. Statistical analysis was performed using Kaplan-Meier survival curves.

Results

Median age was 8.7 years (1.7-17.4); 27 females & 26 males. Common sites of presentation were: lymph node (75%), skin (56%), subcutaneous nodules (36%), oral (29%), woody and facial edema (21.8%/16.4%), pulmonary (14.5%), and gastrointestinal (3.6%). Severe CD4 suppression occurred in 50.9%. 22.6% presented with platelet count < 50 and 20.7% with hgb < 6. Twelve-month disease status revealed: 50.9% in complete remission (CR), 11.3% with stable disease, and 37.7% died. A pediatric KS clinical staging classification was devised as follows: Stage 1: limited to skin or flat oral mucosa lesions, total < 10 lesions. Stage 2: lymph node involvement, subcutaneous nodules, facial edema, +/- skin or palatal lesions, without visceral involvement and < 20 skin lesions. Stage 3: woody edema +/- any of above. Stage 4: clinical pulmonary or gastrointestinal involvement, or having > 20 skin lesions, +/- any of above. There were zero Stage 1 patients. 53.8% were in Stage 2, 21.1% Stage 3, and 25% Stage 4. This staging classification revealed dramatically different outcomes. 75% of Stage 2 patients were in CR at 12 months. Stage 3 patients had 55% CR but 91% overall survival (OS). Outcomes for Stage 4 patients were unfortunate—12 month OS 8% (all p-values < 0.0001).

Conclusions

This novel pediatric clinical KS staging system differentiates patterns with dramatically contrasting prognoses. Identifying high-risk patients is critical to guide treatment strategy and improve overall outcomes.

O-209

Free Paper Session 1

THE DF/BC-HITO OBSERVERSHIP PROGRAM – AN EXAMPLE OF HOW ACADEMIC CENTERS IN RESOURCE-RICH SETTINGS CAN HELP BOOST PROFESSIONAL DEVELOPMENT

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Objectives

The DF/BC-HITO Observership Program was a professional training project developed by DF/BC, HITO, Fundación Teletón México, and the Children's Trust. The goal was to ensure HITO's faculty and nurses were expertly prepared to begin treating patients when the hospital opened in November 2013. HITO is a free-standing pediatric oncology hospital and aims to become a Center of Excellence in pediatric oncology care. The medical curriculum aimed to (a) familiarize and acculturate HITO clinicians to the practice of oncology at a Center for Excellence, (b) provide assistance in the creation of multidisciplinary clinical programs, clinical protocols, and policies and procedures and (c) expose providers to a rich clinical research environment and motivate incorporation of research into clinical practice.

Methods

The Program was grounded on adult learning principles. It (a) assumed learners were independent, intrinsically motivated, and self-directed, (b) combined formal with informal and practical experiences, and (c) encouraged participation, ongoing peer-support, and one-on-one coaching.

Results

The Program ran for 18 months. A total of 14 physicians, 5 nurses, 1 pharmacist, and 2 administrators visited DF/BC between February-November 2013; 1-6 months each. Nursing and pharmacy experience is reported separately. Physicians included oncologists, intensivists, pathologists, infectious disease specialists, radiologists, radiation oncologists, pain and palliative care specialists, and surgeons. Observers developed their goals based on interests, roles, and responsibilities, observed direct patient care, attended clinical and educational conferences, national conferences, and formal course work in quality and research methods, improved their English skills, had one-to-one meetings with disease-specific attendings to review protocols, met regularly with organizers to monitor progress, and presented a summary of their experience at the conclusion of their stay.

Conclusions

Academic institutions and Centers of Excellence can meaningfully contribute to boosting the professional development of providers from low-and-middle-income countries. Support from leadership and foundations is essential for success.

O-210

Free Paper Session 1

FROM PAPER TO POLICY TO PATIENT OUTCOMES: THE PRIORITIZATION OF CHILDREN IN NATIONAL CANCER CONTROL PLANS IN AFRICA

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Objectives

With the increasing burden of noncommunicable diseases, prevention, early detection, treatment completion and palliative care are essential priorities. A country-specific cancer control framework is necessary to organize services, including for pediatric populations.

Methods

We identified African countries reporting to the World Health Organization (WHO) as having national cancer plans, and conducted a comparative content analysis with a health systems perspective. Structured analysis was based on existing development and evaluation frameworks, and elements of cancer control outlined by WHO; items included: timeliness; scope; World Bank country income group; organizing framework; stakeholders; comprehensiveness, and specificity of plan element for pediatrics.

Results

Of 18 African countries reporting a cancer control plan in 2010 and two that have published since, nine current national plans and one continental plan (7 English, 3 French) were accessible through the International Cancer Control Plan portal, representing 4 low-income, 3 lower-middle, and 2 upper-middle income settings: Benin, Cote d'Ivoire, Ghana, Kenya, Mauritius, Morocco, South Africa, Togo and Zimbabwe. Plans spanned from 3 to 9 years (range 2010 to 2019), and four discussed cancer control in the context of other noncommunicable diseases. National plans reported incidence data from national (n=4), subnational (n=3), and hospital (n=2) registries. Two plans explicitly noted families as participatory stakeholders along with government and civil society organizations. All proposed pediatric prevention through public health measures. Early detection, diagnosis, and treatment for children were specified in five plans. One budget itemized pediatric cancer. Palliative care strategies frequently emphasized analgesic access, with specified pediatric needs in two plans. Resources for palliative care were strategized in eight plans and itemized in five budgets.

Conclusions

Explicit strategies and funding for pediatric and palliative services in national cancer plans may help guide prioritized development. Implementation advocacy and funding accountability remain essential to shift plans from paper to improved population outcomes.

O-211

Free Paper Session 2

PARENTAL EXPERIENCES OF CHILDHOOD CANCER TREATMENT IN KENYA

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Purpose

This study explores the socio-economic, treatment-related and psychological experiences of parents during cancer treatment of their children at an academic hospital in Kenya.

Methods

This cross-sectional study used semi-structured questionnaires. Parents whose children came for cancer treatment consecutively between November 2012 and April 2013 were interviewed.

Results

Seventy-five families were interviewed. Cancer treatment resulted in financial difficulties (89%). More information about cancer and treatment was required (88%). More contact with doctors was needed (83%). At diagnosis, cancer was perceived as curable (63%). However, parents were told by health-care providers that most children with cancer die (49%). Parents had difficulties with understanding doctors' vocabulary (48%). Common reasons to miss hospital appointments were: travel costs (52%) and hospital costs (28%). Parents (95%) used complementary alternative treatment (CAM) for their children. Health-care providers told parents not to use CAM (49%). Parents had not discussed their CAM use with doctors (71%). Community members isolated families because their child had cancer (25%), believed that child was bewitched (57%), advised to use CAM (61%), and stop conventional treatment (45%). Parents shared experiences with other parents at the ward (97%) and would otherwise not understand the disease and its treatment (87%).

Conclusions

Parents suffer financial hardships and are dissatisfied with doctors' communication regarding their children's condition. CAM is very commonly used. Doctors need to improve their communication skills and discuss CAM more openly. A parent support group would be useful, financial support and a facility where the parents and children can stay during the course of therapy.

Document not received

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Free Paper Session 2

A PILOT STUDY TO DETERMINE THE OUT-OF-POCKET EXPENDITURES BY FAMILIES OF CHILDREN BEING TREATED FOR CANCER AT PUBLIC HOSPITALS IN INDIA

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Objectives

In the absence of insurance and/or social support, costs can lead to abandonment of treatment. The objective of this pilot study was to determine the feasibility of assessing the out-of-pocket costs in India (a) two weeks prior and (b) 12 weeks following diagnosis.

Methods

A prospective cost of illness design with twice-weekly, repeated assessments over 12-weeks was piloted from a family household perspective. Parents/caregivers, whose child was being treated for cancer at All India Institute of Medical Sciences and Safdarjung Hospital, had their costs and resource utilization, and impact of these costs recorded.

Results

Eleven families participated. The children (3-19 years) were diagnosed with ALL (n=5), Neuroblastoma (n=2), NHL (n=2), Bone sarcoma (n=2), or Wilm's tumor (n=1). Over half of the families' income was from an unskilled worker wage, and at least one parent per family was illiterate or had no schooling. Eight families lived outside New Delhi. The two-week median costs prior to diagnosis were Rs 6565 (US \$107) (range: 438-20076 Rs). Nearly 70% of costs prior to diagnosis were: investigations (55%), supportive care (14%) followed by 30% in indirect medical costs (17% travel, 3% lodging, 8% food, 2% other). The median weekly **costs for 12 weeks following diagnosis were** Rs 2263 (US \$37)/week (Range: 1071-7102 Rs/week). Half of the weekly costs following diagnosis were direct medical costs (supportive care 15%, investigations 8%, chemotherapy 7%); the other half were indirect medical costs (food 25%, 14% travel, 2% lodging, 8% other). To date, five families have been interviewed regarding impact. All have depleted savings, borrowed money, and are in debt. Four families opted selling their assets. Three families indicated their employment was affected and that the schooling of their other children had suffered.

Conclusions

Despite "free treatment" in government hospitals in India significant out of pocket expenses impact employment, schooling and housing.

O-213

Free Paper Session 2

REDISCOVERING THE JOY OF LEARNING - YCMOU INITIATIVE FOR CHILDHOOD CANCER SURVIVORS

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Objectives

Young survivors of childhood cancers, who were deprived of education due to interruptions as a result of long treatment & socioeconomic constraints, are encouraged & inducted to pursue vocational training to achieve their goals. Yashwantrao Chavan Maharashtra Open University (YCMOU) in collaboration with Tata Memorial Hospital (TMH) offers educational assistance to survivors at subsidized rate or free of cost.

Methods

Ugam, a support group of childhood cancer survivors from After Completion of Treatment (ACT) clinic at TMH functioning under survivorship program of Indian Cancer Society (ICS), has collaborated with YCMOU for empowerment of cancer survivors through educational assistance. YCMOU not only provides graduate and post graduate courses like Management training, Media Graphics and Animation etc.; but also offers preparatory courses in English and Hindi. Patients are able to attain reputed degrees at a very nominal rate or free of cost if survivor is below the poverty line.

Results

15 young survivors have enrolled themselves in different courses such as B.Sc. in Media Graphics and Animation, B.Com, BS-CIT, M.B.A., Civil Supervising etc. and have benefited from such an initiative. These survivors are now capable of achieving a respectable trade or profession owing to the strong educational background. Due to the subsidized fees, they can also opt for multiple degrees as per their choice. The survivors are provided official certificates from the university.

Conclusions

YCMOU has allowed survivors to overcome their limitations and financial obstacles. They are now able to chase their dreams by competing with ever challenging world. More survivors are being encouraged to be a part of this project. Establishing a study center within the premises or near the hospital are being implemented by YCMOU to facilitate overall development of patients and survivors.

O-214

Free Paper Session 2

ABSENCE OF SOCIAL SUPPORT NETWORK INCREASES THE RISK OF TREATMENT ABANDONMENT IN CHILDREN WITH CANCER

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Objectives

Treatment abandonment (TA) is the main reason of therapy failure in children with cancer in low/middle income countries. We explore predictive factors for TA in a cohort of children with cancer in Cali, the third largest city in Colombia.

Methods

We included children diagnosed with cancer at Cali's public university hospital (Jan/01/2010-June/04/2013). We extracted information for predictors from interviews applied by the pediatric oncology unit social worker, and unit psychologist, to caregivers. Outcomes were death, relapse, and TA. Event monitoring was carried-out by Cali's pediatric cancer clinical outcomes surveillance system (VIGICANCER). We estimated rate ratios (RR) among different predictors. We adjusted the hazard ratios (HR) for potential confounders using multivariate Cox regression analyses. Because of the small sample available, we finally applied bootstrapping approach to have a more accurate estimate.

Results

During this period, 162 patients were diagnosed, and 98 psychosocial interviews applied. 55% were male, 18% had colombian-indian ethnicity, 42% came from rural areas, 79% had an income below Colombian minimal wage, and 19% were classified as without social support network (SSN). TA was 18.5%. SSN RR was 7.3 (95%CI: 2.5, 20.5). RR for families with >4 children living in home was 8.6 (95%CI: 2.1, 49.3) and for colombian-indian ethnicity was 4.1 (95%CI: 1.2, 13.7). We did not found a significant association for gender, child or caregiver age at diagnosis, caregiver relationship, caregiver education, household conditions, family monthly income, parental job, and place of origin. In multivariate analyses, only SSN and household children preserved their independent relationship with TA. Bootstrapping adjusted HR for SSN was 2.4 (95%CI 1.1, 33.8).

Conclusions

We found a strong association between being classified as without SSN and TA. It was independent of other covariates, including surrogate measures of wealth. This highlights the imperative understanding of social ties around families with children with cancer, for planning strategies to prevent TA.

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Psychosocial interventions: evidence for effectiveness

DOES DEXAMETHASONE INDUCE MORE NEUROPSYCHOLOGICAL SIDE EFFECTS THAN PREDNISONE IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA? A SYSTEMATIC REVIEW

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Objectives

Steroid-induced neuropsychological side effects have a major impact on the quality of life in a large proportion of children treated for acute lymphoblastic leukemia (ALL). Dexamethasone is preferred over prednisone because of its higher anti-leukemic activity at the cost of a higher potency to induce metabolic side effects. To evaluate whether dexamethasone also leads to more neuropsychological side effects than prednisone, we performed a systematic review of the literature.

Methods

Articles were selected in PubMed, Embase and Cochrane on the basis of title and abstract by two independent reviewers using the following inclusion criteria: children with leukemia were receiving dexamethasone and/or prednisone; short and/or long term neuropsychological side effects (mood, cognition, behavior, sleep) were compared between both steroids; original research; written in English. We excluded case series (<10 subjects). We graded their level of evidence using the GRADE system.

Results

Of the 243 potentially relevant articles identified, we included 13 studies for review. Half of the included studies report more neuropsychological side effects with dexamethasone compared to prednisone. However, none of the randomised controlled trials with neuropsychological outcome primarily in view, showed a significant difference between dexamethasone and prednisone on mood and behavior. The randomized trials on long-term cognitive function only showed a subtle significant difference between dexamethasone and prednisone, limited to a minor decrease in word reading and a minor decrease on a IQ measure of fluid reasoning in the dexamethasone group, but both with absence of a clinically significant difference.

Conclusions

Based on this review of the literature, we conclude that the for clinical outcome valuable drug, dexamethasone, does not seem to induce more neuropsychological side effects than prednisone in children with ALL.

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Psychosocial interventions: evidence for effectiveness

EFFECTS ON QUALITY OF LIFE OF PARTICIPATION IN A COMBINED PHYSICAL EXERCISE AND PSYCHOSOCIAL INTERVENTION PROGRAM FOR CHILDHOOD CANCER PATIENTS

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Objectives

The QLIM (Quality of Life in Motion) study was designed to evaluate the effects of an intensive 12-weeks intervention program, combining physical exercise and psychosocial support. In this multi-center randomized controlled trial physiotherapist-led exercise therapy program and a psychosocial intervention aimed to enhance patient wellbeing and self-belief were offered simultaneously. Improved wellbeing and health-related quality of life (HrQoL) is hypothesized to increase the willingness and motivation to engage in sport activities and, as a result, to enhance the efficacy of the exercise program and vice versa.

Methods

Childhood cancer patients, aged 8 to 18 years and on or within the first year after treatment, were asked to participate. All participants underwent physical performance tests and completed questionnaires prior to randomization (T0) and after the 12-week intervention (T1). This abstract presents results of the HrQoL-assessments. Patients and parents filled in the PedsQoL generic core scale, cancer module and multidimensional fatigue module, both on T0 and T1.

Results

Sixty-eight patients (mean age=13.1; SD 3.1) participated. Parents in the intervention group (N=30) reported a significant improvement in HrQoL of their children compared with the parents of children in the control group (N=38) on the subscales Physical Functioning (mean $\Delta T1-T0 = 16.0$ and 6.0 respectively; $p=0.02$), Pain and Hurt (mean $\Delta T1-T0 = 15.7$ and -4.5 ; $p=0.00$) and Procedural Anxiety (mean $\Delta T1-T0 = 12.0$ and -1.1 ; $p=0.04$). No significant differences in improvement between the two groups were found by patient self-report.

Conclusions

In children with cancer short-term positive effects on HrQoL, as perceived by parents, were found for Physical Functioning, Pain and Hurt, and Procedural Anxiety after participation in a combined physical exercise and psychosocial intervention program. The study is continued to determine the longer-term changes.

Grant: Supported by Alpe d'Huizes/KWF (grant number ALPE-VU 2009-4305).

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Psychosocial interventions: evidence for effectiveness

COGNITIVE-BEHAVIORAL TREATMENT FOR INSOMNIA IN ADOLESCENT AND YOUNG ADULT SURVIVORS OF CHILDHOOD CANCER

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Objectives

Pediatric cancer survivors are at high risk for the development of insomnia due to treatment side effects, inpatient hospitalizations and medical late effects. Insomnia is linked to behavioral and emotional disturbances, substance use, and compromised school/work performance in adolescents and young adults. However, insomnia is an undertreated medical issue in pediatric survivors. Cognitive-behavioral treatment for insomnia (CBT-I) has been empirically validated in other cancer populations, but has not been adapted for use with pediatric cancer survivors, and is not offered as part of routine clinical practice even in major cancer centers delivering specialized survivorship care.

Methods

We are piloting an abbreviated CBT-I program in our regional cancer center's survivorship clinic, and evaluating whether this modified treatment (3 in-person sessions, and up to 2 telephone follow ups) would be feasible, acceptable, and effective in a cancer survivorship setting. Participants monitored their sleep using sleep logs, and completed sleep questionnaires and program evaluations.

Results

5 adolescent/young adult survivors of childhood cancer (ages 16-41 years) completed our ongoing CBT-I protocol. All reported improved sleep efficiency (pre to post-intervention: 72.9% to 88.4%), and improved Pittsburgh Sleep Quality Index (10.3 to 7.8), and Insomnia Severity Index (15.5 to 9.5) scores. Participants indicated that the abbreviated intervention was preferred to standard treatment, and were open to web/mobile interventions in the future. All indicated that the intervention was helpful, and would recommend the program.

Conclusions

There is a clinical need to incorporate effective treatment for insomnia into routine care for this at-risk population. Ongoing pilot data suggest that brief CBT-I is feasible, acceptable, and effective for improving insomnia in a pediatric oncology survivorship setting. Our findings support the potential to adapt this treatment model to a web/mobile CBT-I platform. We will discuss our plan to improve dissemination of insomnia treatment for childhood cancer survivors through technologically-enhanced intervention delivery.

O-218

**Measurement: what's new and necessary/ screen or not to screen
CAREGIVER DISTRESS AND PATIENT HEALTH-RELATED QUALITY OF LIFE:
PSYCHOSOCIAL SCREENING DURING PEDIATRIC CANCER TREATMENT**

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Objectives

Prior research has focused on identifying family psychosocial risk factors at cancer diagnosis in order to improve pediatric cancer care. This study aimed to evaluate presence of family risk/resources and caregiver distress in the first year from diagnosis and to determine the associations of family risk/resources and caregiver distress with patient health-related quality of life (HRQOL).

Methods

Sixty-seven parents of children with cancer completed the Check-in About Recent Experiences and Strengths (CARES) protocol via iPad during clinic visits within one year of diagnosis. CARES includes: Psychosocial Assessment Tool (family risk/resources), Strengths and Difficulties Questionnaire (patient adjustment), PedsQL 4.0 (patient HRQOL), Distress Thermometer (caregiver distress), and PTSD Checklist-Civilian 6 (caregiver traumatic stress).

Results

Patients ranged in age from 3 months to 18 years ($M = 9.3$, $SD = 5.5$ years), and 49% were female. The sample was equally distributed across leukemia/lymphoma, solid tumor and brain tumor diagnoses, and mean time since diagnosis was 158.27 days ($SD = 94.6$ days). Distress thermometer scores indicated moderate distress ($M = 4.86$, $SD = 2.69$). Gender, age, type of cancer, and time since diagnosis were not significantly correlated with family risk/resources, caregiver distress, and caregiver traumatic stress. Reduced patient HRQOL was significantly correlated with family risk ($r = -.41$, $p < .001$), caregiver distress ($r = -.43$, $p < .001$), and caregiver traumatic stress ($r = -.33$, $p < .01$).

Conclusions

Moderate levels of distress regardless of time since diagnosis and the association of caregiver distress with reduced patient HRQOL highlights the importance of psychosocial screening and care throughout the course of pediatric cancer treatment. To target timing and focus of psychosocial interventions, our future research aims to screen psychosocial risk based on patient self- and parent report using an adapted version of CARES during and after cancer treatment.

O-219

**Measurement: what's new and necessary/ screen or not to screen
HEALTH CARE PROVIDERS' RATINGS OF THE UTILITY OF PSYCHOSOCIAL
SCREENING TOOLS IN CHILDHOOD CANCER**

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Objectives

The clinical use of standardized psychosocial screening tools in pediatric oncology is rare, and how useful these tools are perceived to be by health care providers' (HCPs) is unknown. This study examined HCPs' perceived utility of two psychosocial screening tools designed for use in pediatric oncology, the Psychosocial Assessment Tool-Revised (PATrev) and (2) the Psychosocial Care Checklist (PCCL).

Methods

Pediatric oncologists (ONC), nurses (NUR) and social workers (SWK) treating patients at four pediatric cancer centres participated. Institutional approval was obtained for the study at each site and participants signed consent forms. Participants were asked to rank how useful they found: (1) psychosocial summary information derived from the parent-completed PATrev; and (2) the PCCL, an instrument completed by HCPs regarding the psychosocial needs of participating families before they received the psychosocial summary information. Usefulness was assessed using a Visual Analogue Scale (VAS). The VAS had a minimum score of 0 and a maximum score of 10; higher scores indicated greater endorsement for the utility of the measure. X^2 were used for analyses; effect sizes are reported.

Results

Seventy-three HCPs participated (32 ONC, 24 NUR, 10 SWK). Nurses reported the greatest utility endorsement of the PATrev summary compared to pediatric oncologists ($d = 0.77$) and social workers ($d = 2.94$). Similar results were found for the PCCL utility for nurses compared to pediatric oncologists ($d = 0.87$), and nurses compared to social workers ($d = 1.94$). Overall, nurses reported psychosocial screening to be more useful than the other HCPs.

Conclusions

These results suggest that there is variable belief in the utility and endorsement of these psychosocial screening tools among practitioners. Future research should examine specific barriers to uptake and implementation of these tools.

O-220

Functioning and interventions for siblings

SIBLINGS OF CHILDREN WITH CANCER: PERCEIVED CHANGES IN THEIR PLACE AND ROLE WITHIN THE FAMILY AFTER CANCER DIAGNOSIS

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Objectives

Siblings of children with cancer have often been reported as expressing a number of social and emotional difficulties. This qualitative study aimed to examine siblings' perceptions of their place and role within the family when a brother or sister is diagnosed with cancer.

Methods

Institutional approval was obtained and participants signed written informed consent. Participants included 22 siblings, aged 7-17 years, who participated in four rounds of the Siblings Coping Together (SCT) Program, an 8-week, manualized, group intervention program for siblings of children with cancer. Data consisted of materials completed by siblings during the sessions ("feelings trees" and "mind maps"), 49 in-between session homework sheets, 33 pieces of artwork/posters, and 31 logs recording events within group sessions completed by observers and group facilitators. A grounded theory framework was used for thematic data analysis.

Results

Three themes emerged regarding changes in siblings' perceptions of their place and role within the family since their brother or sister was diagnosed: *Being treated differently* (perceptions of being a burden in the family, ways they are included or left out of the cancer experience), *perceptions of being less important than the child with cancer* (seeing themselves as less loved than the affected child, having less privileges), and *perception of changes in their role in the family as a whole* (assisting in care giving for the ill child, a sense of increased responsibility for themselves and within the family, e.g. having to do more chores, becoming more independent). Sharing of these thoughts gradually increased over the 8-week sessions and formed the basis for the group intervention.

Conclusions

These preliminary findings provide rich insight of siblings' own views of the changes in their place and role within the family. These views emerged throughout their participation in the SCT intervention, which allowed them to improve their coping strategies.

O-221

Functioning and interventions for siblings

HAVING A SIBLING WITH CANCER: EMOTIONAL EXPERIENCE AND GROWTH THROUGHOUT AN 8-WEEK COPING WITH CANCER INTERVENTION

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Objectives

This qualitative study examined the emotional experiences and growth of siblings of children with cancer while participating in a manualized group intervention program: *Siblings Coping Together*.

Methods

Participants were 22 youth partaking in four different rounds of an 8-week group intervention for siblings of patients at least three months from diagnosis. Siblings were eligible to participate if they were between 7-17 years old. Data was derived from materials (e.g., "feelings trees" and "graffiti walls") completed by siblings during the sessions, 49 in-between session homework sheets, 33 pieces of artwork/posters completed by siblings, and 31 logs recording events within group. A grounded theory framework was used for thematic analysis of data. This study was approved by the institution and participants provided signed consent.

Results

Several overarching themes emerged regarding siblings' emotional experiences during the group: *feelings related to their personal experiences regarding their exposure to cancer* (sense of loss, sense of being dismissed or brushed aside by their family, guilt for having negative thoughts about the ill child, and emotional confusion), *feelings related to their perceptions of their brother's/sister's experiences with cancer* (feeling badly for them, worry about death and their well-being, and hope for their cure), and *feelings related to the family context* (as stressful, emotionally labile, and dependent on the treated child's health). Siblings reported several different ways of attempting to regulate these feelings, both adaptively (e.g., "find someone to talk to") or maladaptively (e.g., avoiding difficult feelings). Sharing of these emotional experiences and how to cope with them improved over the 8 sessions of intervention.

Conclusions

These findings provide rich evidence capturing siblings' views about themselves, the ill child's and family's experience, progressively emerging throughout a group intervention. This information is critical for treatment planning and ultimately helping siblings to navigate the experience of having a brother or sister with cancer.

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Functioning and interventions for siblings

REDUCTION OF ANXIETY LEVELS IN PARENTS AND SIBLINGS OF CHILDREN WITH CANCER AFTER SIBLING PARTICIPATION IN A PSYCHOSOCIAL GROUP INTERVENTION: A RANDOMIZED CONTROLLED TRIAL

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Objectives

Childhood cancer diagnosis and treatment can result in major psychological distress in the family. Programs targeting the specific psychosocial needs of siblings are rare and examination of the effects of these interventions on sibling and parental distress has not been previously investigated.

Objective: To determine if a manualized group intervention program for siblings, *Siblings Coping Together* (SCT), (Experimental Group, EG), improves anxiety in siblings' (directly) and parents' (indirectly) compared to a Control Group (CG).

Methods

Institutional approval was obtained and participants signed consent forms. **Methods:** A multi-site randomized controlled trial (RCT) with repeated measures. Inclusion criteria: Siblings, ages 7 to 16 years, and one parent, of patients at least three months from diagnosis. Both groups completed 8 two-hour weekly group sessions and three assessments (T1, pre-; T2, immediately post-intervention; and T3, three months later). **EG** sessions followed SCT's educational, social, and therapeutic problem-solving plan through games and crafts; **CG** sessions focused on socializing through games and crafts. Parents and siblings completed standardized self-report measures of Anxiety (*Multidimensional Anxiety Questionnaire* and *Multidimensional Anxiety Scale for Children*). Repeated-measures ANOVAs were conducted with partial eta-squared as indices of effect size.

Results

Preliminary analyses were based on 53 participants at T1 and 26 at all 3 assessment points. *Parent Self-Report.* Two significant group x time interactions were found: *physiological panic* reactions ($\eta^2=0.30$) and *social phobia* ($\eta^2=0.20$), suggesting improvements for parents in the EG compared to CG across time. Significant effects of time suggested both groups improved on measures of *total anxiety*, *worry-fears*, and *negative affectivity* ($\eta^2=0.36$, 0.29 , and 0.43 , respectively). *Child Self-Report.* A significant group x time interaction in *panic/separation* suggests improvement in the EG relative to CG, maintained over time ($\eta^2=0.24$).

Conclusions

Preliminary findings suggest major improvements in siblings' and their parents' anxiety, sustained over time, following participation in the manualized group intervention program.

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Functioning and interventions for siblings

A new 1-day systemic intervention for siblings of children who have cancer and their parents: a feasibility and pilot study

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Objective:

The aim of this study was to determine the feasibility and acceptability of a new 1-day systemic intervention for siblings of children with cancer and their parents, and to examine outcomes of a pilot study. Preliminary evidence was gathered to assess whether the current intervention promoted psychological adjustment in siblings in terms of mood, self-esteem, coping, and resilience, reduced psychosocial risk in the family and improved family functioning and communication.

Materials and methods:

This study recruited siblings of children who were being treated for all cancer types at a regional pediatric oncology and hematology centre in the UK over a period of 12 months. Twelve families (17 children and 19 parents) participated in the 1-day systemic therapeutic intervention. The intervention was developed combining three therapeutic components: systemic, narrative and problem solving strategies. The study used a longitudinal repeated measure design and included pre- and post-intervention assessments (4 and 12 weeks follow-up) and a qualitative assessment of participants' experience (8 weeks follow-up).

Results:

Enrolment, retention, attrition and satisfaction data support feasibility and acceptability of the intervention, but also highlight challenges. Outcome data showed changes in the desired directions: at 4 and 12 weeks follow-up, siblings in the intervention groups showed improved scores on the self-esteem, psychological competences, resilience and coping scales, and parents showed improvement on the scales of family functioning and communication and a reduction on the psychosocial risk scale (with Effect Sizes from small to large).

Conclusion:

The current study filled a gap in the current literature proving the feasibility and acceptability of delivering 1-day systemic intervention study for siblings of children with cancer and their parents in a regional centre in the UK. The authors developed a manual of the current intervention that allows for the replication of the current study in different oncology centres.

Keywords: pediatric oncology, siblings and parents adjustment, psychological intervention, family systemic intervention

Document not received

O-224

CEREBROSPINAL FLUID BIOMARKERS OF OXIDATIVE STRESS, MOTOR DEXTERITY AND BEHAVIOR DURING CHEMOTHERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Objectives

To examine associations between cerebrospinal fluid (CSF) biomarkers of oxidative stress, performance on fine motor dexterity tasks, and parent-reported behavior in children undergoing chemotherapy treatment for acute lymphoblastic leukemia (ALL).

Methods

Children diagnosed with ALL (N=89; mean [range] diagnosis age = 7.1 [2.3-14.7] years) were followed from diagnosis through the end of chemotherapy at one of two pediatric cancer centers in the southwestern United States. No children received cranial radiation therapy. CSF was collected at diagnosis and prior to intrathecal injections, and was analyzed for biomarkers of oxidative stress, including concentrations of oxidized phosphatidylinositol (PI) and F2 isoprostane (F2-I). High performance chromatography and ELISA was used for PI and F2-I assays, respectively. Children completed measures of fine motor dexterity, visual processing speed and visual-motor integration following induction, during continuation and at the end of chemotherapy. Parent completed ratings of child behavior at these same time-points.

Results

Compared to age-adjusted population norms (z-score=0, SD=1.0), children demonstrated significantly lower motor dexterity (mean = -1.19; 95% CI = -1.47,-0.91), visual processing speed (-0.24; -0.45,-0.03) and visual-motor integration (-0.22; -0.42,-0.02) following induction. By the end of therapy, visual processing speed normalized (-0.03; -0.26,0.21), while motor dexterity (-0.39; -0.70,-0.09) and visual-motor integration (-0.37; -0.57,-0.18) remained below average. F2-I concentration was significantly correlated with motor dexterity and visual-motor integration at multiple points in therapy. Oxidized PI was significantly correlated with motor dexterity beginning in the continuation phase. Visual processing speed was not related to CSF biomarkers of oxidative stress. Motor functioning during continuation was associated with increased hyperactivity and anxiety, and decreased functional communication at the end of therapy.

Conclusions

Central nervous system oxidative stress occurs following chemotherapy for childhood ALL, and is related to impaired fine motor function. Early intervention should be considered for these children to prevent progressive visual-motor deficits and behavioral problems.

O-225

"LOOKING FOR WHERE THE WILD THINGS ARE": POLYMORPHISMS AS PREDICTORS OF LATE ONSET LONGTERM COGNITIVE AND BEHAVIORAL DISABILITY

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Objectives

'Good news stories in medicine have two particular things in common, they have led to early detection and early intervention (Insel, 2013). While we have been able to cure a complex disease such as childhood acute leukemia in 80% of the children diagnosed, we have not been so good at reducing long-term morbidity or disability developed by some of these patients. The nature of the disability is often cognitive or behavioral, which are both recognized to constitute a major burden of disease. The question then is what drives this late onset long-term cognitive and behavioral disability? Here, the hypothesis was tested that various polymorphisms can partially explain the individual variation in developing anxiety and mood disorder as well as neuro-cognitive and behavioral disorders.

Methods

40 patients (1-18 yrs old) diagnosed with ALL belonging to two pediatric oncology centers were enrolled (protocol AIEOP-BFM-2009) and genotyped for 5HTT, BDNF (val66met) and COMT (val158met) polymorphisms. All patients and their families were subjected to psychosocial assessment (PAT2.1) and a short neurocognitive and behavioral age appropriate screening battery while in treatment and during scheduled follow-up visits.

Results

Patients with SL alleles of 5HTTLPR had a significantly more compromised score in some areas of executive functioning than patients with LL alleles; cognitive areas most affected were those involved in the modulation of emotional responses and flexibility to solve tasks and problems. Due to the sample size and the asymmetric division of the polymorphisms, no clear correlations with polymorphisms of COMT and BDNF were found.

Conclusions

Genes regulating neurotransmitters and vulnerability to stress, such as 5HTTLPR, may represent a factor indicating susceptibility towards the development of cognitive late effects in children treated for ALL, thus, offering a partial mechanism for individual variability among those with similar treatment histories, and providing a possible early predictor for cognitive and behavioral disability.

O-226

EFFECTIVENESS OF AN ADVENTURE-BASED TRAINING PROGRAM IN PROMOTING REGULAR PHYSICAL ACTIVITY AMONG CHILDHOOD CANCER SURVIVORS

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Objectives

Research indicates that regular physical activity enhances the physical and psychological well-being of childhood cancer survivors. Nevertheless, there is growing concern about declining levels of physical activity in childhood cancer survivors. This study aimed to examine the effectiveness of an adventure-based training program in promoting changes in exercise behavior and enhancing the physical activity levels, self-efficacy, and quality of life of Hong Kong Chinese childhood cancer survivors.

Methods

A randomized controlled trial, two-group pretest and repeated post-test, between-subjects design was conducted to 71 childhood cancer survivors (9-16-year olds). Participants in the experimental group joined a four-day adventure-based training program. Control group participants received the same amount of time and attention as the experimental group, but not in such a way as to have any specific effect on the outcome measures. Participants' exercise behavior changes, levels of physical activity and self-efficacy and quality of life were assessed at the time of recruitment, 3, 6, and 9 months after starting the intervention.

Results

Childhood cancer survivors in the experimental group reported significantly higher levels of physical activity and self-efficacy than those in the control group. Besides, there was a statistically significant change in the physical activity levels of childhood cancer survivors in the experimental group.

Conclusions

The adventure-based training program was found to be effective in promoting changes in exercise behavior and enhancing the physical activity levels, self-efficacy, and quality of life of Hong Kong Chinese childhood cancer survivors.

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IMPACT OF POSTTRAUMATIC GROWTH ON SELF-ESTEEM AMONG SURVIVORS OF CHILDHOOD BRAIN TUMORS

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Objectives

Self-esteem is an important resource for childhood brain tumor survivors in their adolescence and adulthood. The purpose of this study was to identify the association between posttraumatic growth (PTG) and their self-esteem among childhood brain tumor survivors. We hypothesized that PTG is related to self-esteem independently of severity of disease, combinations of treatment, relapse, or posttraumatic stress symptoms (PTSS).

Methods

One hundred and thirty eight survivors were recruited at eight hospitals and a clinic in Japan. They were asked to answer a set of questionnaires, including Rosenberg's self-esteem scale, the Impact of Event Scale-Revised (IES-R), Sarason's social support questionnaire (satisfaction) (SSS), and the Posttraumatic Growth Inventory (PTGI) / Posttraumatic Growth Inventory for Children (PTGIC). Besides, severity of disease, combinations of treatment, and relapse, using the intensity of treatment rating scale 2.0 (ITR-2), and information about presence or absence of late effects were collected from their primary physicians.

Results

A total of 108 survivors answered the questionnaires, however, of which 89 were valid for this analysis. As a result of multiple regression analyses, PTG ($\beta=0.229$, $p=0.011$), SSS ($\beta=0.240$, $p=0.011$), ITR-2 (physician report) ($\beta=-0.342$, $p<0.001$), perceived treatment intensity (self-report) ($\beta=0.219$, $p=0.019$), and PTSS ($\beta=-0.365$, $p<0.001$), were independently related to self-esteem after adjusted by sex, late effect, higher brain dysfunction, and difference of questionnaires (PTGI or PTGIC).

Conclusions

In conclusions, the hypothesis was proved. PTG was related to their self-esteem independently of the objective and subjective treatment intensity or PTSS of childhood brain tumor survivors. In addition SSS was also related to self-esteem in the same manner. Therefore, even with a severe disease, undergoing harsh treatments, or PTSS, childhood brain tumor survivors can maintain their self-esteem, when they perceive PTG

or SSS. Knowledge of this finding may empower survivors, their families, and medical professionals.

O-228

AVARTHEC STUDY: CEREBROVASCULAR DISEASE FOLLOWING CHILDHOOD AND ADOLESCENCE CANCER RADIATION THERAPY

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Objectives

To describe clinical and imaging characteristics of cerebrovascular disease (CVD) in survivors after irradiation of brain tumors (BT) during childhood. To identify high-risk patients to develop CVD and to adapt their long-term follow-up (FU). The study could help elaborating recommendations on new radiation techniques considering potential risk factors of cerebrovascular morbidity.

Methods

This study was performed in 13 French centers. Patients alive at the time of the study were irradiated between 1990 and 2002, at the age 0 to 18 years, for a BT. Patients who signed the consent had to have a clinical exam, an angiMRI and fulfill a questionnaire about their quality of life (QOL). MRI images were reviewed independently. Finally, a retrospective analysis of the dosimetry collected radiation criteria, and doses received by the abnormalities.

Results

Out of the 173 included patients, 165 are available for analysis because 6 finally refused the MRI after the inclusion.

Median age at diagnosis and at the moment of the study are respectively 9 and 24 years, Median FU is 15 years

198 CVD have been observed in 118 patients. Most of them are cavernoma (132 cases for 80 patients). 25 serious abnormalities as carotid stenosis and several second tumors have been detected, The average dose received by the site of cavernoma was 43 Gy.

106 QOL questionnaires are available.

Conclusions

71.5% of survivors irradiated for BT during childhood developed a CVD. Characteristics and correlation with dose will be discussed, as well as impact on QOL.

O-229

SINGLE CENTER RESULTS FOLLOWING PROTON BEAM THERAPY WITH ATYPICAL TERATOID RHABDOID TUMORS OF THE CENTRAL NERVOUS SYSTEM

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Objectives

Atypical teratoid rhabdoid tumor (ATRT) is a rare embryonal tumor seen predominantly in infancy and childhood. Outcomes are generally dismal with median survival estimated at around six months to a year. The purpose of this study was to evaluate proton beam therapy (PBT) outcomes in this population.

Methods

Sixteen patients with a diagnosis of ATRT were treated between November 2007 and January 2013 at our center. All patients were treated with PBT. Fraction sizes of 1.8 Gy/fraction were used to deliver between 28 to 33 fractions. Seven patients received craniospinal PBT. There were 12 male and 4 female patients. The median age at diagnosis was 18.5 months, with a range of 5 months to 39 years. Eight had metastatic disease at diagnosis. Fourteen patients underwent surgery. Fifteen patients received chemotherapy.

Results

Mean survival was 1.2 years (standard deviation 0.3 years). The median radiation dose to the tumor bed for all patients was 54 Gy. Eight patients received craniospinal irradiation (CSI) in addition to cranial irradiation with a median dose of 36 Gy. Median follow-up time was 0.81 years (range 0.0-4.16 years). 11 patients are stable, 3 patients are deceased, and 2 patients developed progression of disease. Four patients suffered nausea and vomiting (CTC Grade 2) as a result of treatment, and four patients also suffered moderate skin erythema (CTC Grade 2). Two patients suffered from both weight loss and general fatigue during treatment. All 8 patients with localized disease are alive while those with metastatic disease have shown a steady decline in survivor numbers ($P=0.066$).

Conclusions

PBT is well tolerated in this heavily treated population. In the background of poor survival, these early outcome data are promising, especially in those without metastatic disease. Further follow-up is necessary.

O-230

THE ROLE OF CRANIAL RADIOSURGERY FOR PEDIATRIC PATIENTS

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Objectives

The indications for radiosurgery for pediatric patients are often extrapolated from adult patients. Reduced normal tissue exposure is ideal, but the toxicities of treatment are not well characterized. Outcomes and toxicity are analyzed from our institutional experience of Gamma Knife radiosurgery (GKRS) for pediatric patients.

Methods

A query of the GKRS database was performed to identify patients age ≤ 18 at the time of GKRS. Diagnosis, pre-treatment factors, GKRS data, post-treatment neuroimaging studies, and toxicity information were evaluated. Survival times were calculated using the Kaplan-Meier method.

Results

From 1997 through 2013, 35 pediatric patients were identified; 16 female and 19 male. Median follow up was 43.1 months (Range: 0-204.2). Diagnoses included: AVM (23), schwannoma (3), low-grade astrocytoma (3), pituitary adenoma (1), ependymoma (1), medulloblastoma (1), and metastasis (3). Median age was 14 yrs and median LPS at GKRS was 90. Six patients had prior fractionated radiotherapy and chemotherapy. Ten patients had prior resection: 7 GTR, 1 NTR, and 2 STR. GKRS was the initial treatment for 24 patients and used for recurrence or progression for 11 patients. Median prescription dose was 15 Gy (Range: 12 to 27 Gy), dose conformity was 1.817, dose heterogeneity was 1.996. Median treatment volume was 2.8 cc., and max tumor diameter was 2.63 cm. Following GKRS, 9 patients had progression: 6 distant, 2 local, and 1 combined. One- and 5-year local progression free survival, progression free survival, and overall survival was 96.7% and 87.4%, 87.3% and 70.3%, and 87.7% and 82.4%, respectively. CTCAE v 4.0 CNS toxicity grade 1-2 occurred in 10 pts, and grade 3 in 1 pt. Median time to toxicity was 9 months, (Range: 0-80.3).

Conclusions

Pediatric patients tolerated GKRS well with reasonable toxicity. Local control was good across the spectrum of diagnoses treated. Prospective evaluations should be performed to develop guidelines for the use of radiosurgery in this population.

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SIGNIFICANCE OF PRIMARY TUMOR VOLUME ON RECURRENCE AND SURVIVAL IN PEDIATRIC PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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Objectives

Primary tumor volume (PTV) has been recognized as a promising prognostic indicator in the treatment of adult nasopharyngeal carcinoma (NPC). Our study was designed to analyze the value of the primary tumor volume [gross tumor volume of the primary site (GTV-P)] in predicting the treatment outcome in pediatric patients with NPC treated with intensity modulated radiotherapy (IMRT).

Methods

A retrospective review of 30 consecutive pediatric patients aged <18 years with stage I–IVB NPC was performed. All Patients received three cycles of Induction chemotherapy with cisplatin and 5-fluorouracil, and three additional cycles of cisplatin alone during radiation therapy. Radiation therapy was administered using intensity modulated radiotherapy (IMRT) technique and inverse planning system. Gross tumor volume of primary tumor plus retropharyngeal nodes (GTVprn) was calculated to be an index of treatment outcome.

Results

The median PTV was 45.9cc. Large GTVprn (>55 ml) was associated with a significantly poorer local control, lower distant metastasis-free rate, and poorer survival. 3-year overall survival in the large tumor volume group (>55 ml) and the small tumor volume (≤ 55ml) were 58% and 100%, respectively (p=0.007). The 3-year disease free survival was 28% in the large tumor group and 94% in small tumor volume group (p=0.002) while 3 year local recurrence free survival in the large tumor group 77% and 100% in small tumor volume group (p=0.02). The 3-year overall survival, disease-free survival, local control, and distant metastasis-free rates in all patients were 87%, 76%, 92%, and 76%, respectively.

Conclusions

PTV had a close relationship with survival rates and recurrence rates in pediatric patients with NPC. The large tumor volume group (PTV > 55 mL) was associated with more recurrence and poor survival rate.

O-232

COLORECTAL CANCER SCREENING IN CANCER SURVIVORS TREATED WITH RADIATION THERAPY

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Objectives

Due to increased risk of colorectal cancer(CRC) among childhood cancer survivors who received abdominal or pelvic radiation therapy(RT), guidelines recommend that these survivors should start CRC screening earlier than general population. However, there is no evidence suggesting that earlier CRC screening for these survivors would be effective. We undertook a prospective study to determine the polyp detection rate among young survivors and compare this to the 20% prevalence rate expected among average risk individuals >50 years old for whom CRC screening is accepted.

Methods

Asymptomatic cancer survivors aged 35-49 years who were treated with abdominal radiation or TBI(at least 12Gy), ≥10 years prior were eligible. Patients with past medical history of polyps, Crohn's disease, ulcerative colitis or any colorectal screening within the last 5 years were excluded. All patients underwent a full colonoscopic examination with adequate bowel preparation, and any retrieved polyps were reviewed by a gastrointestinal pathologist.

Results

Fifty five patients (27 males, 28 females), with a median age of 45 years (43-49), were enrolled. A total of 52 polyps were found in 26 patients (47.3% of patients; 95% CI = 31.6%-61.2%). Adenomatous polyps were found in 19 patients (34%; 95% CI = 22%-48%). 32% of all polyps were deemed to be within radiation field (17/52; 95% CI = 20-47%). 61% of all polyps were found beyond the ascending colon beyond the reach of a sigmoidoscope (either in the transverse colon, descending colon or cecum; 32/52; CI = 47%-74%).

Conclusions

The prevalence of adenomatous colorectal polyps in abdominal-RT-treated survivors is comparable to or greater than that described among the general population aged ≥ 50 years, for whom CRC screening is generally recommended. This provides indirect support for guidelines recommending the early initiation of screening. It is recognized that most polyps occurred outside the RT field, which complicates interpretation.

O-233

LIMITED MARGIN RADIOTHERAPY FOR PEDIATRIC PATIENTS WITH EWING SARCOMA ACHIEVES HIGH RATES OF LOCAL TUMOR CONTROL

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Objectives

Determine the rate of local failure (LF) using limited margin radiotherapy (RT) and dose escalation (for tumors $\geq 8\text{cm}$) in pediatric patients with Ewing sarcoma (EWS).

Methods

Eligible patients with EWS were treated on a Phase II institutional trial of limited margin RT. Treatment volumes were based on CT/MR treatment planning datasets. The clinical target volume (CTV) included gross tumor (GTV) plus a 1cm anatomically constrained margin. Planning target volumes (PTV) ranged from 0.5-1cm. Unresected tumors $< 8\text{cm}$ received standard RT dose of 45Gy to the CTV (PTV1) and a boost to 55.8Gy to the GTV (PTV2). For tumors $\geq 8\text{cm}$, RT dose was escalated to include a boost to 64.8Gy to the GTV (PTV2). Patients with marginal resections received adjuvant RT of 50.4Gy to the CTV (PTV1). Initial follow-up occurred every 3 months, including imaging of the primary tumor site.

Results

Forty-one patients with EWS who had localized (22) or metastatic (19) disease were enrolled on trial. Thirteen had primary pelvic tumors. Median (range) age, tumor size and follow-up were 13.4 years (2.9-24.7), 8.6 cm (3.0–17.0) and 44.1 months (2-125, {62 months for patients remaining on-study}), respectively. All patients received systemic chemotherapy. The median (range) RT dose for all patients was 56.3Gy (45.0-65.48). Fifteen patients received adjuvant, 12 standard, and 11 dose escalated RT. Ten patients had distant failure and one patient local and distant failure. The 5-year cumulative incidence of LF was 0.0244 ± 0.0244 . Within local and metastatic patient groups, differences in failure-free survival were not statistically significant based on initial tumor size, age or site of disease.

Conclusions

Treatment with limited margin RT including dose escalation for unresected tumors $\geq 8\text{cm}$ provided favorable local tumor control in this trial. This RT approach warrants further investigation in a larger trial incorporating standardized chemotherapy.

O-234

PRELIMINARY RESULTS FROM THE PEDIATRIC PROTON CONSORTIUM REGISTRY (PPCR): A COLLABORATION OF US PROTON CENTERS TO ACCELERATE PROTON THERAPY RESEARCH

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Objectives

Pediatric proton investigators have united to form the Pediatric Proton Consortium Registry (PPCR) to accelerate research on the role of Proton Radiotherapy(PRT) in children. A comprehensive (680+field) REDCap web-based database for pediatric cancer patients was created. The early demographics and PRT patterns-of-use/care are described here.

Methods

All proton patients <22 years treated at PPCR centers are eligible. The registry captures baseline demographics, insurance status, disease/health information, treatment details, and follow-up of consenting children/families. Basic information on demographics/diagnosis are collected on unenrolled patients.

Results

Six sites are IRB approved, 3 enrolling. 242 pts enrolled, 16 refused/or were missed. Nine more sites will open in 2014. The PPCR data reveals: median age 10.1 (0.7-21.9yrs); 41% female; 77.4%white, 5%black, 6%Asian. 98.5% are insured: 68% private/employer-based, 13.3%Medicaid; 14.8%International, 2%self-pay. Referrals are from pediatric oncologists 55.7%, neurosurgeons 15.8%, and radiation oncologists 14.8% of the time. MA, IL, NY, FL states lead enrollment. Europe, Asia, Australia and Canada comprise 71.9%, 18.8%, 6.3%, and 3.1% of international patients. 59.8% have CNS tumors; 40.2% have non-CNS ; 71.7% of tumors are primary, 23.7% recurrent, 4.5% metastatic. CNS histologies: glioma(20.2%); medulloblastoma(19.3%); ependymoma(18.5%); craniopharyngioma(16.8%). Non-CNS histologies: chordoma(21.3%); RMS(18.8%); bone sarcoma(16.3%); other STS(10%). 4.1% have a genetic syndrome. 5.9% have KPS/Lansky =<60.

Radiotherapy intent was curative in 97.4%. Type of PRT: 74.4% passively scattered; 9.9% pencil beam scanning(PBS); and 8.1% Proton-SRS. Mean total RT dose is 51.4 GyRBE(12-81). 15.1% received CSI, 54.4% received chemotherapy; 15.2% enrolled on COG trial. 39% return to proton center for f/u care.

Conclusions

The PPCR is a successful multicenter US based registry for children receiving PRT. The early demographics and patterns-of-use/care demonstrate the PPCR can be used to understand the population referred for PRT and track their outcomes. All US proton

centers that treat children are invited to join the PPCR.

O-235

HIGH DOSE RATE BRACHITHERAPY IN CHILDHOOD SOFT TISSUE SARCOMAS

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Objectives

To evaluate the efficacy of HDR-BT in children undergoing treatment for STS.

Methods

From 1998 to 2013, 50 children, 7 year median age, with STS received HDR-BT at IOV. Forty-eight have been treated on primary lesion, 2 for relapse. Extremities were most commonly involved (18), followed by head and neck (11), vagina (11), orbit (5), chest-abdominal wall (5). Histology was embryonal rhabdomyosarcoma (26), alveolar rhabdomyosarcoma (11), Ewing-PNET (5), fibrosarcoma (3), Nos rhabdomyosarcoma (2), leiomyosarcoma (2) and myoepithelial carcinoma (1). Ten children had lesions greater than 5 cm (5 limbs, 3 chest-abdominal wall, 2 vagina). Surgical margins were positive in 27 (11 vagina, 7 limbs, 4 orbit, 3 non parameningeal head-neck, 2 chest-abdominal wall), 1 (orbit) had macro residual. All patients underwent local excision, followed by temporary interstitial HDR-BT using iridium-192. Forty-five patients have been treated with HDR-BT alone, while 5 received HDR-BT plus EBRT. HDR-BT dose has been 36 Gy, in 12 fractions, twice per day. All children receiving EBRT underwent irradiation up to a total dose of 32 Gy in 20 fractions of 1.60 Gy, twice per day, after a 18 Gy HDR-BT boost.

Results

At a 8 year median follow up , 45 patients are alive without disease, 1 is alive without disease after amputation. Two children failed locally and after developed lung metastasis, 2 had nodal and lung metastasis without LR; all died for tumor progression. The 5-year local control, DFS, and OS were 94%, 90%, and 92%, respectively. Late mild subcutaneous fibrosis is evident in near all patients. One girl with wrist sarcoma underwent surgery because of finger movements impairment with a very satisfactory outcome. Two children presented esthetically unacceptable scars, very well corrected by plastic surgery. One girl presented hematocolpos at menarche.

Conclusions

HDR-BT, in select groups of children, results in excellent local control and functional outcome with reduced treatment-related morbidity.

O-236

SECOND MALIGNANT NEOPLASMS AND CAUSES OF DEATH IN PATIENTS TREATED OF HODGKIN DISEASE IN CHILDHOOD IN SLOVENIA

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Objectives

We studied the frequency of second malignant neoplasms (SMN) and causes of death in patients (pts) treated of Hodgkin disease (HD) in childhood in Slovenia.

Methods

One hundred fifty-six pts under the age of 16 were treated for HD in Slovenia between 1960 and 2007. At diagnosis they were 3 to 16 (med. 12) years old. Nineteen pts died of HD 1 to 8 (med. 2) years after diagnosis. December 2013 the follow-up time of the remaining 137 pts was 5 to 43 (med. 24) years.

Results

Thirty-one SMNs were found in 28 pts 5-42 (med. 22) years after diagnosis; in 1 (breast cancer) of 13 (8%) treated with ChT alone, in 4 (2 thyroid cancers, 2 basaliomas, one malignant melanoma and pleural mesothelioma) of 16 (25%) treated with RT alone and in 23 (10 thyroid cancers, 3 breast cancers, 2 acute myeloid leukemia, 3 basaliomas and parotid cancer, colon cancer, lung cancer, uterine cancer, RMS of maxillar sinus and intracranial meningeoma one of each) of 108 (21%) pts treated with RT and ChT.

Twenty-five SMNs arised inside RT field Cumulative incidence for SMN was 11,2% at 20 years, 25,5% at 30 years and 32,1% at 40 years of follow-up. Seven pts died of SMN (2 with AML, one with lung cancer, mesothelioma, colon, breast cancer and RMS 7 to 43 (med. 26) years after diagnosis and 6 of other causes: heart damage in 4 pts 23 to 30 (med. 26) years after diagnosis and infection in 2.

Conclusions

In our study incidence of SMNs after treatment of HD in childhood was high, thyroid cancer being the most frequent. SMNs were the most important cause of death more than 10 years after diagnosis of HD. Longlife follow-up including screening for SMNs and heart disease in those patients is of vital importance.

O-237

CAROTID ARTERY DISEASE AFTER NECK IRRADIATION IN LONG-TERM SURVIVORS OF HODGKIN DISEASE IN CHILDHOOD

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Objectives

Some studies have shown carotid artery disease in pediatric cancer survivors treated with neck irradiation (RT), although with contradictory results. We compared parameters of carotid artery disease in patients (pts) treated of Hodgkin disease (HD) in childhood with neck RT and cardiovascular risk factors matched controls.

Methods

Fifty-six pts were treated of HD under the age of 16 in Slovenia between 1975 and 1986; 32 of 40 alive pts received neck RT and were eligible for study, 8 refused cooperation, 24 (8 females, 16 males) were included. They were 3 to 16 (med. 11) years old at diagnosis and had evaluation 27 to 38 (med 33) years later at the age of 29 to 48 (med. 43) years. They received neck RT with 20 to 42 (med. 30) Gy, 19 pts received chemotherapy. Aloka alfa 7 was used to determine plaque and intima media thickness in common carotid arteries. Carotid artery stiffness was measured by new high-resolution echo tracking using colour-coded duplex sonography. The following carotid stiffness indexes were calculated: local pulse wave velocity (PWVb m/s), strain pressure elasticity index (Ep) (kPa), beta index and augmentation index (Aix, %). The variables of the two groups were statistically analyzed by SPSS 20.

Results

Values of local carotid stiffness indexes were significant higher: beta stiffness ($p=0.03$), PWVb ($p=0.021$), Ep ($p=0.005$), Aix ($p<0.000$) and there were significant more arterial wall calcinations ($p<0.000$) in the group of survivors. The intima-media thickness ($p=0.285$) and the number of plaques ($p=0.55$) were not different in the two groups neither was in either group any significant carotid stenosis.

Conclusions

Our results revealed that mild arteriosclerotic changes of carotid arteries are more prevalent in long-term survivors of Hodgkin disease in childhood after neck RT. Follow-up is needed to prevent stroke, associated with advanced carotid disease.

O-238

HELICAL TOMOTHERAPY FOR ASKIN'S TUMOR OF CHEST WALL: CLINICAL OUTCOMES

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Objectives

To evaluate the clinical outcomes of patients with Askin's tumor of the chest wall treated using Helical Tomotherapy.

Methods

The treatment comprised multiagent chemotherapy(CTh) and local therapy in the form of surgery (Sx) & radiation therapy(RT) or definitive RT alone.

Results

Sixty-four pts. between 7-21 yrs (Median: 17Yrs) treated with radical intent between January 2008 - December 2013 were included. Most (63%) were males. Median tumor volume was 840cc. Forty-one (64%) underwent Sx+RT. Surgical margins were close/positive in 24(59%). Median percentage necrosis was 85%. After a median follow-up of 24mths the local control (LC), disease free survival (DFS), & overall survival (OS) were 74%, 54%, & 81% respectively. Tumors with volume more than 850cc had inferior LC (67% vs. 80%, p=0.74) & DFS (58% vs.61%, p=0.89).

Conclusions

Primary tumor volume, surgical resection & margins, percentage necrosis & presence of pleural effusion influenced disease outcomes. The combination of CTh, Sx, & RT resulted in superior outcomes for non-metastatic Askin's Tumor.

O-239

RADIOSURGICAL TREATMENT OF TUMORAL AND VASCULAR BRAIN LESIONS IN CHILDREN

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Objectives

The objective of the present study is to assess the long-term safety and efficiency of Gamma Knife radiosurgical treatment of brain arteriovenous malformations and tumors in children.

Methods

We reviewed the outcome of a series of 55 children (aged 2.4-15.5 years) who underwent radiosurgical irradiation for a tumoral or vascular brain lesion in our center. This included 21 arteriovenous malformations, 1 cavernoma, 8 pilocytic astrocytoma, 4 grade II glioma, 1 glioblastoma, 3 ependymoma, 3 hypothalamic hamartoma, 8 schwannoma, 2 meningioma, 2 choroid plexus carcinoma, 1 craniopharyngioma, and 1 hemangiopericytoma. All patients had single-session radiosurgery using Gamma Knife C or Perfexion, under general anesthesia for 39 patients. Pathologies with a mean size of 2.8 cc (range 0.1-13.6 cc) were irradiated with a mean margin dose of 16.8 Gy (range 10-25 Gy).

Results

The follow-up period of 45 of these patients ranged from 0.5 to 12 years (mean 4.6 years). The obliteration rate of arteriovenous malformations was 86.6%. No bleeding occurred after radiosurgery. The morbidity was limited to 2 children: 1 patient with AVM had seizures after irradiation and 1 patient with vestibular schwannoma from NF2 lost hearing unilaterally. We observed excellent tumor control for patients with pilocytic astrocytomas, grade II glioma, schwannoma and meningioma, hemangiopericytoma. None of our children with glioblastoma, ependymoma, hypothalamic hamartoma or craniopharyngioma had their tumor controlled in the long term after radiosurgery.

Conclusions

Gamma Knife radiosurgery represents a very safe and quite effective therapy for brain arteriovenous malformations and some brain tumors in children.

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SIOP Award Session

SERUM FOLATE LEVELS, METHYLENE TETRA HYDROXY FOLATE REDUCTASE (MTHFR) GENOTYPE, AND COMPLICATIONS DURING INDUCTION CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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Objectives

Majority of the deaths in children from low/middle income countries undergoing treatment for ALL occur during the initial phases of chemotherapy, mostly due to malnutrition and infections. Though folate deficiency is widely prevalent in the developing countries, its effect on the outcome of treatment in these children has not been studied. The present study examines the effect of folate status and the MTHFR genotype on the course and complications of induction chemotherapy.

Methods

Children with ALL registered from September 2011 through August 2013 were assessed for serum folate at baseline and at end of induction and MTHFR genotype (677 and 1298). Clinical and laboratory parameters were monitored during induction chemotherapy. The study was approved by institutional ethics committee.

Results

Folate deficiency was seen in 40 (26%) of 150 children at baseline and 43 (32%) of 134 at end of induction chemotherapy. Folate levels declined from 10.29 ± 7.2 to 8.23 ± 5.9 ng/ml; ($p=0.02$) after induction, being more marked in mutant 677 genotypes. Low counts at day 14 was seen more often in children with baseline folate deficiency ($p=0.001$) and 677 mutation ($p=0.01$). Higher proportion of folate deficient children 14/40 (36%) experienced episodes of febrile neutropenia as compared to 17/110 (15%) children with normal folate ($p=0.01$). 6/10 (60%) children succumbing of neutropenia related sepsis had pre-induction folate deficiency as compared to 33/134 (24.6%) induction survivors ($p=0.02$). Transfusion requirement (both red cell and platelet) was higher in folate deficient children (0.01 and <0.0001 respectively). Higher incidence of mucositis was seen in children with 1298 mutations ($p=0.007$). Concomitant folate deficiency accentuated the adverse effects of mutated genotypes. Multivariate analysis revealed associations of baseline folate deficiency with low counts at day 14 ($p=0.001$) and MTHFR 1298 mutations with mucositis ($p=0.02$).

Conclusions

Folate deficiency and MTHFR mutations led to higher incidence of hematological complications, mucositis and poorer survival in children with ALL undergoing induction chemotherapy.

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SIOP Award Session

SECULAR TRENDS IN SURVIVAL FOR ACUTE LYMPHOBLASTIC LEUKEMIA AMONG CHILDREN LIVING IN AN AREA WITH LOW SOCIOECONOMIC STATUS IN NORTHEAST-BRAZIL

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Objectives

To evaluate the secular trend of survival for acute lymphoblastic leukemia in children living in an area with low socioeconomic status in Northeast-Brazil.

Methods

We evaluated patients up to 19 years with acute lymphoblastic leukemia from 1980 to 2014, treated by pediatric oncologists using standardized protocols in a service linked to a public general hospital. We divided the patients into two cohorts: treated from 1980 to 2004 (cohort A) and from 2005 to 2014 (cohort B). The findings were compared with patients treated from 2005 to 2014 in the single private hospital in the same localization, by the same team and protocols (cohort C).

Results

We obtained 391 patients (cohort A: 287; cohort B: 89; cohort C: 15). The overall mortality rate was 52.4% and the mean overall survival was 148 months (cohort A: 57.5% and 137 months; cohort B: 40.4% and 59 months; cohort C: 26.7% and 106 months respectively). The overall mortality rate was higher in cohort A ($p=0.005$). It was noted that in the cohort A the mortality rate was higher in infants and adolescents compared to toddlers/school children ($p=0.006$ and 0.034 respectively) and the median survival ($p=0.004$ and 0.023 respectively). In cohort B, patients from rural areas had a higher mortality rate ($p=0.045$) and the boys had a longer mean survival ($p=0.025$). For cohorts B and C we have obtained a higher mortality rate among patients living in rural areas ($p = 0.038$), in the same way that the median survival time ($p=0.024$), also higher among boys ($p=0.011$) whose mothers had 11 or more years of schooling ($p=0.044$).

Conclusions

The mortality rate has been considered decreasing, and increased median survival time was associated with male gender, living in urban area, and with mothers with higher level of education.

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SIOP Award Session

OUTCOME AND MORBIDITY OF PRIMARY RESECTION OF HEPATOBLASTOMA IN JPLT-1 AND 2 PROTOCOLS

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Objectives

The Japanese Study Group for Pediatric Liver Tumor (JPLT) was launched in 1991 and conducted two protocols named JPLT-1 and JPLT-2 to evaluate the cure rate of risk-stratified hepatoblastoma (HB). In these protocols, primary resection was permitted in PRETEXT I and II cases followed by postoperative chemotherapy. In this study, we examined the outcome and surgical complications of primarily resected HB cases.

Methods

Among 154 JPLT1 and 335 JPLT2 cases, 54 primarily resected HB cases were enrolled. 16 were PRETEXT I, 26 were PRETEXT II, and 12 were ruptured HBs. Clinical features, surgical procedures and survival rates were compared among these three groups.

Results

All 16 PRETEXT I cases underwent complete resection by left lobectomy or left lateral segmentectomy (n=7), right lobectomy (n=5) and partial resection (n=4). Among them, two cases showed recurrence; one older case (100 mos.) and one partially resected case. All 26 PRETEXT II cases except for one underwent complete resection by right lobectomy (n=8), left lobectomy (n=17) and other resection (n=1). Three cases had portal or hepatic vein involvement. Among them, operation death occurred in one newborn and there was recurrence in 4 cases including 3 cases involved veins and one older case (114 mos.). Of 12 ruptured cases, 7 showed recurrence. Overall survival rates at 5 years of the PRETEXT I, II and ruptured cases were 94%, 85%, and 42%. Event-free survival rates at 5 years in these groups were 88%, 70%, and 32%, respectively. In these cases, 3 cases showed biliary duct complications, which were all cured.

Conclusions

Outcome of PRETEXT I and II cases with primary resection was unsatisfactory because of some recurrence. Primary resection for these cases should be performed by anatomical resection according to strict surgical guidelines. More intensified chemotherapy should be required for the primarily resected cases where the tumors ruptured.

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SIOP Award Session

COMPREHENSIVE UPDATE OF PEDIATRIC RENAL TUMOR EPIDEMIOLOGY: ANALYSIS OF THE FIRST 4000 PATIENTS ON CHILDREN'S ONCOLOGY GROUP (COG) RENAL TUMOR CLASSIFICATION AND BIOLOGY PROTOCOL AREN03B2

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Objectives

The AREN03B2 study is a conduit to risk-stratified enrollment on COG therapeutic renal tumor (RT) studies via real-time central review, and supports a comprehensive biologic tissue and epidemiologic repository. To define the present day spectrum of pediatric RT, we analyzed the first 4000 patients enrolled.

Methods

4000 patients with a radiologically identified RT, extra-renal Wilms (WT) or extra-CNS Malignant Rhabdoid Tumor (MRT) enrolled on AREN03B2 between 2/27/2006 - 9/19/2013. Required submissions included: 1. Abdominal CT/MRI, and chest CT 2. Institutional pathology report, formalin-fixed tissue and diagnostic H&E slides 3. Operative report 4. Tissue for LOH (1p/16q) or *INI1* testing. Available blood, urine, tumor and normal kidney tissues were banked.

Results

3,949/4000 were eligible. Median age at diagnosis was 3.2 years (range 1 day – 29.7 years), 47.4% were males, 7.6% had congenital anomalies, including 3.5% with predisposition syndromes. Histologic distribution in unilateral patients was Favorable Histology WT (FHWT) 75%, Anaplastic WT 5%, Renal Cell Carcinoma 4.2%, MRT 3.7%, Clear Cell Sarcoma of the Kidney 3.4%, Congenital Mesoblastic Nephroma 2.2%, Cystic Nephroma 2.0%, Metanephric Adenoma 0.4%, and 3.0% Other. 41.5% of patients subsequently enrolled on therapeutic studies. Among patients with FHWT, stage distribution was I 20.4%, II 22.0%, III 31.6%, IV 19.8% and V 6.3%. Of stage IV patients, 78.4% had pulmonary only metastases, 2.7% extra-pulmonary only and 17.5 % both. 5.2% had LOH of 1p/16q. The tissue bank has supported over 50 biologic and epidemiologic studies to date.

Conclusions

AREN03B2 is the largest clinical, epidemiologic and biologic databank for pediatric RT, and has presented new insight into pediatric RT epidemiology in the modern era. In contrast to historical cohort studies, only 80% of enrolled unilateral patients had WT, and incidence of rare RTs was increased. The study enables timely risk stratification onto

clinical trials and serves as a valuable repository for RT discovery research.

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SIOP Award Session

INTEGRATIVE GENOMIC ANALYSES IDENTIFY RECURRENT STRUCTURAL ALTERATIONS IN ATYPICAL TERATOID RHABDROID TUMOURS (ATRTS)

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Objectives

ATRTs (Atypical teratoid rhabdoid tumours) represent one of the most aggressive pediatric brain tumours. Paradoxically, ATRTs are reported to exhibit balanced genomes with alterations of the *SMARCB1* locus on chr22, as the sole recurrent somatic genetic event. To better define molecular mechanisms underlying ATRT biology we comprehensively interrogated 63 ATRTs using an integrated genomics approach.

Methods

We integrated a combination of ultra-high resolution SNP genotyping whole-genome/exome and RNA sequencing. Copy number and structural alterations were mapped using orthogonal bioinformatics techniques. Structural alterations and mutations were validated by targeted re-sequencing using the Sanger method and/or MiSeq and Ion Torrent analyses.

Results

ATRTs exhibited few recurrent deleterious SNVs with exception of loss of function mutations in *SMARCB1* (15 SNVs in 63 tumours). As reported previously, we observed a low mutation rate in primary ATRTs. Significantly, we observed structural alterations as predominant genetic mechanisms (~3.2/tumor) in primary ATRTs. Notably, bi-allelic structural events leading to loss of *SMARCB1* function were observed in the majority of primary ATRTs (76% of tumours) and included novel intrachromosomal translocations of *SMARCB1* not detected using conventional diagnostic techniques. We observed novel recurrent structural alterations associated with corresponding copy number driven gene expression changes in novel loci not previously implicated in ATRTs, in nearly 20% of primary ATRTs. These included focal deletions of *BCR*, *MKL1*, *EP300*, *LRP1B*, *CDH13*, *ODZ2* and *ZNF407*.

Conclusions

Our integrated high resolution genomics approach has uncovered novel loci with predicted functions in cell adhesion, DNA damage response and epigenetic regulation that will inform a better understanding of ATRT tumour biology. The identification of novel structural events in *SMARCB1* and other genes indicates that the scope of genetic alterations in ATRTs has to date been underestimated and underscore WGS as an important tool for gene discovery as well as clinical diagnostics in ATRT.

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SIOP Award Session

ARE THERE ANAPLASTIC WILMS TUMORS THAT RETAIN AN INTACT P53 PATHWAY?

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Objectives

The Therapeutically Applicable Research to Generate Effective Treatment (TARGET) project includes 39 Diffuse Anaplastic Wilms Tumors (DAWT) showing anaplasia in >50% of slides. The goal was to evaluate and characterize the p53 pathway in DAWT and to identify novel mutations/targets.

Methods

A single sample of frozen tissue of each tumor underwent Whole Genomic or Exomic Sequencing, gene expression (Affymetrix U133+2) and copy number analyses (6.0 SNP arrays). TP53 immunohistochemistry was performed on available blocks, taken from a different sample of the respective tumors.

Results

High-quality, somatic, non-synonymous TP53 variants were identified in 26/39 (67%) DAWT. No germline mutations were identified. TP53 variants were associated with 17p13 copy number loss in 23/26 DAWT; the remaining 3 had TP53 variants involving both alleles. Of 13 DAWT lacking TP53 variants, 17p13 copy number loss was identified in 6 and a normal 17p13 copy number was present in 7. Significant upregulation of genes involved in the Biocarta p53 and p53 hypoxia pathways was identified in these 7 DAWT, supporting an active p53 pathway in the sample analyzed. No other variants were identified within the p53 pathway. Only 14% of the 7 tumors lacking TP53 abnormalities relapsed versus 53% in the remaining 32 DAWT. We further examined the 7 DAWT without TP53 abnormalities. Abnormal p53 protein accumulation was identified in anaplastic areas by immunohistochemistry in 3, consistent with TP53 mutation not sampled for sequencing. Anaplasia-containing slides are being requested for the remaining 4 cases.

Conclusions

These results support the key role of TP53 loss in the development of anaplasia in the majority of DAWT. Whether anaplasia arises in the absence of TP53 mutation remains unproven. Tissue heterogeneity, difficulties in the performance and interpretation of p53 immunohistochemistry, and the rarity of DAWT remain important obstacles to stratifying patients with anaplasia based on TP53 abnormalities.