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SIOP PODC: Clinical Guidelines for the Management of Children With Wilms Tumour in a Low Income Setting

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Wilms tumour is a relatively common and curable paediatric tumour. Known challenges to cure in low income countries are late presentation with advanced disease, malnutrition, failure to complete treatment and limited facilities. In this article, management recommendations are given for a low income setting where only the minimal requirements for treatment with curative intent are available (setting 1). These include general management, supportive care, social support and registration of patients. Recommendations specific for Wilms tumour care include diagnostic procedures with emphasis on the role of ultrasonography, preoperative chemotherapy with a reduced dosage for malnourished children and postoperative chemotherapy based on surgical staging. Pediatr Blood Cancer 2013;60:5–11. © 2012 Wiley Periodicals, Inc.

Key words: Africa; developing countries; low income countries; nephroblastoma; treatment guideline; Wilms

INTRODUCTION

Great progress has been made in the treatment of children with Wilms tumour over the last decades. In high income countries, survival is now over 85%. Treatment is multidisciplinary and combines surgery, chemotherapy and radiotherapy in a selected group of patients [1,2].

Survival in low income countries is much lower than in high income countries with reported survival in low income settings in sub-Saharan Africa ranging from 11% to 50% [3–7]. Known challenges are late presentation with advanced disease, malnutrition, failure to complete treatment and poorer facilities both for the specific cancer treatment and also for supportive care [4,5,8]. Capacity building, earlier presentation, social support, improved supportive care and a treatment guideline adapted to local circumstances are key to improving results [6,9,10].

Different settings need different strategies to be able to provide locally optimal care to children with Wilms tumour. These recommendations are for children with Wilms tumour in a low income setting where only the minimal requirements for treatment with curative intent are available.

SIOP PODC RECOMMENDATIONS

The International Society of Paediatric Oncology (SIOP) has a section called Paediatric Oncology in Developing Countries (PODC). One of the PODC Working Groups is producing recommendations for the management of childhood cancers in low and middle income countries as defined by the World Bank [11]. Levels of available facilities for the care of patients with Wilms tumour can be defined. Setting 1 is where the minimal requirements for treatment with curative intent are available. These minimal requirements are detailed below.

METHODS

To produce these recommendations we formed a multidisciplinary writing group of clinicians with experience managing children with Wilms tumour in a low income setting, especially in sub-Saharan Africa. A PubMed search was done with the terms ''Wilms tumour'', ''Wilms tumor'', ''nephroblastoma'', ''low income'', ''resource limited'' and ''Africa''. We also searched the reference lists of articles identified by this strategy. We invited one expert on state of the art Wilms tumour treatment from each discipline (surgery, pathology, paediatric oncology) to join the writing group. The draft proposal was sent out for review and presented to a broad group of Wilms tumour experts. This included presentation and discussion at web conferences of the SIOP PODC working group on adapted treatment regimens, the annual meeting of the renal tumour study group (RTSG) and a web conference with clinicians treating children with cancer in sub-Saharan Africa. Their suggestions were incorporated if the writing group agreed. The currently used SIOP Wilms tumour 2001 treatment protocol was used as the basis for the specific Wilms tumour treatment recommendations. The recommendations for setting 1 are based on available published evidence and personal experiences (expert opinion) with consensus among members of the writing group if no higher level of evidence was available.

Additional Supporting Information may be found in the online version of this article.

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Consensus meant that everyone in the group agreed with the recommendation given. When recommendations in the article are based on expert opinion only this is indicated in the text as "EO".

MINIMAL REQUIREMENTS FOR CURATIVE INTENT TREATMENT OF WILMS TUMOUR PATIENTS

We list what we consider the minimal requirements for management of patients with a Wilms tumour with curative intent in Table I. Note that pathology services and radiotherapy are not considered absolute minimal requirements as children can be cured without these facilities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS: DIAGNOSTIC FACILITIES; IMAGING AND PATHOLOGY

The diagnosis of Wilms tumour can be made with reasonable certainty based on history, physical examination and ultrasonography of the abdomen. Typical presentation of a child with Wilms tumour in a low income setting is a malnourished child of about 3 years with a large abdominal or flank mass, who is relatively well without acute pain or severe general malaise, but with haematuria and hypertension [3,4].

Ultrasonography of the abdomen is extremely useful to confirm the diagnosis [12–14] (Table III). It is also a non-invasive, useful diagnostic tool for many general paediatric patients in setting 1. An ultrasonographic examination of the abdomen is done to confirm the diagnosis and answer the following questions: Is the tumour intra-renal? Is the tumour cystic, solid or both? Are there intravascular extensions or thrombi (especially in the inferior vena cava)? Are there any tumours in the opposite kidney? Are there abdominal or liver metastases? If possible estimate the size of the tumour by measuring the three dimensions (length $\times$ thickness $\times$ width $\times$ 0.523 $\approx$ volume (cm^3) to enable objective assessment of change in tumour size during treatment [15].

Probes (3.5 MHz) that are usually used for adult patients are needed to scan large tumours and even then it can be difficult to get a good view. It is helpful to scan from the back and to try to visualise the kidneys. In large (diameter more than 15 cm) Wilms tumours, the affected kidney is often completely obliterated or only a rim of tissue remains. The destructive, heterogeneous mass is cystic or a varying mixture of solid and cystic components. In setting 1, ultrasound doppler may not be available and it needs adequate training to be used well. If available, it is useful in determining blood flow in the renal and inferior caval vein or seeing if these vessels are obstructed by tumour (thrombus). Postero-anterior and lateral chest X-rays are made to detect lung metastases that present as white round lesions often in the periphery of the lungs.

Burkitt lymphoma (BL) is an important differential diagnosis in BL endemic areas. Patients with abdominal BL are usually more malnourished than patients with Wilms tumour [16,17]. Patients with BL often have masses elsewhere and tumour growth is fast. Ultrasound scans may reveal one or multiple solid masses that are nearly uniformly homogenous. BL can diffusely infiltrate the kidneys resulting in homogenous enlargement, in contrast to the renal destruction and heterogeneous tumour seen in Wilms [18]. Children with neuroblastoma often present with advanced disease in setting 1 and are generally in much poorer condition than children with Wilms tumour. They are often in severe pain and have profound anaemia. They may have subcutaneous nodules or bilateral orbital hematomas, sometimes referred to as racoon eyes that are typical of neuroblastoma.

Diagnostic biopsy before preoperative chemotherapy is not standard practice according to the current SIOP Wilms protocol [19]. Likewise, in setting 1, cytology by fine needle aspiration (FNA) or tru-cut biopsy (histology) at diagnosis is only recommended (if available) when there is serious doubt about the diagnosis. Non renal tumours like BL should normally be differentiated by ultrasonography. If a biopsy is indicated, an approach from the back is preferred both for percutaneous core needle biopsies (tru-cut) and FNA to avoid tumour seeding. According to the SIOP WT 2001 protocol, these biopsies/procedures do not upstage the tumour [20].

SURGERY

General surgeons, urologists, or paediatric surgeons may operate on a patient with a Wilms tumour [10]. It is important that a prescribed, formal operative protocol is followed. As a general rule, the more experience the surgeon has for operation on Wilms tumour, the better [21,22]. The South African and SIOP surgery protocols can be found at the freely accessible cure4kids website at the SIOP PODC working group on adapted treatment regimens for Wilms tumour (www.cure4kids.org).

Assessment of the resectability of a tumour should be done by a team consisting of surgical, paediatric and anaesthetic staff that take into account the complexity of the operation, the patient's general condition, co-morbidities and local facilities. Anaesthetists must be made aware of co-morbidities such as anaemia, hypertension, poor nutrition, pulmonary infection and the possible side effects of preoperative chemotherapy [23].

Arrangements for close postoperative monitoring should be confirmed before any operation starts. Endotracheal intubation and muscle relaxation are essential. Blood should be available. Venous access should be in the upper limbs lest caval injury mandate temporary caval occlusion. A urinary catheter is essential to monitor intra-operative urine production and a nasogastric tube is helpful in keeping the stomach decompressed. It is wise to avoid resection of adjacent organs. The mesocolon and a segment

TABLE I. Minimal Requirements for Treatment With Curative Intent

1. Basic laboratory services: full blood count, thick blood film for malaria parasites, HIV antibody test, stool and urine microscopy
2. Basic radiology facilities: chest X-ray, ultrasonography
3. Chemotherapeutic drugs: vincristine, actinomycin D, doxorubicin and expertise and facilities for safe administration
4. Supportive care: safe blood transfusions, intravenous broad spectrum antibiotics, adequate pain medication and adequate nursing care
5. An appropriately trained surgeon, adequate surgical facilities with staff and facilities for perioperative care
6. Free medical treatment and social support (meals, money for travel) for impoverished families to enable parents to complete treatment

of descending colon can be safely resected en bloc, but if it becomes obvious during the operation that the pancreas, duodenum or other organs are involved, it is better to stop the operation and consider giving more chemotherapy [24]. Para-aortic lymph node sampling is better done after the main tumour has been removed.

A report on the surgical staging, including difficulty of operation, abdominal metastases, sampled nodes and possible tumour spill or incomplete resection, is essential and will determine the intensity of postoperative chemotherapy.

Postoperative analgesia is important. If feasible and an infusion pump is available consider an opiate infusion otherwise follow your institutional protocol. Intramuscular injections should be avoided.

Delays in surgery happen. These are caused by surgical emergencies, lack of staff or theatre equipment. Still, delays in surgery are one of the known reasons of abandonment of treatment and are best avoided [3,5]. If a delay is unavoidable, we recommend continuing preoperative chemotherapy with vincristine only in an attempt to achieve some tumour control without risking neutropaenia at the time of surgery (EO).

CHEMOTHERAPY

Reliable and continuous access to the chemotherapeutic drugs (vincristine, actinomycin D and doxorubicin) is important. Especially vincristine, but also actinomycin D can cause painful, chemical burns with extravasation. To reduce the risk of extravasation a fresh IV cannula should be placed in a vein where a leak is clearly visible. Check the correct placement by giving a bolus of normal saline before chemotherapy and check regularly during the 6-hour infusion of doxorubicin.

Adequate hydration should be given to all patients receiving actinomycin-D, especially those <1 year of age, to avoid hepatic veno-occlusive disease. Hepatic veno-occlusive disease VOD (liver swelling/enlargement and tenderness, thrombocytopenia, ascites and weight gain) is usually a self-limiting condition but can be fatal. Supportive care consists of careful fluid balance with fluid restriction. If there is any suspicion that VOD has occurred, consider omitting the next dose and then either cautiously re-introducing 50% of the dose on the following occasion or, if toxicity was severe, avoid actinomycin D altogether in the future. The specific side effects of vincristine, especially neuropathy (jaw pain, reduced/absent reflexes, foot drop and constipation) increase with cumulative dose and need to be assessed during treatment.

A full blood count and differential should be done at diagnosis, before the second dose of actinomycin D preoperatively and before each course of postoperative chemotherapy. Chemotherapy, if containing actinomycin D or doxorubicin, should be delayed if the absolute neutrophils count is below 1.0×10^9/L or if the child has a fever.

Availability of the chemotherapeutic drugs is included in the minimal requirements for treatment with curative intent. If actinomycin D is temporarily unavailable, one may consider replacing actinomycin D with doxorubicin for children with localized disease who are treated preoperatively with the two-drug regimen. For children with metastatic disease one may consider replacing actinomycin D with cyclophosphamide, etoposide or carboplatin using conventional dosing. We recommend doing these replacements in consultation with an expert on Wilms tumour treatment contactable through the SIOP PODC working group on adapted treatment regimens for Wilms tumour (www.cure4kids.org).

TABLE II. Summary Practical Recommendations and Priorities for General Management

1. Ensure availability of oral morphine and use WHO pain ladder
2. Establish a dedicated palliative care team
3. Formulate and implement a local management plan for febrile neutropaenia
4. Implement nutritional assessment and nutritional support
5. Guarantee dedicated nurses for the children's cancer ward and provide training
6. Ideally, provide medical treatment free to the patient
7. Invest in providing social support (travel money, free board and lodging)
8. Provide good and fair counselling on diagnosis and need to complete treatment
9. Invest in ultrasonography equipment and training for clinicians
10. Establish an accurate patient registration system, supervised by a clinician

NURSING CARE

In low income countries, there is often a shortage of nurses and they are rotated between wards. Caring for children with cancer and preparing and administering chemotherapeutic drugs in a safe manner requires dedicated, trained nurses (Table II).

PREOPERATIVE CHEMOTHERAPY

Preoperative chemotherapy should be used for children with Wilms tumour in setting 1. Preoperative chemotherapy is given to reduce surgical complications, especially tumour rupture, and to downstage the tumour at surgery. This allows for less intense postoperative chemotherapy without radiotherapy [1]. Studies have shown that this is also true for small, seemingly easily resectable tumours [25]. This is a logical strategy for patients who have large tumours, in a setting where supportive care is limited and radiotherapy not available as is the case in setting 1.

TABLE III. Specific Recommendations for Wilms Tumour Diagnosis and Treatment

1. Diagnose Wilms based on clinical presentation and adequate ultrasonography
2. Give preoperative chemotherapy
3. Prevent extravasation of chemotherapeutic drugs
4. Delay chemotherapy if absolute neutrophil count is below 1.0×10^9/L
5. Provide adequate hydration with actinomycin D to prevent veno-occlusive disease
6. Start with a lower dosage of drugs (2/3) in severely acutely malnourished children
7. Reduce doxorubicin dose to 30 mg/m^2 if neutropaenia occurs
8. Perform surgery according to a formal operative protocol and avoid pressure of time
9. Avoid resections of adjacent organs
10. Postoperative chemotherapy can be based on surgical staging if needed

We recommend standardized preoperative chemotherapy such as is administered to patients on SIOP protocols. Another issue is whether SIOP preoperative chemotherapy should be prolonged or given with increased/reduced intensity. Intensifying or prolonging preoperative chemotherapy may reduce disease-related deaths (unresectable disease, unfavourable stage distribution and relapse). However, more intense preoperative chemotherapy is likely to lead to more treatment-related deaths. This is a delicate balance and the ideal balance for setting 1 is unknown.

The SIOP 9 study showed that prolonged preoperative chemotherapy (8 weeks instead of 4) in patients with a unilateral tumour did reduce tumour size further, but did not favourably affect stage at surgery. This study was in European patients with relatively small tumours. It is unknown whether this is true in patients with advanced disease/large tumours. SIOP preoperative chemotherapy caused considerable hematologic morbidity and treatment-related mortality in malnourished Malawian children [26].

We favour prolonging treatment over intensifying treatment when there is a need to shrink tumours further to facilitate surgery. Intensification during prolongation (i.e., adding doxorubicin to the two drug regimen for localized disease) can be chosen for children who tolerated preoperative chemotherapy well [26,27].

PROPOSED TREATMENT REGIMENS FOR PREOPERATIVE CHEMOTHERAPY IN SETTING 1

The following treatments are based on the SIOP Wilms tumour 2001 protocol. For localized disease this consists of a 4-week regimen of vincristine (1.5 mg/m^2, maximum 2 mg) and actinomycin D (45 μg/kg IV, maximum 2 mg). For metastatic disease a 6-week regimen of vincristine and actinomycin D with the addition of doxorubicin (50 mg/m^2 IV infusion, weeks 1, 5) is used (Fig. 1). Patients below 12 kg should have a 2/3 dose reduction of chemotherapeutic agents [27].

We also recommend starting with a reduced dosage (2/3 of all drugs) in acutely malnourished children in a poor general condition. Both vincristine and actinomycin-D are given as intravenous push, whereas doxorubicin is given over 6 hours to avoid irreversible long-term cardiac side effects [28]. These regimens must be modified according to haematological tolerance. If neutropaenia occurs, give actinomycin D every three instead of 2 weeks, but continue vincristine weekly at full doses. Reduce the doxorubicin dose to 30 mg/m^2 if neutropaenia occurs.

In metastatic disease chest X-ray and/or abdominal ultrasound scans should be done at week 6 to reassess and three additional weeks of chemotherapy should be considered if there is any sign of their continued presence. If metastases have not disappeared or not become resectable after 9 weeks, we recommend stopping curative treatment. Usually parents go home with their child who needs on-going palliative care.

PATHOLOGY

If available, reliable and timely pathology services have an important role in making a histological diagnosis and in determining the postoperative chemotherapy. Postoperative chemotherapy is then based on the tumour type (risk classification) and stage at surgery [20,29]. Stratifying tumours into low-, intermediate- and high-risk groups is based on histological sub-classification (Supplementary Table I) [20,29]. Staging is based on the extent of the tumour (roughly; Stage I—tumour limited to the kidney, completely resected; Stage II—tumour outside kidney, completely resected; Stage 3—incomplete resection; Supplementary Table II). Correct staging is only possible if the specimen is inked and there is a block guide. Accurate diagnosis, sub typing and staging of nephroblastoma is not easy and can be improved through international collaboration and rapid central pathology review.

PROPOSED TREATMENT REGIMENS FOR POSTOPERATIVE CHEMOTHERAPY

The first dose of postoperative chemotherapy consists of vincristine alone and is given once gut peristalsis is re-established following surgery and within 21 days of the last preoperative chemotherapy dose. The other drugs are added at week 2 of postoperative chemotherapy if surgical recovery is complete. If not, consider giving a second postoperative vincristine only and delay the other drugs until week 3. Radiotherapy is not available in setting 1.

Postoperative Chemotherapy Based on Pathology Examination (If Available)

For children with localized disease at diagnosis; postoperative chemotherapy can be based on the individual tumour's histological subtype (risk classification) and stage at surgery if this is available. Our recommendation for the risk stratification of

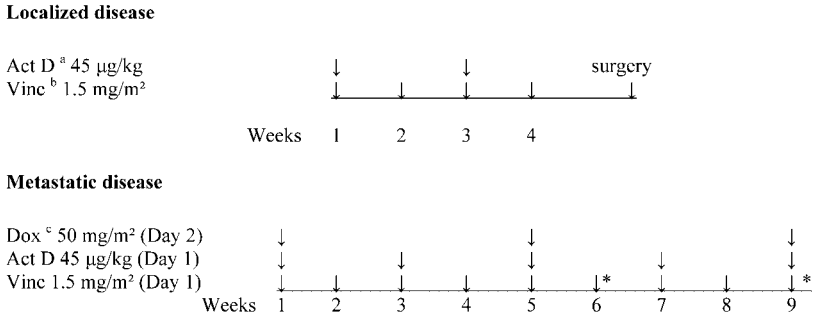


Fig. 1. Treatment flow sheets of preoperative chemotherapy for localized and metastatic disease.

TABLE IV. Advised Postoperative Treatment Strategies Based on Tumour's Type (Risk Classification) and Pathology Stage for Setting 1

	Stage I	Stage II	Stage III
Low risk	No further treatment	ACT-D/VCR 5 cycles	ACT-D/VCR 5 cycles
Intermediate risk	ACT-D/VCR 1 cycle	ACT-D/VCR 5 cycles	ACT-D/VCR/DOX 5 cycles
High risk	ACT-D/VCR/DOX 5 cycles	ACT-D/VCR/DOX 5 cycles	ACT-D/VCR/DOX 5 cycles

ACT-D, actinomycin D; VCR, vincristine; DOX, doxorubicin.

postoperative chemotherapy based on pathology examination is in Table IV. Pathology staging and sub typing (especially Stage I and low risk) must be reliable to follow this stratification. Treatment flow algorithms are in Figure 2. The proposed interval is 3 weeks. If this is too intense as defined, for instance, because of treatment delays due to neutropaenia, the interval can be extended to 4 weeks, especially if patients come from home and live far away. Children with metastatic disease at diagnosis but complete remission by the time of surgery should have the three drug-five cycle postoperative regimen (Fig. 2).

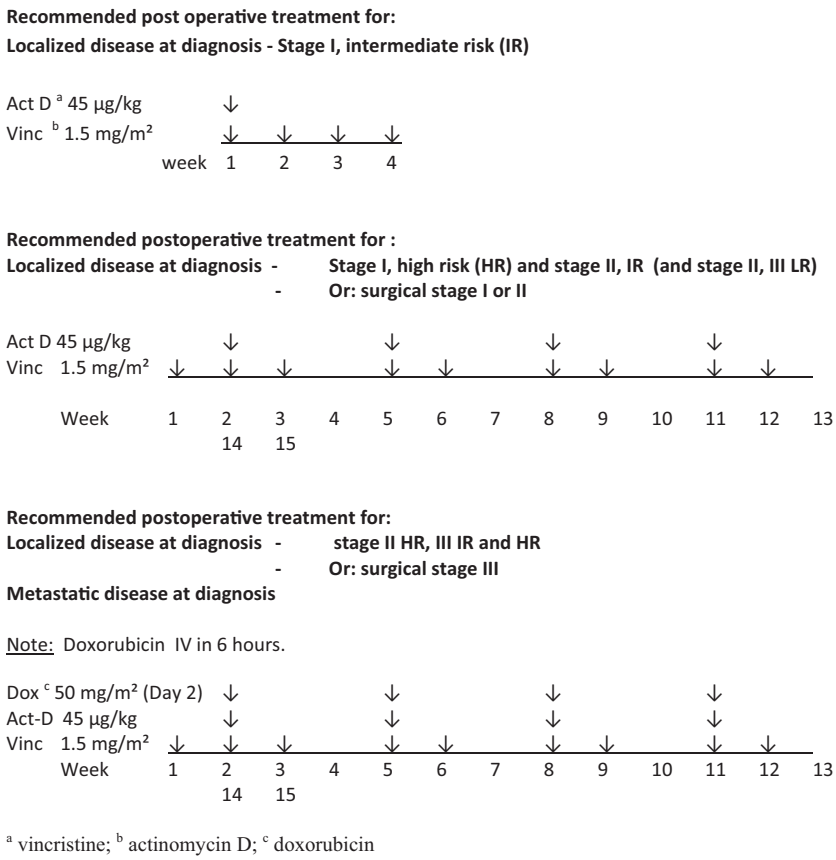
Postoperative Chemotherapy Based on Surgical Stage

If reliable pathological staging and risk classification are not available in time to determine postoperative chemotherapy, we recommend stratifying postoperative chemotherapy upon surgical staging. This includes assessment of the lymph nodes by the surgeon by gross inspection (Supplementary Table III). Surgical staging involves not only reading the operation notes but also discussion with the surgeon. A difficult operation may well mean that spillage occurred and the tumour should be upstaged. Surgical Stage 1 or 2 (complete and easy tumour resection): 5 cycles of vincristine and actinomycin D. Surgical Stage 3 (incomplete or difficult resection or rupture/spill): 5 cycles of vincristine, actinomycin D and doxorubicin (EO).

SPECIAL CASES

Children Below the Age of 6 Months

The current SIOP 2001 Wilms tumour protocol recommends immediate nephrectomy for children under the age of 6 months. The reason for this is the relatively high proportion of non-Wilms tumour (e.g., congenital mesoblastic nephroma) and the relatively



[a] vincristine; [b] actinomycin D; [c] doxorubicin

Fig. 2. Treatment flow sheets of postoperative chemotherapy.

good prognosis of Wilms tumour and increased risk of severe chemotherapy-related side effects in children of this age [20]. There are no data available to recommend differently in setting 1. In setting 1, primary nephrectomy can be considered for children below the age of 6 months with relatively small tumours that seem easily resectable (EO).

Cystic Partially Differentiated Nephroblastoma

Cystic partially differentiated nephroblastoma (CPDN) is a renal tumour with very distinct features and an excellent prognosis when treated with surgery only. It classically presents in very young children (<1.5 years) with a completely cystic renal tumour with very thin septa on ultrasound scan. Primary nephrectomy can be considered in these children.

Bilateral Tumours

It is challenging to cure children with bilateral Wilms tumour in setting 1. Tumour resection with a partial nephrectomy only is needed on at least one side to avoid the need for lifelong dialysis. Preoperative chemotherapy can be used to shrink the tumour and to achieve a situation where this is possible.

Relapse of Disease

Relapse of disease carries a dismal prognosis in setting 1. Curative treatment (with three drug preoperative chemotherapy) can be tried in children with a late (>6 months after the end of treatment) relapse after being treated with two drugs only for local disease (EO).

SUPPORTIVE CARE

SIOP preoperative chemotherapy can cause considerable morbidity and mortality in malnourished children [26]. Patients are often severely and acutely malnourished at presentation and this is associated with more severe chemotherapy-associated toxicity [17,30,31]. Infectious complications are the most common cause of treatment-related mortality in low income countries [8]. Therefore, a local management plan has to be established that will ensure that febrile patients who are possibly neutropenic will receive prompt and appropriate antibiotics. Adequate nutritional assessment and nutritional support needs to be implemented [30,32]. Adequate pain control is important, especially for children with progressive disease. Availability of morphine, the most effective and inexpensive pain control drug should be ensured. We recommend establishing a dedicated palliative care team with protected time to counsel families and organize care.

SOCIAL SUPPORT TO PREVENT FAILURE TO COMPLETE TREATMENT

Failure to complete treatment is the most common cause of treatment failure for children with cancer in low-income countries [5,33]. There are many reasons. One of the most important is cost. Usually parents do not have the money to pay for medical treatment and the associated costs (travel costs, food and lodging during stay in the hospital) [34]. Whenever possible, treatment should be free of charge to poor families to enable them to finish the treatment. Social support is needed for families who cannot bear these additional costs. This may consist of a place to stay, meals for the patient and parent during hospitalisation and money for travel when they need to return. Adequate counselling on the nature of the disease and the importance of completing treatment are equally important.

A PATIENT REGISTRY AND REPORTING OUTCOME OF PATIENTS

We strongly recommend that every centre, whatever the therapeutic options, establishes a patient registry. The registry may be hand written, a computer spreadsheet or the Pediatric Oncology Network Database (POND) registration database [35]. The system is less important than the quality of the data collected. Data should be as complete as possible and include all patients even if they received no treatment or died before completing therapy. Data need to be entered carefully and thoroughly with supervision from the responsible clinicians on the working diagnosis, cause of death etc. The reasons for death/failed treatment should be documented. An established classification of causes of treatment failure in low-income countries is: failure to complete treatment, disease related (progression or relapse of disease) and treatment related (toxicity). Each of these three causes needs a different response to be able to improve results. In the early phase of treatment it is often difficult to distinguish whether a death is caused by the disease or treatment as many of these children present with very advanced disease. When in doubt, we recommend classifying such a death during treatment as treatment related as this is the most accepted and the most sensitive approach to detect a treatment that is too intense for the setting and causing treatment-related deaths.

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