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SIOP PODC: Recommendations for Supportive Care of Children With Cancer in a Low-Income Setting

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These supportive care recommendations were prepared to guide doctors who practice in areas with significantly limited resources but who have sufficient infrastructure and training to treat children with cancer with curative intent. The success of any cancer treatment regimen depends largely on the availability and quality of supportive care and this also determines the intensity of treatment that can be delivered. We present practical recommendations on how to prevent infections, general nursing care, management of febrile neutropenia, nutritional assessment and support, treatment of co-infections and the social support to help prevent failure to complete treatment in resource poor settings. Pediatr Blood Cancer 2013;60:899–904.

Key words: Africa; developing countries; febrile neutropenia; low-income countries; malnutrition; supportive care

INTRODUCTION

While progress has been made in the treatment of childhood cancer in high-income countries, 80% of children with cancer live in low- and middle-income countries where survival rates are lower. Reported survival rates in sub-Saharan Africa range from near zero to 50% for children with Wilms tumor in Malawi and 61% for children with Burkitt lymphoma (BL) in Cameroon [1–3]. Treatment-related mortality and failure to complete treatment are common [4–6]. Failure to complete treatment, often called abandonment of treatment, is largely preventable with sufficient funds and appropriate interventions [2,7–9]. Treatment-related mortality can be reduced by adequate supportive care. The available level of supportive care determines the intensity of treatment that can be given without an unacceptably high treatment-related morbidity and mortality [10].

Facilities, staff, drugs, infrastructure, and funds are limited in low-income countries. Published evidence is lacking on how to provide effective supportive care for children with cancer in sub-Saharan Africa. This article provides recommendations for effective supportive care in a setting with basic facilities and is written to guide clinicians who may have little or no formal pediatric oncology training. It includes recommendations on how to prevent infections, general nursing care, management of febrile neutropenia, nutritional assessment and support, treatment of co-infections, and the social support required to reduce failure to complete treatment.

SIOP PODC RECOMMENDATIONS

The various levels of facilities available for childhood cancer care have been categorized by SIOP PODC (Paediatric Oncology in Developing Countries) as Setting 1 being facilities where only the minimal requirements for treatment with curative intent are available. Recommendations for the management of children with Wilms tumor, endemic BL, Kaposi sarcoma (KS), and retinoblastoma in Setting 1 have been developed [11–14]. Recommendations in this article can be used in combination with specific cancer treatment recommendations.

METHODS

To develop these recommendations a writing group was formed which included clinicians with long experience in delivering supportive care in sub-Saharan Africa and clinicians who are state of the art supportive care experts in high-income countries. The recommendations 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. Consensus meant that everyone in the group agreed with the recommendation given. Recommendations in the manuscript that are based on expert opinion are indicated in the text as (EO). Expert opinion was used mainly to judge what recommendations are feasible. The goal was to provide additional recommendations if drugs and/or facilities are available and refer to clinical practice guidelines developed in high-income countries to be considered for use where applicable. Prioritized topics are specific for cancer supportive care, such as nutritional assessment, nausea, mucositis and those that affect outcome such as febrile neutropenia and social support. Other topics, such as pain control and palliative care, which are less cancer specific and for which appropriate guidelines are available are not discussed in detail. The draft proposal was sent for review to a broad group of experts in childhood cancer and supportive care in low-income settings, including the chairs of the SIOP PODC working groups of nursing, supportive care and refusal and abandonment of treatment. Their suggestions were incorporated if the writing group agreed (Table I).

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TABLE I. Practical Supportive Care—Specific Recommendations

1. Hand washing or disinfectant hand gels are essential to prevent cross infections
2. Implement nutritional assessment and nutritional support
3. Ensure availability of oral morphine and use WHO pain ladder
4. Invest in providing social support (travel money, free board and lodging)
5. Reduce the risk of extravasation of chemotherapy
6. Formulate and implement a local management plan for febrile neutropenia
7. Avoid mucositis by not using significantly toxic regimens that cause this
8. Children with HIV/AIDS and cancer can be treated like other patients (EO)
9. Chemotherapy should not be delayed in children with TB (EO)
10. Anti-emetics may be needed to reduce vomiting
11. Painful procedures should be performed in a separate room using proper medication
12. Blood transfusion guidelines must be adapted to local conditions

GENERAL REMARKS

Prevention of Infections

Ideally, children with cancer should be on a separate ward from children with infectious diseases (EO). They should share toilets and an outside play area with the non-infectious group of hospitalized children. If isolation is possible on the ward, this should be prioritized for children with prolonged and profound (absolute neutrophil count $<0.5 \times 10^9$/L) neutropenia (EO). Hand washing, prior to and after examining each patient, is essential to prevent spreading infections from patient to patient [15,16]. Disinfectant hand gels at the bed side, if available, can help prevent cross-infections[17]. These gels can be easily prepared following the WHO simple formula for low-cost preparations (www.who.int/entity/gpsc/5may/Guide_to_Local_Production.pdf).

Bed nets are required in malaria-endemic settings [18]. Treatment regimens are usually less intensive than in high-income countries and cause less severe neutropenia. Prophylactic antibiotics are not used routinely. Pneumocystis jiroveci is a common cause of pneumonia in HIV infected children in sub-Saharan Africa [19]. In Ghana and Malawi, cotrimoxazole prophylaxis against pneumocystis pneumonia (PCP) infection is used for children with acute lymphoblastic leukemia (ALL). Evidence is lacking for whether or not to recommend the routine use of prophylactic antibiotics and anti-malarial drugs in all children with cancer in a Setting 1. PCP prophylaxis and prophylactic anti-malarial drugs should be considered for children with leukemia and lymphoma (EO).

Nursing Care

Adequate nursing care is essential, but in many public hospitals nurses are few and overworked. It is often difficult to maintain a core of experienced nurses who can deliver cancer therapy and appropriate supportive care safely. Training is important especially for procedures such as preparing and administering chemotherapy and to prevent or manage side effects. Nurse training is best done locally or in a setting with similar circumstances (EO). A model of how to organize nurse training regionally according to this principle has been developed and successfully implemented in Central America [20].

Chemotherapy Delivery

Chemotherapy should be prepared in a quiet, dedicated area where nurses are not disturbed. They should be aware of the risks to themselves when mixing drugs and when possible prepare cytotoxic drugs under a hood with an extraction fan, wearing a mask, and protective clothing. The bags or syringes with chemotherapy should be carefully labeled including at least the name of the patient, the name of the drug and the concentration. Children should be regularly reweighed during treatment before chemotherapy is ordered and drug doses adjusted to a recent weight.

Chemotherapeutic drugs can cause painful, chemical burns when extravasation occurs. To reduce the risk of extravasation, an IV cannula should be placed in a vein where leakage or subcutaneous infusion can be seen easily; ante-cubital fossa veins should be avoided whenever possible. We recommend considering placing a new IV cannula for vincristine infusions (EO). Correct placement of a cannula is checked by confirming blood refill of the line and by a bolus of normal saline before the chemotherapy is given and assessed regularly during longer infusions by examining the skin around the IV cannula for any swelling, pain, or redness.

FEBRILE NEUTROPENIA

Risk of Neutropenia

Infections are the most common cause of treatment-related mortality in low-income settings [2,21]. Malnourished children develop more severe neutropenia with the same regimens than well-

TABLE II. Recommended Doses of Drugs—Pain Control (Modified WHO Pain Ladder*)

Step 1: A non-opioid ± an adjuvant; for example, Paracetamol 10–15 mg/kg every 4–6 hours oral or ibuprofen 5–10 mg/kg every 6–8 hours oral
Step 2: A strong opioid ± adjuvant ± step 1; for example, Oral morphine start with 0.15–0.3 mg/kg every 4 hours oral and increase if needed
Frequently used adjuvant drugs:
Neuropathic pain: for example, amitriptyline 0.2–0.5 mg/kg/day
Raised intracranial pressure: corticosteroids; e.g. dexamethasone 0.15 mg/kg/dose every 6 hours

*The WHO ladder of pain control has been reduced from 3 to 2 steps. The middle step (of codeine) has been super ceded by going directly to the more effective morphine (30% of people do not respond to codeine and it has considerable side effects).

nourished children [22]. Bacterial infections in neutropenic children can rapidly develop into septic shock and death [23].

Fever Protocol

Fever may be the first sign of a bacterial infection and needs immediate action. The cause should be assumed to be bacterial until proven otherwise. A local fever protocol is helpful so that febrile (possibly neutropenic) patients receive appropriate antibiotics as soon as a fever develops [3]. Fever in the presence of neutropenia (neutrophil count of $< 0.5 \times$ or $< 1.0 \times 10^9$/L with expectation of further decrease is defined as febrile neutropenia [24]. Broad spectrum antibiotics should be started without delay in children with febrile neutropenia [24,25]. Children in Setting 1 are often malnourished with associated impaired immunity. We recommend that all children with a neutrophil count below 1.0×10^9/L start antibiotics when they have a fever (EO). In settings where physicians are few and blood counts are not readily available the nursing staff should take a blood culture whenever possible and start broad spectrum antibiotics immediately in any febrile child on treatment (EO). If the health unit is in an area endemic for malaria, thick blood films for malaria parasites should be done.

Every treatment facility needs a management plan for febrile neutropenia that includes the choice of first and second line antibiotics, dosages, and other standing orders to facilitate uniformly rapid administration of the first dose of the antibiotic routinely used at the site (EO). The best empiric therapy depends on local antimicrobial resistance patterns, available antimicrobials and cost. In many settings the available antibiotics are limited and second line, broad spectrum antibiotics such as third generation cephalosporins are reserved for severe or initially unresponsive infections. First-line antibiotics must cover common Gram positive and Gram negative bacteria [25]. Gram negative bacteremia may be relatively more frequent in low-income settings due to absence of prophylactic antibiotics and central venous lines [23,25]. In many settings, a broad-spectrum penicillin (e.g., ampicillin) plus an aminoglycoside (e.g., gentamicin) is a sensible and affordable first-line regimen [3,26]. Aminoglycosides should be avoided or used with caution in dehydrated patients or those who are suspected of having an acute kidney injury. Therapy can be modified if and when a blood culture result is available. If a child remains febrile for longer than 48 hours, ceftriaxone or another third generation cephalosporin is a good second choice. Ciprofloxacin is an inexpensive alternative that usually covers pseudomonas which is not often sensitive to ceftriaxone. In a sick child who does not tolerate oral intake these antibiotics should be given parenterally. The antibiotics ampicillin, gentamicin, ceftriaxone, and ciprofloxacin are all included in the WHO essential drugs list (http://www.who.int/medicines/publications/essentialmedicines/en/index.html). Anti-fungal treatment should be considered in neutropenic patients with prolonged fever which is unresponsive to antibacterial therapy (EO).

NUTRITIONAL ASSESSMENT AND NUTRITIONAL SUPPORT

Nutritional Assessment

Acute and chronic malnutrition are common in many resource-limited settings. Of children younger than 5 years in sub-Saharan Africa; 39% are stunted with a short height for age and 9% are acutely malnourished [27]. A high proportion of children are severely, acutely malnourished at the time of their cancer diagnosis; in Malawi this was found to be 55–60% [28].

Acute malnutrition is associated with reduced immunity, an increase in severe chemotherapy-related side effects, altered pharmacokinetics such as higher serum levels of vincristine and other cytotoxic medications, additional surgical complications and increased morbidity and mortality [22,29].

Weight for height with age-related cut-off levels can be used for children without a tumor mass to assess nutritional status. In children with a large tumor, especially of the abdomen, weight can be a misleading measure of nutritional status. Clinical assessment of wasting is important in these children, but for a quantitative assessment at diagnosis, we recommend using mid upper arm circumference (MUAC; Fig. 1). MUAC is independent of tumor mass [30]. The WHO has defined cut-offs for acute malnutrition and severe acute malnutrition in children between 6 months and 5 years (Table III). For older children (5–10 years) we recommend using the same cut-offs, although there is less evidence to support this practice (EO) [31].

Nutritional Support

Nutritional support is important using a diet rich in energy (calories) and protein. Some hospitals provide meals for the children, but additional foods or supplements may be needed to provide sufficient calories protein and micronutrients. Many poor families do not have the money to buy enough food while staying in hospital. Locally acceptable and affordable foods should supplement the diet. All children in Malawi receive ready-to-use-therapeutic-foods based upon peanut butter. This food is energy and protein rich with added micronutrients [32,33]. In Cameroon, patients on chemotherapy in Baptist hospitals are given one egg a day and 200 ml of WHO F100 milk which provides essential vitamins and trace elements. Parents are given a rice ration and the equivalent of one US dollar a day to purchase foodstuffs to cook. With these supplements, MUAC and/or triceps skin fold (TSF) increased in almost two-thirds of children with BL during the 28-day induction treatment [26].

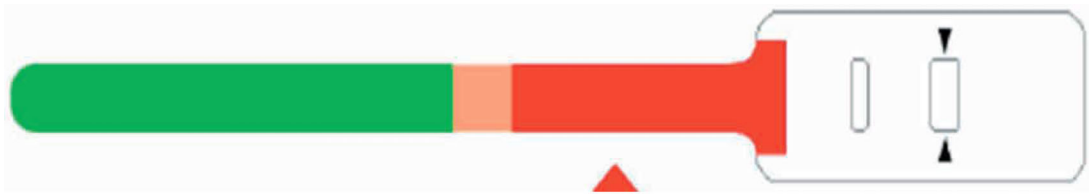

Fig. 1. Mid upper arm circumference (MUAC) tape. Red indicates severe acute malnutrition, defined as a MUAC<110mm or bilateral pitting edema; Pink indicates moderate acute malnutrition, defined as a MUAC>110mm and <125mm; Green indicates normal MUAC>125mm.

TABLE III. Assessment of Nutritional Status—Cut Offs

Age group	Acute malnutrition	Severe acute malnutrition
6 Months to 5 years	MUAC<125mm	MUAC<110mm
>5 Years without a tumor mass[a]	Weight for height<−2SD	Weight for height<−3SD
>5 Years with a tumor mass[b]	MUAC<135mm[c]	MUAC<115mm[c]

[a]For example, ALL; [b]Clinical assessment is more important, MUAC is more variable than in younger group especially in pubertal children; [c]Empiric cut off.

Nasogastric tube feeding is not readily accepted by parents who associate its use with a poor outcome. Tube feeding should not be discouraged and time should be taken to counsel parents and children properly as to the necessity of assisted enteric feeding. It is recommended for acutely malnourished children who do not want to eat, but have an intact gastrointestinal system.

Anti-Emetics

Anti-emetics may be needed to reduce vomiting. In Cameroon and Malawi, metoclopramide (10 mg or 100–400 μg/kg) is given orally 30 minutes before chemotherapy and has shown to be a reasonably effective regimen.[3,26] If available, this can be replaced by or combined with diphenhydramine, which has the advantage of being relatively cheap and reducing the extrapyramidal symptoms associated with the use of metoclopramide. If available, a selective serotonin antagonist (e.g., ondansetron, tropisetron) is recommended during emetogenic therapy [34]. If necessary and available, dexamethasone can be added (5 mg/m^2 stat 30 minutes before chemotherapy, followed by 5 mg/m^2 divided in two to three doses) [34].

Pain Control

Guidelines for pain control in children which are applicable in low-income settings are available and are not detailed in this article [35]. Non-opioid analgesic medications are widely available and their use has been standardized by the WHO in the "WHO step ladder of pain control" (Table II; http://www.who.int/cancer/palliative/painladder/en/) [36]. Morphine is the most effective and inexpensive analgesic and should be available in tablet and syrup form [36]. Unfortunately, many barriers, such as import regulations, administrative barriers, or inappropriate fear of addiction, limit accessibility. Other medicines such as dexamethasone for increased intracranial pressure and amitriptyline or carbamazepine for neuropathic pain may be indicated [35].

Analgesia for Painful Procedures

Painful procedures should be performed in a separate room and not in the child's bed so that the bed remains for the child as much as possible a safe place. A careful explanation of the procedure should be given to the child and parent to decrease anxiety. The room should be prepared before the child is brought in for the procedure. Leaving a child while supplies are gathered unnecessarily increases anxiety. Distraction by play, music or relaxation techniques can be effective in reducing anxiety and perception of pain during painful and scary procedures. If available, local anesthetic cream (e.g., EMLA creme) can help to reduce pain associated with drawing blood and lumbar punctures. Ketamine given under the supervision of an experienced physician provides adequate anesthesia for many short procedures such as lumbar punctures, fine needle aspirates, and bone marrow aspirates. Patients need adequate clinical monitoring and resuscitation equipment must be available in the rare event of respiratory depression.

If available, widely used drugs to sedate for painful procedures include chloral hydrate (suppository or oral, 50–75 mg/kg, given 30–45 minutes before procedure) or midazolam (suppository 0.25 mg/kg, given 45 minutes before the procedure) [37,38]. Suppositories should be avoided in neutropenic children. Oral and parenteral morphine, ketamine, midazolam, and diazepam are included in the WHO list of essential drugs for children; chloral hydrate is not (http://www.who.int/medicines/publications/essentialmedicines/en/index.html).

Palliative Care

Adequate supportive care includes appropriate palliative care. A dedicated palliative care team can help care not only for children with cancer but also the other children in the hospital with conditions with a poor prognosis such as end-stage AIDS, renal failure, or heart failure [39–41]. Detailed palliative care recommendations are beyond the scope of this manuscript, however, literature, including a handbook from the International Network of Cancer Treatment and Research (INCTR), is available (http://inctr-palliative-care-handbook.wikidot.com/) [42,43].

Mucositis

Severe mucositis is difficult to manage in settings with severely limited resources [10]. We recommend avoiding mucositic regimens. Adequate pain control is important. For local mouth care, an antiseptic solution such as gentian violet (0.25%) assists with healing [44–46]. A local anesthetic spray is particularly useful for children with painful oral ulcerations who will not drink or eat. Systemic acyclovir should be given to children with suspected herpetic gingival stomatitis [47]. Nystatin drops or tablets (or oral fluconazole, if available) should also be prescribed to treat candidiasis [47]. The antiviral and antifungal medications included in the WHO essential drugs list are acyclovir, nystatin, and fluconazole (http://www.who.int/medicines/publications/essentialmedicines/en/index.html). Regular rinsing of the mouth helps remove residual food debris. A solution of baking soda or salt and water is recommended for rinsing 5–6 times a day. Cool drinks and soft foods are tolerated best. Fizzy drinks and acidic, sharp-edged (e.g., chips), or spicy foods should be avoided. Local forms of yogurt are often acceptable to a child (EO).

HIV/AIDS

In sub-Saharan Africa, 2.3 million children are living with HIV (http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf). There is limited published experience about the

intensity of treatment in children with HIV/AIDS and cancer in low-income settings [48]. Concerns have been raised about potential pharmacokinetic interactions, cumulative hematological and neurological toxicity and additional treatment-related complications, especially infections, in HIV-infected patients [49,50]. Adult HIV infected patients in a high-income country who received treatment of the same intensity had similar treatment-related morbidity and mortality to patients who were HIV negative [51,52]. Concomitant administration of chemotherapy and HAART was shown to be without excess toxicity in adult patients with non-Hodgkin lymphoma and Hodgkin disease in a high-income country [53–55]. We recommend treating children with HIV/AIDS and cancer in Setting 1 like all other patients (EO) [48]. Children who are very malnourished and in poor condition may need a lower-intensity initial therapy while treating co-morbid illnesses and may then tolerate normal doses in subsequent chemotherapy cycles (EO). Antiretroviral therapy (ART) should be continued or can be started simultaneously, if indicated, with the chemotherapy (EO) [49,52].

Other Co-Infections

Prevalence of malaria in Africa is up to 300/1000 population in some countries, tuberculosis is from 25 to >300/100.000 with an 11-fold risk of developing TB shown in children with malignancies compared to other children [56,57]. Intestinal parasites have been found in up to 40% of children with malignancies [58]. Co-infections, such as malaria, intestinal parasites, and schistosomiasis, need to be identified and treated according to national guidelines. Screening for TB in children with malignancies should be considered. A skin test may be falsely negative in children with severe acute malnutrition and/or widespread malignancy.

Tuberculosis treatment lasts for several months. Chemotherapy should not be delayed for these children, especially when treating fast-growing malignancies such as BL. If necessary, the anti-TB drugs can be started simultaneously with chemotherapy (EO).

INDICATIONS AND RISKS OF BLOOD PRODUCTS

Anemia

Anemia is common among children in low-income settings. Causes include nutritional deficiencies (iron, vitamin B12, folic acid), common infections (malaria, hookworm), and sickle cell disease. Chemotherapy is expected to cause the hemoglobin to drop further.

Transfusions may carry a risk of infections (e.g., HIV, hepatitis B, C, and E), contamination or mismatch [59]. These are more likely to occur when there is no national blood transfusion service and families have to donate blood [60]. Blood is often in short supply which is why strict indications as to when to give a blood transfusion are needed [61]. According to guidelines a blood transfusion is indicated for children with acute malarial anemia in sub-Saharan Africa settings when their Hb is below 6 g/dl [62,63]. Those guidelines recommend using higher Hb levels as a criterion for a blood transfusion for children in poor general condition or having a serious infection and are also recommended in this article for children with cancer on chemotherapy (EO) [62,63]. This recommendation must be adapted to local conditions and guided by the risk-benefit calculation to the individual patient in a specific setting. Thresholds for transfusion are also influenced by the age of a child with older children having higher normal values [61]. Packed red cells (10–15 ml/kg) are given over 3–4 hours [61].

Platelets

If platelets are available, they should be given to a child with active bleeding and low platelets counts. Non-steroidal anti-inflammatory agents, aspirin, and combination products that contain these agents should be avoided.

Social Support to Enable Parents to Complete Treatment

There are many reasons for failure to complete therapy, the most common cause of treatment failure in children with cancer in many low-income settings [7,64]. One of the most important is cost; the cost of treatment (drugs, tests), associated costs (stay in the hospital, food during hospital stays, travel costs), and loss of income [6,8,64]. The total estimated cost of treatment, hospitalizations, and investigations should be made clear to parents from the beginning. Whenever possible, treatment should be free of charge to poor families to enable them to complete 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 hospitalization and money for travel when they need to return. Mobile phones are useful, inexpensive means of communication in rural areas and may prevent failure to complete treatment or misunderstandings about treatment once the patient goes home.

School and Play

Some children will stay on the inpatient ward for a long time. They need to play and continue to learn. Play has a positive impact on the ward atmosphere. Simple games that children can enjoy either together or on the bed, such as colourful, noisy toys, dolls, drawing materials, or building blocks, are excellent. The children can play together in a dedicated area of the ward. School should continue for older children so that they can keep up with their peers at home.

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