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Review

Strategies to improve care for children with cancer in Sub-Saharan Africa

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ABSTRACT

Great progress has been made in the care of children with cancer in recent decades. Worldwide, more than 80% of children with cancer live in resource-limited countries where access to care is poor. Sub-Saharan Africa is the world's poorest region. Child mortality is high, caused by largely preventable and treatable conditions. Paediatric cancer accounts for only a small fraction of deaths and understandably receives little attention from local policy makers or global health agencies. The survival of children with cancer is very poor. Challenges to improving survival include advanced-stage disease at presentation, failure to start or complete treatment (abandonment), inadequate hospital infrastructure and medications, lack of trained health care providers, lack of cancer registration and follow-up and lack of treatment guidelines adapted to local medical facilities. We propose a stepwise approach that integrates paediatric cancer treatment with existing general paediatric care. Priority is given to interventions (improvement of supportive care, diagnostic facilities) that also improve general paediatric care. Minimal requirements for diagnostic procedures include complete blood counts, HIV and malaria tests, blood cultures, histopathology and simple imaging (X-ray and ultrasonography). Feasible interventions include adequate palliative care, curative treatment for Burkitt lymphoma and Wilms tumour and symptomatic treatment for Kaposi sarcoma.

1. Introduction

Great progress has been made in the care of children with cancer in recent decades. However, more than 80% of children with cancer worldwide live in resource-limited countries where access to care is poor. In Sub-Saharan Africa, the world's poorest region, child mortality is high, caused by largely preventable and treatable conditions such as pneumonia, diarrhoea and malaria, often complicated by malnutrition.

2. Child health in Sub-Saharan Africa

The probability of death before age 5 (the 'under five mortality rate', U5MR) is considered a robust indicator of children's general well being. Sub-Saharan Africa has the world's highest U5MR (Tables 1 and 2), with a regional average of 160 per 1000 live births per year.[1]

Basic health interventions, such as insecticide-treated bed nets (to prevent malaria), vaccinations, vitamin A

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Table 1 – Characteristics of selected countries in Sub-Saharan Africa, North Africa, Europe and Latin America.

	Malawi	Senegal	Tanzania	Ghana	South Africa	Morocco	Netherlands	Brazil
Socioeconomic and demographic indicators								
Population (millions)[b]	13.6	12.1	39.5	23.0	48.3	30.9	16.4	189.3
Population <15 years (millions)[b]	6.4	5.8	17.6	8.9	14.0	8.9	2.9	53.0
Gross national income per capita (US$)[a]	170	750	350	520	5390	1900	42 670	4730
Total per capita expenditure on health (US$)[c]	64	72	N.A.	N.A.	869	N.A.	3.383	765
Per capita govt expenditure on health (US$)[c]	14	12	N.A.	N.A.	437	N.A.	2.311	164
Under five mortality rate (1990)[a]	221	149	161	120	60	89	9	57
Under five mortality rate/1000 (2006)[a]	120	116	118	120	69	37	5	20
Under five mortality rank (2006)[a]	32	35	34	32	55	78	167	113
Life expectancy (years)[a]	47	53	52	59	50	71	79	72
Nutrition								
Children <5 years, % stunted[a]	46	16	38	22	25	18	–	11
Children <5 years, % wasted[a]	3	8	3	5	3	9	–	2
HIV								
HIV prevalence rate (age 15–40 years) (2005)[a]	14.1	0.9	6.5	2.3	18.8	0.1	0.2	0.5
No. of HIV-infected children (×1000)[a]	91	5	110	25	240			
Health								
Access to clean water (%)[a]	73	76	62	75	88	81	100	90
Immunisation coverage (%)[a,*]								
1× DPT	99	99	94	87	99	99	98	99
All 3 DPT	99	89	90	84	99	97	98	

[a] UNICEF, The State of the World's Children 2008: child survival. http://www.unicef.org/publications.[1]
[b] US Census Bureau, International Data Base. http://www.census.gov/ipc/www/idb/.[2]
[c] World Health Organisation. National Health Accounts. http://www.who.int/nha/en/.[3]
* Percentage of 1-year-old children immunised with 1× diphtheria, pertussis, tetanus (DPT1) or all 3 DPT (DPT3).

Table 2 – Characteristics of selected regions.

	Sub-Saharan Africa	North Africa/ Middle East	Latin Am/ Caribbean	South Asia	Industrialised Europe/West
Socioeconomic and demographic indicators[a]					
Population (millions)	749	382	560	1.542	969
Gross national income per capita (US$)[a]	851	2104	4847	777	37,217
Under five mortality rate (1990)	187	79	55	123	10
Under five mortality rate/1000 (2006)	160	46	27	83	6
Life expectancy (years)	50	69	73	64	79
Nutrition[a]					
Children <5 years, % stunted	38	25	16	46	–
Children <5 years, % wasted	9	8	2	18	–
HIV[a]					
HIV prevalence rate adults (15–40 years) (2005)[a]	6.1	0.2	0.6	0.7	0.4
No. of HIV-infected children (×1000)	(2000)	33	54	130	13
Health[a]					
Access to clean water (%)	55	88	91	85	100
Immunisations coverage					
DPT1	83	95	96	82	98
DPT3	72	91	92	63	86

[a] UNICEF, State of the World's Children 2008: child survival. http://www.unicef.org/publications.[1]

supplementation and provision of clean water are needed, as better access to treatment and prevention of pneumonia, diarrhoea and malaria. The prevention of severe acute malnutrition and of mother-to-child HIV transmission will also reduce mortality from infectious diseases. Simple, low-cost solutions, if widely adopted, could bring about remarkable improvement.[1]

3. Paediatric oncology in Sub-Saharan Africa

Cancer is not a numerically significant cause of childhood mortality in Sub-Saharan countries. Assuming that the annual incidence of childhood cancer is roughly similar in Sub-Saharan countries and in Europe (140 per million children <16 years of age)[4] and that few children are cured in Sub-Saharan Africa, annual childhood cancer mortality would be only about 0.14 per 1000 children – a low figure when compared to the mean U5MR in Sub-Saharan Africa (160 per 1000 live births). Despite this, treatment and appropriate symptomatic care are important for children with cancer, their families and peers.[5] The development of a paediatric cancer unit with a multidisciplinary care team integrated into the paediatric department can positively affect the entire hospital by improving the quality of supportive care, diagnosis and training for all. Finally, a well-organised paediatric cancer unit in a low-resource setting can attract international and local funding.

Information regarding epidemiology of childhood cancer in Sub-Saharan Africa is sparse. Available data show that the epidemiology of some cancers, known to be associated with infections, differs from the rest of the world. Burkitt lymphoma causes about 50% of all childhood cancers in malaria-holoendemic regions, with an estimated incidence of 35 children per year.[6,7] Where HIV/AIDS is prevalent, especially in Southern and Eastern Africa, Kaposi sarcoma (KS) is a common childhood malignancy accounting for 7–29% of reported cancers.[8,9] Hepatocellular carcinoma is more common where hepatitis B is endemic.[10] The reported incidence of acute lymphoblastic leukaemia is much lower than in industrialised countries, probably because the signs and symptoms of leukaemia (anaemia, fever) resemble those of acute severe malaria.

4. Challenges in the management of children with cancer in Sub-Saharan Africa

4.1. *Late presentation and underdiagnosis*

Children have little access to health care in low-income countries,[1] especially children with complex or chronic diseases such as cancer. Children often present with advanced disease because of the lack of health care facilities, transportation and information about the disease and treatment options. Parents often go first to traditional healers.[11]

Many children remain undiagnosed. The magnitude of underdiagnosis is difficult to estimate because of the lack of population-based registries and diagnostic capabilities. In Malawi, which has 6.5 million children below 15 years of age, about 900 cases of childhood cancer can be expected each year (based on European incidence rates). Fewer than 300 cases per year are recorded, leaving two-thirds of children unaccounted for. Findings were similar in a survey of the status of paediatric oncology care in 10 low- and mid-income countries, including two Sub-Saharan countries (Tanzania and Senegal).[12]

Awareness campaigns incorporated into existing community health initiatives can reduce delays in diagnosis. This strategy was successfully used for retinoblastoma in Honduras.[13] Such awareness campaigns should not dilute or hamper other important public health messages, such as the promotion of vaccination and insecticide-treated bed nets. Another option is to provide a separate, strong cancer awareness message on a designated day, such as International Childhood Cancer Day (February 15).

4.2. *Abandonment of therapy – failure to complete treatment*

Failure to complete paediatric cancer treatment is a common problem in low-income countries.[14,15] Several studies have identified related factors and effective interventions. In Recife, Brazil, abandonment of treatment for acute lymphoblastic leukaemia (ALL) was reduced from 16% to 1.5% by social support that included housing, travel expenses, family education and job training.[16] Most families in Sub-Saharan Africa are unable to pay for their child's cancer treatment.[17] Even if the child receives free hospitalisation and treatment, it will be difficult for many to pay for the additional costs. Treatment often takes weeks or months. In Malawi, the child and one family member usually stay in the hospital during this time. Interviews showed that the absence from home (work on the field, loss of income) and extra costs during the stay in the hospital (food) are important concerns for parents.[11] Free medical care, social support (food, travel money) and counselling are crucial to prevent abandonment of therapy. Successful strategies depend on effective partnerships between different organisations to provide these according to a well-organised plan specifying each party's responsibilities.

4.3. *Malnutrition*

Children diagnosed with cancer in low-income countries are commonly malnourished.[9,18,19] Malnourished children have an increased risk of infection, post-surgical complications and mortality,[20] and they are less able to tolerate chemotherapy.[21] In Malawi, the highly prevalent chronic malnutrition is exacerbated by advanced cancer, such that more than half of the children are acutely malnourished at cancer presentation.[9] Nutritional support is crucial during treatment, but parenteral feeding is unavailable in most Sub-Saharan settings, and gastric tube feeding is not readily accepted by parents. Locally made peanut butter-based ready-to-use therapeutic food (RUTF) offers an effective nutritional support alternative.[22,23]

4.4. *Adjustment of intensity of treatment*

Another challenge is to adjust the intensity of cancer treatment to local circumstances. The adequate intensity of therapy is dictated by several factors. These include the level of supportive care, e.g. availability of blood products, antibiotics, diagnostic and therapeutic infrastructure, and quality and quantity of medical personnel. Treatment tolerance of the patient (nutritional status and chronic underlying disorders such as anaemia, HIV/AIDS) must also be taken into account[24] to avoid unacceptable treatment-related toxicity.[25] In general, regimens that cause severe mucositis or bone marrow suppression should be avoided.

4.5. *Supportive care*

Adequate pain control and nutritional support are essential as are specific guidelines for the rapid start of broad-spectrum antibiotics when a neutropenic patient develops fever. If a physician is not readily available, it is prudent to have nursing staff draw a blood culture and start antibiotics immediately. Blood products (although perhaps not platelets) are usually available in general hospitals. However, it may take hours to prepare them for administration, and the local risk of transfusion-related infectious diseases such as HIV/AIDS and hepatitis B and C needs to be considered.

4.6. *Diagnosis and evaluation of treatment outcome*

Histological confirmation of a clinical diagnosis is important to guide management and evaluate treatment results. Most general hospitals in Sub-Saharan Africa have access to basic histology, but the results are frequently not available on time to influence clinical decision making. International collaboration to train pathologists in the diagnosis of paediatric cancer and the creation of regional diagnostic facilities may reduce the barriers to correct and timely diagnosis.

Short- and long-term follow-up is essential to evaluate the results of treatment but requires substantial time, effort and resources. Barriers to successful follow-up include families' competing priorities, long distances they must travel to the hospital, poor transportation, inadequate communication systems and seasonal weather conditions.

Outcome analysis and reporting should clearly specify the cause of treatment failure as disease-related (progression or relapse), treatment-related (toxic death) or abandonment of treatment, defined as loss to follow-up before the completion of therapy. For the purpose of survival analysis and reporting, we recommend that abandonment of therapy be considered an adverse event. Patients lost to follow-up after completing treatment need to be censored at the date last seen.

5. Minimal requirements for management of childhood cancer in Sub-Saharan Africa

The aims and priorities of a paediatric cancer unit should be in balance with the level of general paediatric care. We suggest an approach in which cancer care for children in Sub-Saharan hospitals is integrated as much as possible with general paediatric care, although a separate, dedicated unit within the paediatric department is needed for chemotherapy and infection control. Nurses dedicated to the unit are very important in providing the necessary level of care.

When establishing cancer care it is useful to target cancers that are common and curable, such as Burkitt lymphoma and Wilms tumour. Children who cannot be cured because of advanced-stage disease, treatment complexity and/or costs must receive adequate palliation. Table 3 outlines a stepwise, prioritised approach to developing paediatric cancer care in Sub-Saharan African hospitals. We give priority to interventions that will also benefit general paediatric care (e.g. adequate pain control, diagnostic facilities and supportive care). Each step must be accompanied by staff training. Patient registration, active follow-up and efforts to raise awareness of childhood cancer should begin as early as possible.

Table 3 – A prioritised, stepwise approach to the development of paediatric cancer care in Sub-Saharan Africa: the top 10 priorities.

1. Adequate pain control measures, including access to morphine
2. Diagnostic facilities
   - Malaria and HIV tests, complete blood count, blood cultures
   - Pathology: cytomorphological and histological diagnosis
   - Ultrasonography, X-ray
3. Treatment for Burkitt lymphoma (in the malaria or Burkitt belt of Africa)
4. Supportive care
   - Social support to prevent abandonment of treatment
   - Support to counter the toxicity of treatment; e.g. blood products
   - Infection control measures; e.g. antibiotics
   - Nutritional support
5. Treatment for Wilms tumour (if paediatric surgeon is available)
6. Palliative chemotherapy for Kaposi's sarcoma
7. Treatment for retinoblastoma (if an ophthalmic surgeon is available)
8. Promotion of early diagnosis
9. Evaluation of results
   - Data management – registration of patients
   - Active follow-up system
10. Treatment of other lymphomas, leukaemias and solid tumours

Note: each step must be accompanied by training and staff development.
Steps 8 and 9 should begin as early as possible while the other steps proceed.

6. Feasible interventions

6.1. *Palliation and pain control*

Many children presenting with advanced-stage solid tumours have a poor prognosis and require palliative care, including adequate pain control. The WHO analgesic ladder for children is useful to guide pain management.[26] Availability of morphine, the most effective and inexpensive pain control drug, must be a top priority. Several barriers, among which lack of funding and lack of an adequate distribution system, issues regarding importation of the drug and the widespread fear of risk of addiction may, unfortunately, limit the availability of morphine.[27] A palliative care team should have dedicated time to counsel families about treatment and outcome, answer their questions and address their fears. This team can also care for other children with chronic conditions and a poor prognosis, such as those with end-stage AIDS, renal or cardiac disease.

6.2. *Treatment strategies*

Effective treatment strategies are feasible if they are relatively simple and well tolerated. Cure is a realistic goal in patients

with Burkitt lymphoma or Wilms tumour, and significant symptom control can be achieved for patients with Kaposi sarcoma.

6.2.1. *Burkitt lymphoma*

Burkitt lymphoma (BL) is the most commonly diagnosed childhood cancer of tropical Africa (~50% of all admissions for childhood cancer in many Sub-Saharan countries).[6,7] It is a fast-growing, chemotherapy-sensitive tumour. In high-income countries, where very intense and costly protocols requiring intensive supportive care are available, survival is greater than 90%.[28]

Over the past 10 years, Burkitt lymphoma treatment plans adapted to the available supportive care and patients' comorbidity have been developed.[25,29]

The current treatment for children with Burkitt lymphoma (all stages) in Malawi is intravenous cyclophosphamide 40 mg/kg on day 1 and oral cyclophosphamide 60 mg/kg on days 8, 18 and 28. Intrathecal hydrocortisone (12.5 mg) and methotrexate (12.5 mg) are also given at each treatment cycle. The cost of this 28-d protocol (chemotherapy and supportive care drugs) is less than US$50. One-year event-free survival is 48%, which is a reasonable indicator for survival as the risk of relapse is <5% after 1 year.[30] The treatment-related mortality is ~5%.[21]

Previous attempts to use more intense treatment in Malawi incorporating high-dose methotrexate resulted in unacceptably high treatment-related mortality (11 of 42 patients, 26%).[25] The French-African paediatric oncology group (GFAOP) had a similar experience in their Sub-Saharan units and are now using cyclophosphamide monotherapy in those.[31] They recently described their large study in several French-speaking African countries, including settings both in North Africa and in Sub-Saharan Africa. Two more intense modified LMB89 Burkitt lymphoma protocols (including high-dose methotrexate and cytarabine) were used. Of the whole group of 306 patients, 71 (23.2%) died during treatment; 40 of these deaths (13.1%) were attributed to infection.

Further efforts are needed to increase survival of patients with Burkitt lymphoma in Sub-Saharan Africa without increasing treatment-related mortality.

6.2.2. *Wilms tumour*

Wilms tumour is curable with multimodality therapy including surgery, chemotherapy and (in selected cases) radiotherapy. Overall long-term survival is now 85–90% in high-income countries.[32]

Adequate treatment requires imaging (radiography and ultrasonography), chemotherapy (vincristine, actinomycin and doxorubicin), a skilled surgeon and appropriate surgical facilities. The diagnosis can be based on clinical symptoms in combination with ultrasound showing an intrarenal mass or absent kidney on the affected side. The addition of radiotherapy improves prognosis for only a small subgroup of patients.

There are several reports on treatment of Wilms tumour in Sub-Saharan Africa. Reported survival rates range from 11% in Sudan to 70% within the collaborative network of the French-African paediatric oncology group (GFAOP).[15,33,34] Among the main challenges are late presentation and abandonment of therapy (ranging from 15% in Malawi to 68% or more in Sudan).[15,34] In Malawi, three of 20 patients (15%) abandoned treatment despite free medical treatment, food provision during their stay, travel support and counselling.[34]

In Europe, preoperative chemotherapy is given to reduce the tumour size and the risk of tumour rupture during surgery. This strategy results in a more favourable tumour stage after surgery,[35] less intense post-operative chemotherapy and less need for irradiation. Preoperative chemotherapy is a logical strategy in LMI countries, where tumours are often large at presentation, supportive care is limited and radiotherapy is unavailable. Preoperative chemotherapy consists of a 4-week regimen of vincristine and actinomycin for localised disease and a 6-week regimen with doxorubicin for metastatic disease. This regimen was feasible, tolerable and efficacious in Malawi.[34] Due to advanced disease at presentation, 25% of tumours (5 of 20) were unresectable after preoperative chemotherapy.[34] Continued efforts are needed to prevent abandonment and to encourage early presentation.

6.2.3. *Kaposi sarcoma*

The incidence of AIDS-related Kaposi's sarcoma (KS) in Sub-Saharan children has increased over the past 10–20 years as more children have been infected with HIV.[9] Where HIV prevalence is high, as in Southern and Eastern Africa, KS is now the second most common malignancy in children.[8,9] KS is caused by HHV-8 (or KS-associated herpes virus, KSHV), almost always in combination with HIV immunosuppression. It commonly causes skin lesions, can cause painful and functionally debilitating lymphoedema and may present with oral cavity lesions that can be painful and hamper food intake. It may also cause gastrointestinal disease or life-threatening pulmonary disease. KS is a stage IV AIDS – defining disease and qualifies a child in Malawi to start anti-retroviral therapy (ART). ART is the first-line treatment for KS but extensive, symptomatic KS warrants additional chemotherapy. Efficacy has been reported with the following (affordable) treatment strategies: vincristine monotherapy, vincristine plus bleomycin and oral etoposide monotherapy.[36] Thalidomide is an effective palliative therapy for widespread KS.[37]

Outpatient care for HIV-infected patients, including monitoring of disease progression and treatment response, takes place in HIV clinics. Patients are often admitted to general hospitals when they require more intense treatment and care. Chemotherapy for symptomatic KS is usually, but not exclusively, given in hospitals by doctors who provide HIV/AIDS care and/or childhood cancer care.

6.2.4. *Treatment guidelines for other childhood cancers*

In general, children who present with solid tumours and advanced disease have little chance of survival. Curative therapy is feasible for localised Hodgkin lymphoma and localised retinoblastoma. For ALL, a recently described graduated-intensity treatment approach provides a useful starting point in resource-limited settings.[38] Management of brain tumours with curative intent is difficult in the absence of a neurosurgeon and radiotherapy, as in the case in most of Sub-Saharan Africa. Current cancer treatment guidelines for children in Malawi have been summarised in the form of a practical manual.[39]

7. General approach to prioritisation and collaboration

Priorities for improvement of paediatric cancer care should be set by local staff who can best judge the feasibility of interventions. Improvements in diagnostic and treatment facilities should contribute when possible to general paediatric care. Experience has shown that small, well-considered steps can yield considerable sustainable progress over time. Well-planned clinical research projects that are locally relevant, such as simple audits, are invaluable and another way to improve care. Government support and commitment are important, but funding may be limited or unavailable. Therefore, the existing local infrastructure must be the starting point for any cancer care initiative.

Many low- and mid-income countries have substantially improved paediatric cancer care by establishing partnerships with institutions in high-income countries.[24,31,33,34] Collaborations according to the twinning model typically also include local public-sector and private-sector alliances and international organisations.[25,40,41] Dedicated local non-governmental organisations such as parent support groups have played a crucial role in providing medications, housing and psychosocial support for patients and their families. It remains to be determined whether this type of twinning programs can be successfully implemented in the most impoverished countries, including many of those in Sub-Saharan Africa.

Conflict of interest statement

None declared.

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