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The Management of Children With Kaposi Sarcoma in Resource Limited Settings

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Kaposi sarcoma (KS) is common where HIV infection is endemic. Antiretroviral therapy (ART) has reduced the incidence in well-resourced settings but in some parts of the world access to ART is delayed. These recommendations are for use where only minimal requirements for treatment are available. Consensus was sought for the management of childhood HIV-associated KS in this setting. There are no randomised controlled studies of chemotherapy for KS in children and these recommendations have drawn on consensus of a group of experts and published reports from studies in adults. Pediatr Blood Cancer 2013;60:538–542.

Key words: Africa; HIV; Kaposi sarcoma; resource-limited settings; treatment

INTRODUCTION

In the 1980s a rapid increase in the number of KS cases was reported that was almost entirely confined to individuals with HIV infection [1–3]. It affected young people of both sexes and was aggressive, multifocal and widespread [4,5]. As the HIV epidemic increased in Africa so did the incidence of KS and it is now one of the most prevalent cancers in men, women and children in many parts of the continent [6–8]. It is an AIDS defining disease. In well-resourced settings most HIV infected people access antiretroviral therapy (ART) as soon as they need it. In low-income settings despite remarkable success in rolling out ART to many infected people there is still delay in diagnosis and starting medication. This means that HIV-related KS is less common in well-resourced settings, but is still increasing where HIV is endemic [9,10]. Neither HIV or widespread KS are curable and treatment is aimed at disease reduction and providing a good quality of life. There have been no randomised controlled trials of treatments for children with KS and these treatment recommendations for use in resource-limited settings are based on reports of the few published adult trials and the expert opinions of clinicians looking after children with KS in resource-limited settings.

METHODS

A writing group was formed of clinicians with experience in caring for children with KS in sub-Saharan Africa. A PubMed search was made with the terms 'Kaposi Sarcoma', 'Kaposi's sarcoma', 'KS', 'low income', 'resource limited' and 'Africa'. We also searched the reference lists of articles identified by this strategy. Expert opinion was sought from paediatricians working in low-income settings where HIV is endemic. The recommendations are based on available published evidence and personal experience (expert opinion), with consensus among members of the writing group if no higher level of evidence was available. Recommendations in the manuscript that are based on expert opinion are indicated in the text as (EO).

Diagnosis

Where histological services are scarce the diagnosis is made clinically: the patient is HIV-infected and the KS lesions are characteristic [1]. Skin lesions are usually multifocal and widespread, and may be flat, raised or nodular. They range in colour from pink to a dark purple and are not usually painful. In the mouth they are found on the hard palate, gums or tongue. Facial nodules are commonly accompanied by peri-orbital oedema and haemorrhages [5]. The scrotum may be swollen and infiltrated; it is frequently the site for skin nodules and oedema. They are more numerous on the lower limbs than the arms, and have a predilection for the groins and genitalia. Lesions are seen in the instep of the foot or the toes but are infrequent on pressure areas of the soles of the feet, the scalp and the buccal mucosa. Advanced lesions tend to ulcerate and are prone to secondary infection. Gastro-intestinal lesions may cause bleeding, intussusception, pain and weight loss. Respiratory system involvement includes tracheal and bronchial nodules or patches leading to cough, shortness of breath, haemoptysis and sometimes chest pain. Pleural effusions develop which are often bilateral, bloody and highly proteinaceous. Chest X-ray typically shows bilateral perihilar lymph node enlargement, lower zone parenchymal infiltration and pleural effusions [11]. Lymph nodes (LNs) are commonly involved. Gantt et al. [12] from Uganda reported that 60% of the cases of KS in lymph nodes were in young children with relatively high CD4 counts. It is hypothesised that this occurs because a high level of circulating HHV8 immediately after an infection results in conversion to KS [13]. Lymphadenopathy may be generalised, firm and may be surrounded by a characteristic brawny oedema. It is common for LNs in the groins and femoral canals to be affected. Woody oedema of the legs causes difficulty in walking and may cause pain. KS has been reported to occur in skeletal muscle, bone and marrow [14].

If the diagnosis is in doubt, samples for cytology or histology should be taken. A fine needle aspirate (FNA) is often bloody but if spindle cells are seen, the diagnosis of KS can be confirmed [15]. A punch biopsy of a superficial lesion is useful. An early KS patch will contain abnormally shaped, dilated vessels surrounded

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

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TABLE I. AIDS Clinical Trial Group Staging Classification for Kaposi Sarcoma

	Good prognosis	Poor prognosis
(T) Tumour	Localised skin lesions	Ulcerated lesions
	Lymphadenopathy	Oedema
	Minimal nodular disease	Oral lesions
		Visceral involvement
(I) Immune status	CD4 $>$ 200/mm^3	CD4 $<$ 200/mm^3
	CD4% $>$ 15%	CD4% $<$ 15%
(S) Severity systemic illness	No B signs	B sign
	Karnofsky score $>$ 70	Karnofsky score $<$ 70
	No AIDs defining illness	
	No opportunistic infections	Opportunistic infections
	No oral candidiasis	Oral candidiasis

by a mononuclear-cell infiltrate containing plasma cells in the superficial to deep dermis with rare proliferation of spindle cells, atypical nuclei and mitoses. Advanced nodular lesions are characterised by slit-like vascular spaces surrounded by spindle cells [15]. If there is lymphadenopathy without skin nodules, a LN excision biopsy may be necessary to confirm the diagnosis.

An HIV antibody test should be done. KS is not invariably associated with HIV in children. Cases continue to be identified in whom both HIV antibody and PCR tests are negative. Children with HIV-related KS are often anaemic and thrombocytopenic and a complete blood count (CBC) should be done. There may be associated infections such as candidiasis, pneumonia or septicaemia to identify and treat.

Stage

The AIDS clinical trial group staging classification is used to stage KS and takes into account the extent of tumour, immune status and severity of systemic illness [16–18] (Table I). This score was developed before the HAART era and now with patients on antiretroviral therapy, the systemic and tumour scores are more useful as prognostic indicators than the CD4 count [18]. It has not been validated in children.

Treatment

Treatment options depend on local diagnostic and treatment facilities, the skill and experience of the clinical team caring for the child and available supportive care. KS is now largely an opportunistic malignancy of HIV disease. It is responsive to treatment but complete cure is probably only achieved in a child whose KS is focal or limited to very few sites [12]. Quality of life should be balanced against treatment with curative intent. Children with HIV-related KS have multiple problems associated both with the tumour and with the underlying HIV infection and their care includes input from the HIV team, palliative care, nutritionists and general clinicians.

The Paediatric Oncology for Developing Countries (PODC) which is a sub-group of the International Society of Paediatric Oncology (SIOP), defines four settings with different levels of care (Table II). These management guidelines are written for use in setting 1 where only minimal requirements for curative care are available. The minimal requirements for management of patients with HIV-related KS are the ability to provide consistent ART and prophylactic cotrimoxazole. Basic laboratory and radiological services should be available (Table II). Appropriate chemotherapeutic drugs should be available with the expertise to administer them safely. In this setting chemotherapy will be drawn up by the ward nurses and they need a physical space in which to do this safely. Supportive care such as the ability to give safe blood transfusions, intravenous broad-spectrum antibiotics, adequate pain medication, nutritional support and nursing care should be available. If possible free medical treatment and social support including money for travel should be given to impoverished families. Poor families frequently abandon treatments because of financial and social constraints and efforts to reduce this improve outcomes [19–21].

Treatment Regimens

There is scant literature to guide the management of KS in children in resource-limited settings. A Cochrane review found five randomised studies, none in children, and results were inconclusive [22]. Several drugs have been used in combination or singly and found to be helpful; but no large randomised controlled trials have been undertaken. Outcomes can be measured as cure and/or as improving the quality of life. Two retrospective audits, one from Uganda and one from South Africa report the treatment and outcome of 73 and 70 children respectively [12,23]. Eleven percent of children in Uganda and 20% in South Africa were already on ARTs before the start of chemotherapy. In Uganda outcome was available for 32 (46%) and in South Africa for 60 (85%). In Uganda 13 were treated with vincristine alone and 23 were given vincristine and bleomycin. Overall there was complete clinical remission in 20/32 (62.5%), partial response in 11/32 (34%) and none in one. Outcome was uninfluenced by the different agents used or whether they were given singly or in combination. Two did well on ARTs alone. In South Africa 52 received chemotherapy of whom 37 received bleomycin, doxorubicin and vincristine; nine received bleomycin and vincristine and six received vincristine. Overall 28 (40%) were alive for an average of 16 months follow up, though 10 still had disease; 46% died. The effect of different treatments on outcome is not stated and though the numbers were too few for statistical significance the authors felt that the combination of ARTs and chemotherapy gave better results than either one alone.

Antiretroviral therapy should be given to HIV-infected children, but there is no evidence to indicate whether ARTs should be started before, at the same time or after chemotherapy. KS IRIS (Immune Reconstitution Inflammatory Syndrome) has been reported in adult patients following initiation of ART [24–26]. Reports from Mozambique and South Africa suggest that KS IRIS occurs in 10–11.8% of adult patients [25,26]. It is associated with a baseline haemoglobin concentration of less than 10 g/dl and a low CD4 count [25]. Typically there is clinical deterioration with fever, swelling and pain at the site of lesions—the so-called 'KS flare' [24]. Nor is it clear if chemotherapy should be given to limited KS. In a prospective review, 254 adults with limited AIDS-related KS on ART in London were followed for 12 years (1996–2008). Five-year treatment-free survival was 74% while 22% (n = 37) had to go on to chemotherapy. Overall survival at 5 years was 91% [27]. Thalidomide inhibits angiogenesis [28] and in adults with KS has led to clinical improvements

TABLE II. Definitions of Settings 0–3 by Standard of Care, Available Staff and Supportive Care for Treatment of KS

Setting	Medical facilities	Specialists	Drugs	Supportive care	Diagnostic facilities
0	Basic	None	Antiretroviral therapy Cotrimoxazole prophylaxis	Pain medication Oral antifungal and Antiseptic (GV paint) solutions, Broad spectrum antibiotics	HIV testing Physical exam
				Antimalarial drugs Nutritional support	Thick films for malaria Stool and urine microscopy
1 Minimal requirements for care	Pediatric ward and clinic area where treatment can be provided	(Surgeon) Paediatrician Nurse	+Vincristine (Bleomycin) (Doxorubicin) (Etoposide) (Thalidomide)	+Group and cross match Mouth care Whole blood Morphine Social support	+Full blood count CD4 count Chest X-ray Ultrasonography 2nd line ART
2	Ped oncology ward Radiotherapy Pathology Multidisciplinary care	Pathologist Paediatric surgeon Paediatric oncologist Radiation oncologist Oncology nurse	+ Daunorubicin Actinomycin Vinblastine	+ Blood products	+ HIV viral load CT-scan
3 'State of the art'	Intensive care unit	Paediatric pathologist Paediatric radiologist Paediatric radiation oncologist Pharmacist (oncology) Intensivist	Individualised ART therapy Pegilated liposomal doxorubicin Placitaxel Interferon alpha Cryosurgery Intralesional chemotherapy Hypofractionated radiotherapy	+ Mechanical ventilation Haemodialisis Inotropic support	Special stains Immunohistochemistry Cytogenetics HHV8 PCR

comparable to those obtained with some cytotoxic chemotherapy regimens [29–31]. In both HIV and non-HIV associated KS there is evidence that oral thalidomide at 3 mg/kg every evening for 4 months leads to a reduction in the number and size of skin nodules, reduces oedema and improves appetite and general well-being when measured by the Lansky score. It is given in the evening because it may make patients drowsy [32]. In Malawi, 49 HIV-infected ART-naive children with KS were given thalidomide for 4 months: 75% responded with tumour reduction and an improved Lansky score of whom 90% maintained a good response for 6 months [33]. Thalidomide should be used with caution and guardians should be warned that the drug can cause limb deformities if taken in early pregnancy [34]. For this reason it should not be given to post-menarchal girls. Most children tolerate it well; the Malawi study reported that some children complained of constipation but no child developed peripheral neuropathy [33]. The additional effects of improving appetite and sleep can be beneficial to sick, anorexic and debilitated children (EO).

MANAGEMENT OF KS IN SETTING 1

Diagnosis

The diagnosis of KS can be made with reasonable certainty based on history and physical examination. Any clinical suspicion of KS must be accompanied by HIV testing. We recommend cytology or histology at diagnosis in patients when there is doubt about the diagnosis. If the child is stable we advise waiting for the pathologist's report. If the child is very ill or lesions appear to be increasing in size or number, then treatment should be commenced while waiting for report (EO).

Surgery

Surgery is seldom required except for single nodules that ulcerate and bleed or cause obstruction. Simple excision or cryosurgery of the bleeding nodule or of one that is prone to trauma, such as on the tongue or palate, can be undertaken.

Supportive Care

Prevention and treatment of infections, mouth care, nutritional support and management of anaemia are important. Bleeding may require blood transfusions, platelets and fresh frozen plasma. Steroids are given if there is airway obstruction. Children are often malnourished, anaemic, febrile and in pain. They may have sore mouths, be anorexic and find it difficult to sleep. They may have co-infections such as TB, malaria or chronic lung disease and a low threshold for treating infections is indicated. It is important to assess nutritional status, provide nutritional support, and ensure good local (oral) and systemic analgesia.

If chemotherapy is being provided travel and accommodation costs should be covered. KS is not only an AIDS defining disease

TABLE III. Chemotherapy Regimens for Kaposi Sarcoma in Low-Income Settings

Single agent regimens
Oral
Etoposide 100 mg/m^2 po three times a week
If tolerated, the dose can be increased to 200 mg/m^2
The maximum cumulative oral dose is 10 g/m^2 which is usually reached after about 4 months
Thalidomide 3 mg/kg as an evening dose for 4 months
Intravenous
Vincristine 1.5 mg/m^2 weekly for 3 weeks and then fortnightly, to complete six courses[a]
Intravenous or Intramuscular
Bleomycin 15 iu/m^2 IV or IM weekly for 3 weeks and then fortnightly, to complete six courses
Two agent regimens
Vincristine 1.5 mg/m^2 IV and bleomycin 15 iu/m^2 IV or IM weekly for 3 weeks then fortnightly to complete 6 courses[a]
Three agent regimens[b,c]
These protocols require a haemoglobin >8 g/dl and absolute neutrophil count (ANC) $>1 \times 10^9$/mm^3 and platelets $>100 \times 10^9$/mm^3 before each course
ABV[d]
Day 1 and 15 doxorubicin 25 mg/m^2 IV in 50 ml 5% DW over 30 min; bleomycin 10 iu/m^2 IV in 0.9% saline over 15 min; vinblastine[e] 6 mg/m^2 IV bolus
This is repeated for four courses
AVA[f]
Alternating courses are given, every 3 weeks, of A&B to a total of four courses of each
Day 1 doxorubicin 50 mg/m^2 and vincristine 1.5 mg/m^2 IV weekly $\times$ 3
Day 1 actinomycin D 1 mg/m^2 and IV vincristine 1.5 mg/m^2 IV weekly $\times$ 3[f]
Cyclophosphamide 600 mg/m^2 is added to each course if the response is inadequate
Low dose ABV[d]
Vincristine 1.5 mg/m^2, daunorubin 10 mg/m^2 and bleomycin 10 iu/m^2 IV monthly for one to six courses depending on tumour response. If visceral disease is present the daunorubicin and bleomycin doses can be increased to 20 mg/m^2

[a]Single doses of vincristine or actinomycin should not exceed 2 mg; [b]Cumulative doses of doxorubicin should not exceed 300 mg/m^2; [c]When anthracyclines are given, a baseline echocardiogram should be done and repeated after a total cumulative dose of 200 mg/m^2; [d]A, adriamycin (doxorubicin); B, bleomycin; V, vincristine; [e]Vinblastine can be replaced with vincristine at a dose of 1.5 g/m^2; [f]A, adriamycin (doxorubicin); V, vincristine; A, actinomycin D.

but also the disease that may ultimately cause the child's demise. Guardians need careful honest counselling to make them aware of the problems ahead without taking away all hope.

Chemotherapy Regimens for Setting 1

All HIV positive patients should be started on ART immediately if KS is limited and after 3–4 weeks of chemotherapy, if the KS is extensive (EO). Some protease inhibitors have anti-HHV8 activity and in theory are more effective in KS patients, but there is no evidence that protease inhibitor-containing regimens are superior to NNTRI-containing regimens in the treatment of KS [33,35]. In Setting 1 the choice of drugs for ART is guided by national policy. If the child is already on antiretroviral therapy, viral load should be measured as the development of KS may indicate ART failure, and second-line treatment may be needed.

The chemotherapy given will depend on drug availability and stage of KS. More extensive KS needs combination chemotherapy but some children tolerate such regimens poorly. Studies in adults report that triple therapy (doxorubicin, bleomycin and vincristine, ABV) results in more rapid and longer reduction in numbers and size of KS lesion numbers than dual therapy (vincristine and bleomycin), which in turn is superior to single drug treatment (doxorubicin) [36,37,38]. In a small study of 12 adults receiving bleomycin and 12 receiving ABV, five in the bleomycin group had KS progression but in the ABV group 4 showed a partial response and eight had stable disease. Survival was unaffected by the drugs given [39]. In a study of 61 adults with extensive KS, 48% of the 30 who received low dose adriamycin and 88% of the 31 receiving ABV had partial or complete regression ($P = 0.004$). Survival was unaffected by group [40]. When liposomal daunorubicin was compared with ABV, as second line therapy in previously treated cases, the outcome was similar for each group (25% vs. 28% complete or partial response) [41]. Liposomal daunorubicin and pegylated doxorubicin are very expensive for low-income settings. A prospective study of 50 adults with HIV-related KS receiving monotherapy with vincristine was undertaken in Malawi. At 6 weeks there was a 64% tumour response and the median progression-free survival was 30 weeks [42].

Chemotherapeutic Protocols

Table III lists chemotherapy regimens that are used where only minimal treatment is available. The triple drug regimens are more toxic than the single or dual drug regimens. All children weighing less than 12 kg should have dose reductions of two thirds (EO). A simplified formula to calculate body surface area is $\sqrt{\text{weight} \times \text{height}/3,600}$, though this widely used method is not validated for malnourished children [43]. Formulae are liable to human error and it may be easier and safer to use a chart such as UKCSSG Estimation of Body-Surface Area in Infants and Children [44].

ASSESSMENT OF TREATMENT RESPONSE

An objective measure of the effect of treatment on KS is counting the number of visible or palpable KS nodules and making serial, two-dimensional measurements of the size of four to six selected nodules. Reductions in size and number are evidence of a treatment effect. An example of how to record these findings in diagrammatic form is in Supplemental Figure 1. Oedema will usually disappear gradually, appetite and sleep will improve and pain will be controlled. The Lansky score is a useful tool to measure activity and well-being (Supplemental Table IV).

Research Questions

There is a dearth of evidence on the management of KS in low-income settings. Answers are needed to such questions as when is ART alone sufficient treatment? There is no evidence as to whether chemotherapy should be started before, with or after starting ART and nor is it clear how many different drugs should be given, in what combination and for how long. HIV infection may cause cardiomyopathy and it is not known if anthracyclines have increased cardiotoxicity in these children. The oedema that surrounds KS lesions, especially of the lower limbs is slow to improve and the role of steroids in managing the oedema has not been studied. Widespread HIV-related KS is not curable and metronomic treatment with low dose chemotherapy with or without thalidomide may be a useful way of controlling the disease.

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