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Treatment strategies for Kaposi sarcoma in Sub-Saharan Africa: Challenges and Opportunities

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Abstract

Purpose of review—The purpose of this review is to summarize recent published literature on treatment of AIDS-associated Kaposi sarcoma (KS), the most common HIV-associated malignancy and a leading cancer diagnosis in sub-Saharan Africa (SSA), and to highlight the challenges faced in treating KS in this resource-limited environment.

Recent findings—There are few prospective clinical trials for KS treatment in SSA, along with a relatively poor cancer treatment infrastructure, leading to late diagnosis and poor access to therapy. The only prospectively-randomized trial of chemotherapy compared antiretroviral therapy (HAART) alone to HAART with combination chemotherapy with doxorubicin, bleomycin and vincristine (ABV), and documented a significantly higher rate of tumor regression for the combination along with improvement in quality of life and no adverse effects on HIV control. Other studies suggest that gemcitabine may be an active second-line chemotherapeutic agent after failure of HAART and ABV and suggest that AIDS-associated KS in children may respond well to HAART with chemotherapy. There are also (primarily retrospective) data suggesting a beneficial effect of HAART on KS, but some evidence for KS as a manifestation of immune reconstitution inflammatory syndrome.

Summary—Opportunities and need exist for prospective research to establish evidence-based guidelines for the most effective treatments for KS in SSA.

Keywords

Kaposi sarcoma; chemotherapy; sub-Saharan Africa; AIDS-associated cancer; HIV/AIDS

Introduction

Kaposi sarcoma (KS) is the most common malignancy associated with HIV infection in sub-Saharan Africa (SSA) and is a cause of significant morbidity and mortality. Although much has been published about the epidemiology of KS and the KS-associated herpesvirus (KSHV/HHV-8) in SSA and other studies have described the often advanced-stage initial clinical presentation of HIV-associated KS and recent references are provided here as background [1–12], there have been few published studies of KS treatment in the SSA setting. The paucity of information on KS therapy can be attributed, at least partly, to the scarcity of resources available for provision of KS treatment. This review focuses on studies published in 2009–2010 describing treatments for KS in SSA, and considers some of the challenges and barriers to be overcome in developing improved KS treatment and prevention strategies.

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Chemotherapy Studies in SSA

In 2007, Bihl et al. [13] reported preliminary results in a subset of 33 patients entered into a prospectively randomized clinical trial known as the "KAART" trial. This study compared antiretroviral therapy (ART) with a combination of stavudine, lamivudine and nevirapine (HAART) alone to HAART plus combination chemotherapy using a standard "ABV" regimen (doxorubicin 20 mg/m^2, bleomycin 10 U/m^2 and vincristine 1.4 mg/m^2 every 2 weeks) in treatment-naïve HIV+ patients with KS in South Africa. Although this paper cited a trend toward a better clinical outcome for patients treated with HAART plus chemotherapy, the major findings concerned immune reconstitution and the development of KSHV-specific T-cell responses in a subset of patients. Of particular interest was the finding that a significant reduction in KSHV viral load was observed only in those individuals who received HAART with chemotherapy [13]. This finding is consistent with a similar observation that administration of chemotherapy to patients with HIV-associated non-Hodgkin lymphoma was associated with a decrease in KSHV viral load [14]. Although the final results of the KAART trial have not yet been reported in a definitive manuscript, they have been published in abstract form [15*,16*,17*] and presented at international meetings. A total of 112 patients were randomized, 59 to HAART alone and 53 to HAART plus chemotherapy. Nearly 90% had advanced-stage KS. Although there was no significant difference between the groups in overall survival at 12 months, the overall response rate (complete and partial) at month 12 was significantly higher in the chemotherapy arm (66%) than in the HAART-only arm (39%), $p=0.005$, and time to response was 2.7 times faster in the chemotherapy arm. Certain aspects of quality of life trended toward greater improvement in the chemotherapy arm, and complete or partial response was associated with increased global health scores ($p<0.001$). Importantly, there were no significant differences in CD4 improvement, HIV viral load decay, adverse events, or adherence between the treatment arms. These results belie the widely held belief that use of myelosuppressive chemotherapy would lead to depletion of the CD4 count and limit the protective effects conferred by HAART, which has led some authors to advocate the use of relatively non-myelosuppressive, single-agent vinca alkaloids [18]. In some settings, however, single-agent vincristine has been commonly used to treat KS because of its availability and low cost, despite obvious drawbacks including low efficacy and a high risk of peripheral neuropathy [19].

Strother et al. [20*] reported that the antimetabolite, gemcitabine, was an active second-line agent in HIV+ patients showing progressive KS despite initial treatment with ART and subsequent treatment with a standard, first-line chemotherapy regimen that included doxorubicin, bleomycin and vincristine (ABV). This retrospective analysis, performed in western Kenya, described 23 patients who received gemcitabine as a single chemotherapeutic agent between 2006 and 2007. All patients had "poor risk" KS based on one or more criteria described in the ACTG staging classification for KS [21]. Although the treatment regimens were not standardized, most patients received intravenous gemcitabine at a dose of 1000 mg, with a planned dosing interval of every 14 days. However, planned doses were often missed or delayed; lack of transportation to the treatment site was the most common reason for missed or delayed doses. Nonetheless, 11 of 32 patients showed complete (3 patients) or partial (8 patients) regression of KS (48% response rate) and 65% of patients showed symptomatic improvements, which included reduced pain intensity, decreased use of analgesics, increased performance status, and increased weight. Significantly, there were no treatment-related deaths and relatively modest hematologic toxicities, although admittedly blood counts were performed before only 48% of chemotherapy cycles and adverse events may consequently have been missed. Although the retrospective nature of the study and the lack of uniform response guidelines, treatment

doses and schedules, and follow-up for toxicity, represent limitations of this study, the data suggest that gemcitabine is worthy of further prospective study in HIV-associated KS.

Although most of the world literature on the presentation and treatment of HIV-associated KS concerns adult patients, in SSA children infected with HIV frequently develop KS. Gantt et al [22**] recently reviewed the presentation and outcome of 73 children with HIV-associated KS referred to the Uganda Cancer Institute in Kampala between October 2004 and June 2007. In addition to describing a predominantly lymphadenopathic clinical presentation of KS, especially in younger children, that differed from the predominantly cutaneous presentations seen in adults and older children, the authors also described the therapeutic response to various treatments, which included chemotherapy (either single-agent vincristine or a combination of vincristine with bleomycin) and/or ART. Although no details of chemotherapy doses or treatment schedules were supplied in the report, the authors reported a high response rate – most often complete – among children who received chemotherapy together with ART. Of 26 children who received either vincristine or the vincristine/bleomycin combination with ART, 17 showed a complete response and 6 showed a partial response. Only one of 26 children showed no response and the response of 2 children was unknown. Although 15 children were reported as having received ART only, the KS response of 13 children was unknown while 2 were reported as showing a complete response. The lack of follow-up for the majority of patients treated with ART alone is disappointing, as it is not known whether this reflects a disproportionately poor outcome in this patient subset.

A small series of nine pediatric KS cases has also been described by investigators from a center in Cape Town, South Africa [23]. The report highlighted some atypical KS presentations in the pediatric age group, including small bowel intussusceptions. Although the authors wrote that chemotherapy was used in addition to ART to achieve KS remission in 6 cases, the nature of the chemotherapy regimen was not specified. Intussusception has also been reported as a presenting sign of KS in African children in Durban, South Africa, with often fatal consequences [24].

Antiretroviral Therapy and KS in SSA

Although there is considerable evidence that the widespread introduction of HAART has been associated with a markedly reduced incidence of KS in well-resourced countries, the limited data currently available from SSA have not documented a similar decrease [25**, 26*]. This may be at least partly attributable to the incomplete access of individuals in SSA to HAART, varying levels of coverage in different parts of SSA as distribution programs for ART expand, and earlier time of acquisition of KSHV infection. However, one study from KwaZulu Natal, South Africa suggests that as HAART has become increasingly available, a higher proportion of patients with KS were able to receive and benefit from chemotherapy along with a decreased need for palliative treatment and improved follow-up [27*]. In addition, as described earlier in the KAART study [15*,17*], 39% of patients initially randomized to receive HAART without chemotherapy were reported to have shown KS regression at month 12 after randomization (intent-to-treat analysis), although it is not clear whether any of these patients had chemotherapy added to their treatment regimen subsequent to randomization.

Borok and colleagues [28**] have recently published the results of a study performed in 90 patients with AIDS-associated KS in Harare, Zimbabwe between 2003 and 2005, at a time when the initial ART offered was a fixed combination of three nucleoside reverse transcriptase inhibitors, abacavir, lamivudine and zidovudine, (i.e., without including either a non-nucleoside reverse transcriptase inhibitor or an HIV protease inhibitor). The primary

objectives of the study were to assess KS regression in response to ART at week 96 and to investigate whether KS regression was associated with suppression of HHV-8/KSHV replication. Significantly, adjunctive chemotherapy was permitted and was administered to 50 of the 90 study subjects, most often with a combination of bleomycin and vincristine (82% of patients) and after a median of 34 weeks after initiation of ART; 22 participants received adjunctive radiotherapy after a median of 29 weeks after initiation of ART. As with other studies, the vast majority (>80%) of participants had advanced-stage KS at entry. Although only 19% of participants showed complete or partial KS response at 96 weeks, it is noteworthy that the use of adjunctive chemotherapy in this setting was associated with significantly increased odds of survival (OR, 4.75). Paradoxically, however, the use of adjunctive chemotherapy was associated with significantly decreased odds of KS regression. As the authors note, this is likely the result of preferentially prescribing chemotherapy for those patients who had survived beyond the initial period of high mortality from infectious complications, but who had not shown KS regression from ART alone, whereas those patients whose KS improved with ART alone were not prescribed chemotherapy. 70% of patients treated with ART in the study were confirmed alive at 96 weeks, which compares favorably with the median survival of only about 6 months for KS patients in Zimbabwe, regardless of receipt of chemotherapy, prior to the availability of ART [29]. Higher baseline plasma HHV-8 DNA levels were associated with significantly poorer survival and KS response, and advanced KS stage was associated with poorer response.

While these observations suggest that the administration of HAART improves the outlook for KS patients in SSA, an observational cohort study of HIV-infected adults with AIDS-associated KS from three primary care HIV clinics in a poor township in Cape Town, South Africa indicated that more than one quarter of patients with AIDS-associated KS did not receive HAART [30*]. Although nearly 70% of the 215 KS patients in this study presented with disseminated, advanced stage (T1) KS according to ACTG criteria, only 29% of patients received systemic chemotherapy. Factors associated with mortality included lack of receipt of both chemotherapy and HAART. The reasons underlying lack of treatment with either HAART or chemotherapy were not clear, although the authors cited “incomplete access to chemotherapy for those with advanced disease” and early diagnosis as important issues [30*]. Another analysis of short-term (6- and 12-month) outcomes after initiating HAART in Malawi, found that those who presented with KS showed a significantly poorer survival and were more often lost to follow-up than those with a non-KS diagnosis [31].

Although most evidence indicates that HAART has a beneficial effect on KS, there is evidence that some individuals, despite a good virologic and immunologic response, show a seemingly paradoxical response, i.e., development of KS within a relatively short interval after starting HAART, or acute worsening of pre-existing KS, often with a prominent inflammatory component – so called KS Immune Reconstitution Inflammatory Syndrome (KS-IRIS). A recently-published study from Mozambique followed 69 HIV-infected individuals with evidence for KSHV infection (based on either detection of anti-KSHV lytic antibodies or a clinical diagnosis of KS) after initiation of HAART [32*]. During the first 10 months of HAART therapy, 8 patients (11.6%) were reported to have developed KS-IRIS after a median of 13.8 weeks. Multivariate analysis identified clinical pretreatment KS, detectable pre-HAART plasma KSHV DNA, hematocrit less than 30%, and higher pre-HAART plasma HIV-1 RNA viral load as independent predictors of KS-IRIS. It is noteworthy, however, that the median time to development of KS-IRIS in this study was longer than the 3-month timeframe often considered as part of the IRIS definition. Of 6 patients in whom a standard, every 4 week, ABV chemotherapy regimen was added to HAART, 4 showed a complete or partial response.

Challenges and Opportunities

In 2008, an estimated 34,000 individuals (22,000 males and 12,000 females) were diagnosed with KS in SSA, with KS thus representing the third leading cancer diagnosis in males and the fourth leading diagnosis in females in the region [33**]. Many challenges exist in the provision of treatment for KS in SSA and in determining the optimal treatment for this most common malignant complication of HIV infection. These challenges are, for the most part, generic issues that affect the treatment of all types of cancer in this part of the world, and are not specific to KS or HIV-infected individuals. However, given that HIV-infected people in SSA frequently have access to diagnostic and therapeutic services through dedicated HIV programs, there may be unique opportunities to detect and treat AIDS-associated KS in this context.

A common theme in publications about KS in SSA is the advanced stage at diagnosis and/or referral for treatment. Although to some extent, this may reflect the difficulty of diagnosing visceral (i.e., non-cutaneous, non-oral) KS presentations, which appear to be more common in SSA than in the U.S. or Europe, it is likely that better training and education of health care providers, as well as public information campaigns to heighten awareness of the early manifestations of KS (e.g., unexplained skin lesions, pigmented oral lesions, unexplained limb or periorbital edema), would lead to earlier recognition and treatment of KS. As KS is often the first event leading to a diagnosis of HIV infection in SSA, earlier recognition of KS could also lead to earlier diagnosis and treatment of HIV.

Providing standard treatments for AIDS-associated KS, and performing clinical trials to identify optimal treatment regimens, face a number of common infrastructural problems. With few exceptions, facilities for the diagnosis and treatment of cancer in most of SSA are minimal [34], there are few trained cancer specialists and training programs (although, as described by Orem and Wabinga [35], this is being addressed in some cases through international partnerships), and while chemotherapy may be available, access is restricted because the drugs are imported, expensive, and beyond the means of many patients even in the case of relatively “low-cost” generic products. For some of the chemotherapy trials cited here [20*, 29], the drugs tested were donated by foreign pharmaceutical companies, but are not otherwise available in country. The availability of transportation to treatment sites is not a given [20*], and is apparently a major cause of non-adherence to treatment and loss to follow-up. Potential opportunities for closing the gaps between developed and developing countries in cancer treatment and outcomes have recently been put forward [36*,37*] and if applied could provide greater access to the limited number of currently available treatments for KS in SSA. Developing evidence-based guidelines for the most effective treatments for established KS, and also for prevention of KS in individuals at high risk for KS development, will require randomized, prospective trials of the sort now being planned and conducted by the AIDS Malignancy Consortium and the AIDS Clinical Trials Group.

Conclusions

KS is the most common AIDS-associated cancer in SSA and a leading cancer diagnosis in the region. Nonetheless, there is relatively little data on its response to treatment and on the most effective treatment regimens. Much of the available information on the response of KS to chemotherapy and/or antiretroviral therapy comes from retrospective reviews of patient records. In addition, infrastructural inadequacies in the provision of cancer care in SSA present great challenges for developing evidence-based guidelines for the most effective treatment. Opportunities exist to conduct well-controlled, prospectively randomized clinical trials that will address gaps in the knowledge base regarding KS.

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Key Points

- Although it was estimated that over 34,000 people would be diagnosed with Kaposi sarcoma in sub-Saharan Africa in 2008, the infrastructure to conduct clinical trials to define the most effective treatments for AIDS-associated Kaposi sarcoma is weak.
- There is evidence, primarily from retrospective studies, that chemotherapy and antiretroviral therapy can lead to Kaposi sarcoma regression and improvements in quality of life and survival in HIV-infected patients in sub-Saharan Africa.
- Barriers to optimal care for AIDS-associated Kaposi sarcoma, and for other malignancies in sub-Saharan Africa, include late diagnosis of cancer, a lack of trained cancer professionals and treatment centers, low or inconsistent availability of therapeutic agents, and overall poverty which limits access to treatment and to follow-up care.