AIDS-RELATED KAPOSI'S SARCOMA: MANIFESTATIONS AND MANAGEMENT STARTEGIES WITH HAART AND ADJUVANT THERAPIES

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ABSTRACT

AIDS-related Kaposi sarcoma varies widely from a few mucocutaneous lesions to more florid ones with life threatening visceral involvement. Highly active antiretroviral therapy (HAART) has radically improved the outcome of this disease, and is pivotal to any treatment of the tumour. Late disease will require adjuvant chemotherapy for some duration to induce remission. Less expensive chemotherapy regimens may be needed in sub Saharan Africa heavily burdened with the disease and poverty. Various biologic agents are undergoing clinical trials at different stages and may prove useful in controlling the disease when combined with HAART and chemotherapy.

KEYWORDS

Kaposi sarcoma; AIDS; Antiretroviral therapy; Management.

INTRODUCTION

Kaposi sarcoma (KS), a multifocal tumour comprised mostly of cells of endothelial origin with a unique spindled shape, was first described by Moritz Kaposi, a Hungarian dermatologist, in 1872.[1] Although KS can present is any of the four clinicopathologic forms/types,[1,2] AIDS-related Kaposi sarcoma (AIDS-KS), is an aggressive, epidemic type of Kaposi sarcoma and the most common presentation of KS first described in young homosexual or bisexual men with HIV as part of the AIDS epidemic in 1981.[2]

Highly active antiretroviral therapy (HAART) is an integral part of the treatment of AIDS-KS and has reduced its morbidity and mortality, with adjuvant therapies mostly reserved for late disease. In sub Saharan Africa, management is more complicated due to poor access to HAART and effective adjuvant therapy. In this review, we look at the clinical manifestations of AIDS-related Kaposi sarcoma (AIDS-KS), the various strategies available for its management, and treatment challenges in sub-Saharan Africa.

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CLINICAL MANIFESTATIONS

The manifestation of AIDS-KS can vary from a slowly progressive disease to an aggressive and life threatening one, with those patients not on HAART having a graver prognosis[3]. In more developed countries, the disease is generally more common in males affecting a much higher percentage of homosexual or bisexual men than heterosexual ones[4] while in Africa, although still more common in men, more women and children are affected[5]. Early AIDS-KS may appear as a subtle macular mucous or cutaneous lesion and subsequently develops into plaques and then nodules.[6,7] The lesions often become numerous and may involve the lymph nodes and visceral organs like the gastrointestinal tract, the lungs and the liver and there may be associated lymphoedema. Lesions can ulcerate, become painful, or invade deeper structures like the bone.[8,9] Visceral organ involvement rarely leads to symptoms.[10] That notwithstanding, gastrointestinal lesions could cause odynophagia, vomiting, abdominal pain, intestinal obstruction or bleeding. Pulmonary lesions may be an asymptomatic finding on a radiograph or manifest as cough, breathlessness, haemoptysis or chest pain. Pulmonary involvement could lead to death directly from the disease, though most patients with AIDS-KS die of opportunistic infection.[4]

Table 1. AIDS Clinical Trials Group Staging Classification[14]

	Good Risk (0)	**Poor Risk (1)**
	(Any of the following)	**(Any of the following)**
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease [Note: Minimal oral disease is non-nodular KS confined to the palate.]	Tumor-associated edema or ulceration
		Extensive oral KS
		Gastrointestinal KS
		KS in other non-nodal viscera
Immune system (I)	CD4 cells = = 200/microliter	CD4 cells <200 per cubic millimetre
Systemic illness (S)	No history of OIs or thrush [Note: OIs are opportunistic infections.]	History of OIs and/or thrush
	No "B" symptoms [Note: "B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting >2 weeks.]	"B" symptoms present
	Performance status =70 (Karnofsky)	Performance status <70
		Other HIV-related illness (e.g., neurological disease or lymphoma)

Extracutaneous lesions have been described in certain atypical locations like the musculoskeletal system, the heart, the nervous system, even developing within wounds and blood clots.[11] In a study of 49 young homosexual men with AIDS-KS in North America in 1983, Krigel et al reported that 63% had widely distributed, innumerable skin lesions, 27% had localised or fewer than five skin lesions, and 8% had no skin lesions, and 61% had generalised lymphadenopathy and 43% had one or more gastrointestinal tract lesions.[12]

Oral cavity lesions are frequent in this disease, occurring in about 20% of patients with AIDS-KS.[13] The AIDS Clinical Trial Group (ACTG) Oncology Committee published a group staging system for the evaluation of AIDS-KS based on the extent of the tumour, severity of immunodeficiency, and systemic illness variables.[14] A subsequent prospective study of 294 patients enrolled in ACTG therapeutic trials for AIDS-KS in the United States (US) showed that each of these three variables was independently associated with survival.[15] The staging system is as shown in Table 1[14]

MANAGEMENT STRATEGIES

The current concept in the management of AIDS-KS involves an optimised standard regimen by a team experienced in treating HIV and Kaposi sarcoma.[16] HAART has led to a marked reduction in the incidence, morbidity and mortality of AIDS-KS.[17,18] The aim of treatment is symptom palliation, tumour shrinkage, and prevention of disease progression.[19] Although treatment may lead to reduction in skin, mucosal and visceral lesions with alleviation of the associated symptoms, there is no data available to show this improves survival.[20] Treatment strategy should be based on the stage of the disease, and also include prophylaxis and treatment of opportunistic infections, in addition to HAART and antitumor treatment.[4] According to the AIDS Clinical Trial Group, many good risk patients may respond well to HAART alone, while poor risk patient will require an additional treatment modality to HAART such as chemotherapy which could be discontinued on disappearance of lesions.[21]

HAART

HAART is associated with a decrease in the incidence of AIDS-KS and reduction in the size and number of its lesions therefore patients with AIDS-KS should first of all be placed on HAART due to its benefits. The response to HAART ranges from 20 to 80%, with worse outcome in patients with more advanced tumour, and patients that were not on HAART before developing the tumour .[22] Though there are few studies available on the efficacy of various HAART regimens, experimental studies may favour use of protease inhibitor containing regimens.[23] In early disease, HAART alone may be sufficient as treatment. A meta-analysis found that 81% of patients without advanced AIDS-KS showed a complete response to HAART, while only 5 cases of response to HAART alone were documented in literature among persons with more advanced AIDS-KS.[23] In patients with more advanced disease, it is therefore expedient to combine HAART with adjuvant therapy.

Local therapy

A few localized AIDS-KS lesions can be amenable to surgical excision, cryotherapy, or electrodessication.[4] Intralesional vinblastine injection has also been found to be very effective.[24] A phase III randomized double-blind trial on the efficacy and safety of topical application of 0.1% Alitretinoin in cutaneous AIDS-KS showed that it is beneficial, with an overall patient response rate of 37%. [25] The study also showed it was generally well tolerated. Local radiation therapy at doses of at least 20Gy is very effective, especially when targeted at localized skin and oral mucosal lesions.[26] At fractions of 8Gy, effective treatment of skin lesions can be achieved with fewer adverse

reactions.[27]

Systemic cytotoxic chemotherapy

Systemic chemotherapy is utilized for bulky, symptomatic, more aggressive, or life threatening lesions.[21] Various studies have been done on the use of anthracyclines, taxanes, vinca alkaloids, bleomycin, and etoposide as single agents, or in combination, for the treatment of AIDS-KS.Three of these agents, pegylated liposomal doxorubicin, liposomal doxorubicin, and paclitaxel have been approved by the Food and Drug Administration (FDA) based on their clinical efficacy and reasonable side effects profile.[18] In several randomized control studies, patients showed much better response rates (vs. for pegylated liposomal doxorubicin or liposomal daunorubicin (45%–60%) , compared to the combination of doxorubicin, bleomycin, and vincristine (20%–25%) .[28] The liposomal anthracyclines also showed a more acceptable toxic profile. As an adjunct treatment to HAART in the treatment of AIDS-KS, pegylated liposomal doxorubicin and paclitaxel used as single agents showed response rates near 50%. [29]

Not much has been done to evaluate the effectiveness of these preferred agents in treating AIDS-KS in sub-Saharan Africa where the burden of this disease is greatest, probably due to the unavailability of these drugs.

A recent study comparing bleomycin/vincristine to vincristine monotherapy as treatment for AIDS- KS among 449 patients starting HAART in Malawi showed improved tumour response in 53% of the patients on bleomycin/vincrisine as opposed to 29% of those on vincristine alone.[30] Nearly all the patients (98%), however, showed only a partial response.

Biologic treatment

Biologic agents studied in the treatment of AIDS-KS include interferon alpha-2a and interferon alpha-2b, bevacizumab, thalidomide, matrix metalloproteinase inhibitors like COL-2, and interleukin 12.[31-38] The interferon alphas were among the first biologic agents used in the treatment of AIDS-KS following trials in the 1980s before the advent of HAART.[4] Little is known about how they suppress AIDS-KS lesions although this may be linked to the antiproliferative and immunomodulatory properties.

In two separate studies amongst AIDS-KS patients, the interferon alphas showed response rates of 33-45% and 3-33% at high and low doses respectively, depending on the extent of the disease, earlier treatment with chemotherapy, history of opportunistic infections, CD4 count, beta-2-microglobulin level, and the presence of circulating interferon.[31,32] There was significantly more toxicity in the patients given high doses. This high dose monotherapy is rarely given today; rather the drug is given in combination with other antiretroviral drugs.[2] High dose monotherapy is also associated with other morbidites such as neutropenia and the response is quite slow, maximal after 6 months hence it is not advisable for rapidly progressive symptomatic AIDS-KS. Bevacuzimab is a monoclonal antibody against vascular endothelial growth factor-A (VEGF-A), a factor known to contribute to the pathogenesis of Kaposi sarcoma. A phase II study of bevacuzimab in AIDS-KS patients showed a response in 5 out of 16 patients who did not improve with HAART and chemotherapy.[33] Thalidomide is another therapeutic agent which is known to inhibit angiogenesis associated with tumour progression, partially by inhibiting fibroblast growth factor. When administered to a 14 year old girl with AIDS-KS oral ulcers, thalidomide was associated with regression of the lesions, disappearance of the KS-associated herpes virus DNA from the blood, and a reduced viral load in the

AIDS-KS tumour sample.[34] COL-2, a topical MMP inhibitor showed 44% response in a clinical trial but with poor tolerance by patients.[35] Matrix metalloproteinases (MMPs) help angiogenesis by breaking down extracellular matrix. Although they are involved in wound healing, MMPs can be associated with malignant tumours, and are expressed in KS.[36,37] Interleukin-12 enhances type I T-cell responses and exhibits anti-angiogenic effects.[38] A phase I pilot study of interleukin 12 showed 71% partial or complete response in 24 patients with AIDS-KS whose tumour was progressing while on HAART.[38]

Antiviral therapy

Antiviral medication targeting Kaposi sarcoma associated herpes virus with cidofor has not been demonstrated to be effective by itself in the treatment of AIDS-KS.[39,40]

CONCLUSION

The aggressive progression of AIDS-KS demands early and prompt diagnosis of the disease with its varied manifestations, and the immediate commencement on HAART and, where necessary, as in late disease, effective adjuvant treatment. In sub-Saharan Africa, there is difficulty in readily accessing these expensive medication therefore more research is needed to discover a more affordable yet and equally effective treatment strategy.

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