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Clinical aspects and management of AIDS-related Kaposi's sarcoma

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Abstract

AIDS-related Kaposi's sarcoma (KS) is a tumour of vascular endothelium, which is seen predominately in men who have sex with men. The majority of affected individuals have advanced immunosuppression at the time of the initial KS diagnosis. The disease may present with cutaneous lesions, or with involvement of visceral organs, of which the gastrointestinal tract is most common. KS may also present with lymphoadenopathy or with isolated lymphoedema, even in the absence of cutaneous lesions. Affected individuals are uniformly co-infected with HIV and with Human Herpesvirus type 8 (HHV8). HHV8 is present within KS tissues, and is aetiological in the pathogenesis of disease, along with aberrant cytokine expression, production of multiple angiogenic peptides, and immune dysregulation. While not presently curable, multiple treatment options exist and must be evaluated in terms of the specific needs of the individual patient. Various local therapies are aimed at eradicating small lesions, while acknowledging that the KS in general, or its likelihood of recurring will be unaffected. Systemic chemotherapy is used to treat extensive visceral involvement. Knowledge of the pathogenesis of disease has led to the development of novel treatment strategies, aimed at HHV8 as the target of therapy, or at the inflammatory cytokine or angiogenic milieu necessary for KS growth. Use of highly active anti-retroviral therapy, aimed at controlling the underlying HIV infection, has been associated with a dramatic decrease in the incidence of KS, and may also be useful in the treatment of existing KS disease.

Keywords: Kaposi's sarcoma; AIDS; AIDS-KS; AIDS malignancies; Treatment of KS; Therapy for AIDS-KS

1. Clinical presentation of disease

AIDS-related Kaposi's sarcoma (KS) can be diagnosed at any stage of HIV infection, although it more commonly occurs in the setting of severe immune suppression [1]. KS most frequently presents as cutaneous lesions, which may occur in any site but usually begin in the head and neck area, upper torso or extremities. The lesions may be quite symmetric and often occur in skin lines or creases. These lesions are pigmented, and have a characteristic appearance, ranging from pink to purple, or brown and brownish-black in colour. The lesions can either be flat, plaque-like or nodular, and may vary in size from a few millimetres to several centimetres. Lesions can also coalesce to form large areas of tumorous involvement. These large lesions are often associated with oedema, which is poorly responsive to therapy.

The oral cavity is commonly involved with KS, occurring in approximately 20% at the time of initial diagnosis [2,3]. Oral lesions usually appear as purple or brownish plaques on the soft palate or gingiva. While usually asymptomatic, these lesions can cause pain and discomfort and may bleed quite easily [2]. Involvement of the oral cavity has been associated with KS in other areas of the gastrointestinal tract [3].

Visceral involvement by KS occurs in over 50% of cases, although only a subset of patients become symptomatic. Although any organ may be involved, the gastrointestinal tract is the most common site of extracutaneous KS [1]. Stomach, colon or small bowel may all be affected, while KS in the liver, spleen, pancreas and omentum are also well described. When symptomatic, KS in the gastrointestinal tract most commonly presents with abdominal pain, weight loss or diarrhoea, which may be bloody.

Pulmonary KS is the second most common site of extracutaneous involvement, and is the most life-threatening form of the disease [4]. Patients often present with shortness of breath or cough and haemoptasis may occur. Radiographical findings are quite variable, and may be difficult to differentiate from those found in various opportunistic infections. Isolated or generalised pulmonary nodules may be present, as well as diffuse

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reticular-nodular infiltrates and pleural effusions [2,4]. Gallium and thallium scans may differentiate KS from other infectious aetiologies [5]. The diagnosis of pulmonary KS is usually made at the time of bronchoscopy.

2. Diagnosis

Even though experienced clinicians can often make the diagnosis of KS based upon appearance alone, the lesions of several other entities may look quite similar, such as bacillary angiomatosis or various vasculitides [6]. It is thus important to confirm the initial diagnosis of KS by biopsy.

3. Staging

Early trials of various therapeutic agents for KS were impeded by the lack of a uniform staging system for the disease. Furthermore, prognosis is related to factors other than the tumour burden itself, such as the underlying immunological state of the host and the presence of other HIV-related illnesses. With these concepts in mind, the AIDS Clinical Trials Group (ACTG) devised a staging system, based upon the extent of tumour, the status of the immune system in terms of CD4 cell count and the presence of other systemic HIV-related illness [7]. Employing this 'TIS' staging system (tumour, immunological status, systemic illnesses), Krown and colleagues performed a prospective evaluation, and confirmed the clinical utility of this approach (Table 1) [8].

4. Treatment: general considerations

AIDS-related KS is not currently curable. Moreover, the pace of disease is quite variable, ranging from a very indolent process, requiring little if any therapy, to a rapidly progressive disease, leading to patient demise [1]. Multiple therapeutic options exist, and must be evaluated in terms of the specific needs of the patient in question. Furthermore, these therapeutic options differ in their specific target of therapy. Thus, use of highly active antiretroviral therapy (HAART) is aimed at improving the underlying HIV infection, thereby improving immune function, and this approach has been used in an attempt to treat known KS. Various local therapies are aimed at eradicating small lesions, while acknowledging that the KS in general, or its likelihood of recurring, will be unaffected. Systemic chemotherapy is used to treat extensive visceral involvement, which may not be affected by any other form of treatment. Newer treatment approaches are aimed at Human Herpesvirus type 8 (HHV8) as the target of therapy or at the inflammatory cytokine or angiogenic mileau necessary for KS growth. This area is one of rapid change, with many new options currently under study or recently approved for use in patients with AIDS-related KS.

5. Use of highly active antiretroviral therapy (HAART)

HIV contributes to the pathogenesis of KS by inducing the immunosuppression necessary for the clinical expression of disease. In addition, the HIV *tat* protein induces a number of cytokines known to promote HIV replication, while also inducing KS cell growth, invasion and angiogenesis [9,10]. Suppression of HIV replication or of HIV *tat* protein expression could thus be considered as potential therapeutic targets. Furthermore, with the significant decline in KS incidence coincident with the widespread use of HAART therapy [11], the efficacy of HAART as a specific treatment for KS has been entertained. At this time, no prospective, randomised trials have been completed which address this issue. However, there are several anecdotal reports of KS regression while on HAART alone [12–14].

Table 1
TIS staging system for AIDS-related Kaposi's sarcoma (KS) [7,8]

	Risk status	
	Good risk (0)	Poor risk (1)
Characteristics	All of the following:	Any of the following:
Tumour (T)	Tumour confined to skin and/or lymph nodes and/or minimal oral disease[a]	Tumour-associated oedema or ulceration; extensive oral KS; gastrointestinal KS; KS in other non-nodal viscera
Immune system (I)	CD4 cells $\geqslant 150/mm^3$	CD4 cells $<150/mm^3$
Systemic illness (S)	No history of opportunistic infection or thrush; no B symptoms;[b] performance status $\geqslant 70$ (Karnofsky)	History of opportunistic infection and/or thrush; B symptoms; performance status <70 (Karnofsky); other HIV-related illness (ex: neurological disease, lymphoma)

[a] Minimal oral disease defined as non-nodular KS confined to the palate.
[b] B symptoms: fever, drenching night sweats, and/or $>10\%$ involuntary weight loss.

A recent study of 78 patients with AIDS-related KS, who had previously received specific therapy for KS, sought to determine the time to treatment failure, both before and after the initiation of HAART therapy [15]. The median time to KS treatment failure before starting HAART was 6 months. In contrast, the median time to KS treatment failure from the start of HAART was 1.7 years ($P < 0.0001$). Use of HAART with or without protease inhibitors was equally efficacious. Of interest, loss of HIV viral control (HIV RNA levels > 5000 copies/cc) was associated with a statistically increased risk of requiring therapy for KS, while change in CD4 cell count was not [15].

These data would suggest that effective antiretroviral therapy should be the first attempted therapeutic intervention in patients with newly diagnosed AIDS-related KS.

6. Treatment of localised KS

6.1. Alitretinoin topical gel (Panretin® gel)

This 0.1% topical, patient-administered gel has recently been licensed for use in patients with AIDS-KS and has been associated with a 35–50% response rate [16]. The gel is applied to affected areas two times per day, with a gradual increase to 3 or 4 times per day, depending on the tolerance of the patient. Response may occur between 2 and 14 weeks after the initiation of therapy. Toxicity consists of local skin reactions.

6.2. Local radiation

Local radiation has been used effectively in patients with classic Mediterranean KS and is also efficacious in patients with AIDS-related disease [17]. However, radiotherapy is associated with tissue fibrosis over time and may be problematic in the long-term management of patients with extensive lymphoedema, as is often seen in extensive KS lesions involving the extremities. Furthermore, even relatively low doses of radiation may be associated with significant toxicity in HIV-infected individuals, resulting in mucositis even at doses as low as 120–1800 cGy [18]. None the less, complete remission of local disease may be achieved in 20–70% of cases [17–19].

6.3. Intralesional injections of chemotherapy

Local injections of vinblastine (0.1–0.2 mg) or vincristine (0.1 mg) have been employed in AIDS-KS lesions, resulting in response rates of 70–90% [20,21]. However, hypo- or hyperpigmented scars may remain. Furthermore, these injections are often quite painful.

6.4. Cryotherapy

Liquid nitrogen may be quite useful in the therapy of localised KS lesions, with response rates of approximately 85% using ACTG criteria [1,2,22,23]. Hypopigmented scars may result, however, and local KS recurrence is not uncommon.

6.5. Laser therapy

Photodynamic therapy has also been used effectively in localised KS lesions, based upon the destruction of tumour cells by laser light, after binding of a chemical photosensitiser to these cells [24,25]. While relatively painless and capable of treating multiple lesions at one time, the KS often recurs within months [25].

6.6. Surgical excision

KS is a systemic disease, even though apparently localised at the time of diagnosis. While surgical excision may be associated with excellent local control [1], recurrence at the site of excision is quite common. Furthermore, the likelihood of systemic relapse is unaffected by this means of therapy.

7. Treatment of disseminated disease

7.1. Cytotoxic therapy

Cytotoxic chemotherapy is indicated for patients who have rapidly progressive muco-cutaneous disease causing oedema, ulceration and pain, or in those with symptomatic visceral disease. The most active agents include the vinca alkaloids, bleomycin, anthracyclines and paclitaxel.

The vinca alkaloids which have been evaluated in AIDS-KS include vinblastine, vincristine and, recently, vinorelbine [26–28]. Vinblastine has been associated with major responses in 25% of KS patients, with responses lasting approximately 4 months [26]. The major side-effect of vinblastine is myelosuppression. Vincristine is also effective as a single agent, and is significantly less toxic to the marrow. However, vincristine causes neurotoxicity, similar to that seen with commonly used antiretroviral drugs such as didanosine, stavudine and zalcitabine, and doses must be adjusted accordingly [27]. To offset the toxicity profiles of these two agents, a regimen of alternating weekly vincristine and vinblastine has been studied, with a response rate of 43% [29].

Bleomycin has also been studied as a single agent in AIDS-KS. In a study of 60 patients with AIDS-KS, 48% achieved partial responses with either intramuscular (i.m.) administration of 5 mg/day for 3 days or

continuous infusion at 6 mg/m^2/day for 4 days [30]. A study of 17 patients with AIDS-KS used a 72-h continuous infusion of bleomycin at a dose of 20 mg/m^2/day, repeated every 3 weeks [31]. Partial remissions were seen in 65%, although the median duration of response was only 3 months (range 1–24 months).

Doxorubicin at a dose of 20 mg/m^2 every 2 weeks or 15 mg/m^2 given weekly has resulted in response rates ranging from 10 to 48%. The major side-effects include neutropenia, nausea, vomiting, hair loss and mucositis [32]. Oral etoposide has also shown some efficacy in patients with advanced AIDS-KS [33].

Combinations of low-dose doxorubicin, bleomycin and vincristine (ABV) or BV, administered by vein every 2 weeks, were among the most commonly administered regimens for the treatment of systemic KS at the outset of the epidemic [34–36]. The ABV regimen, consisting of doxorubicin, 10–20 mg/m^2; bleomycin, 10–15 U/m^2; and vincristine, 1–2 mg, has been associated with response rates ranging from 25–88% [34,35]. The BV regimen, consisting of bleomycin, 10–15 U/m^2 and vincristine, 1–2 mg, has been associated with response rates of 23– 72% [35,36]. However, these combinations are associated with myelotoxicity, and their use as first-line treatment has recently been replaced by newly developed liposomal anthracyclines.

8. Liposomal anthracyclines (DaunoXome and Doxil)

Liposomal encapsulation alters drug kinetics, resulting in a prolonged half-life. Furthermore, increased accumulation in KS tissues, as high as 5–50-fold when compared with the normal surrounding tissue, results in enhanced cellular toxicity [37–39]. Liposomally-encapsulated daunorubicin (DaunoXome) and doxorubicin (Doxil) have been studied extensively in the treatment of AIDS-KS [40–44]. The dose limiting toxicity for liposomal daunorubicin is bone marrow suppression, while liposomal doxorubicin is associated with hand/foot syndrome, consisting of pain and erythema of the palms and soles. Compared with combination chemotherapy with ABV or BV, the toxicities of liposomal anthracyclines are substantially reduced [40–44]. Hair loss, in particular, is rare with liposomal preparations. In addition, the incidence of cardiac toxicity, even after high cumulative doses, appears to be reduced.

Liposomal doxorubicin has been studied in both previously treated and untreated patients with advanced KS [42,44]. In previously-treated patients, partial responses of 27% were seen in terms of overall disease response, and 48% by target lesion evaluation.

In two independent phase III studies in KS, both liposomal daunorubicin (40 mg/m^2 intravenously (i.v.) every 2 weeks) and doxorubicin (20 mg/m^2 i.v. every 2 weeks) as single agents had activity equivalent or superior to combinations of ABV or BV, with the duration of response, time to treatment failure and overall survival also similar to that achieved with the combination chemotherapy [41–43]. Based on these large randomised studies, the liposomal agents are now considered first-line therapy in the treatment of patients with advanced AIDS-KS. Liposomal daunorubicin has also been shown to be safe and effective in patients with pulmonary KS [45].

9. Paclitaxel

Preliminary *in vitro* studies have demonstrated that KS cells are highly responsive to low doses of paclitaxel [46], through the induction of apoptosis.

Employing paclitaxel at a dose of 135 mg/m^2 given every 3 weeks as a 3-h infusion, two studies were completed at the National Cancer Institute [46,48]. Attempts were made to increase the dose, if possible [48]. Eligible patients had no or one prior therapy for KS, and needed chemotherapy. The response rates were 65% [46] and 71% [48], including responses in all 5 patients with pulmonary KS [48]. The response rate was similar in both previously treated and untreated cases. The most significant toxicities were hair loss and bone marrow suppression.

In another trial conducted by Gill and colleagues, 56 patients with advanced KS with or without prior therapy were treated at a dose of 100 mg/m^2 given every 2 weeks as a 3-h infusion [49]. The treatment was well tolerated with a lower incidence of neutropenia than reported in other studies. After a median of 10 cycles of therapy, 59% demonstrated a major response to treatment. The median duration of response was 10.4 months and is the longest of any trial reported thus far. Based on the high response rates and long duration of responses seen in these trials, paclitaxel is now considered the treatment of choice in patients who have failed first-line systemic therapy.

10. Pathogenesis-based therapies

KS cells secrete several factors which induce proliferation and migration of endothelial cells, including angiogenic factors basic fibroblast growth factor ((bFGF), vascular endothelial growth (VEGF), interleukin (IL)-8) and cytokines (IL-1, IL-6, Oncostatin-M). These factors, which are critical for the growth and spread of KS, have been targeted for therapeutic development; these include anti-angiogenic agents, retinoic acids and antiviral agents.

11. Anti-angiogenic compounds

11.1. Thalidomide

Thalidomide has been shown to inhibit angiogenesis, to block tumour necrosis factor (TNF)-alpha production, and to inhibit basement membrane formation and intercellular adhesion molecules. Studies of oral thalidomide in AIDS-KS have been performed, starting at a dose of 200 mg/day with dose escalation to 1000 mg/day, based on individual tolerance. 13 patients were studied in one trial; partial response was reported in 6 patients, lasting a median duration of 31 weeks. Toxicities include somnolence, neutropenia, rash, fever, myositis and depression. Three patients were removed from study due to toxicity [50].

11.2. IM-862

IM-862 is a dipeptide that was identified from soluble fractions of the thymus. It appears to have anti-angiogenic effects *in vivo*, as shown in chicken allantoic membrane (CAM) assays. Additional tests in murine tumour models, in syngeneic mice bearing various tumour types, and in human tumour xenografts showed a dose-dependent inhibition of tumour growth. A randomised phase II trial in KS has recently been completed, using a fixed dose of 5 mg, and comparing the regimen given intranasally either every other day or 5 days on followed by 5 days off the drug [51]. Approximately half of the 44 patients treated in this trial had more than 50 mucocutaneous lesions and the majority had previously been treated with chemotherapy for KS. IM-862 was well tolerated, with adverse effects limited to mild and transient headache, fatigue, tingling and nausea. Major responses were documented in 36% of patients, with five complete and 11 partial responses.

12. Retinoids

Retinoic acids (RAs) mediate numerous biological activities by regulating cellular genes, including mediators of the immune response, such as IL-6 and the IL-6 receptor. RAs have been evaluated in KS, and have shown activity in both preclinical and clinical studies. The mechanism of anti-proliferative effects are partially due to inhibition of IL-6 production, mediated by repressing the IL-6 promoter at the NF-IL-6 binding site, with no apparent effect on the IL-6 receptor [52].

Several retinoid compounds have been tested in clinical trials for KS. A topical preparation of all-*trans*-retinoic acid (ATRA) showed high response rates [53]. ATRA as an oral compound has also been studied [54] in 24 patients using a dose escalation scheme to improve patient tolerance. The median dose delivered was 90 mg/m^2 and major response was achieved in 17% after a median of 22 weeks (range 12–28 weeks).

Liposomal encaspulation of ATRA has also been studied in an attempt to prevent the decline in plasma levels seen after prolonged dosing of the oral preparation. In a multicentre trial of 81 AIDS-KS patients, liposomal ATRA was escalated from 60 to 120 mg/m^2, given once or three times a week [55]. A response rate of 23% was observed, with higher response rates with the three times/week dosing.

Recently, oral 9-*cis*-retinoic acid has been tested systemically in a trial of 66 patients conducted by the AIDS-Malignancy Consortium (AMC) [56]. Doses of 60–100 mg per day were given based on patient tolerability. Treatment-related toxicity included headache, fatigue, alopecia, dry skin and elevation of triglycerides, leading to study withdrawal of 15 patients. Major responses were reported in 37%. Antiretroviral therapy, including protease inhibitors were used commonly during this trial, thus complicating the study results in terms of efficacy.

A second trial of 9-*cis*-retinoic acid was conducted in 57 KS patients treated at a dose of 60 mg/m^2, increasing to a maximum of 100 mg/m^2 [57]. Only 37 patients completed the study. The overall response rate was 37%, the median time to response was 8.7 weeks, and median duration of response was 33 weeks. Baseline CD4 count did not influence the probability of response. Patients on HAART had a higher probability of treatment response.

13. Antiviral approaches targeting HHV8

The discovery of HHV8 as the aetiologic agent for KS has raised the possibility of the use of antiviral agents as treatment or prophylaxis for AIDS-related KS. In this regard, *in vitro* drug sensitivity studies have shown that HHV8 is very sensitive to cidofovir, moderately sensitive to ganciclovir and foscarnet, and only weakly sensitive, or ineffective to acylovir [58,59]. Thus far, no prospective study has been completed which evaluates the clinical efficacy of this approach in AIDS-KS. However, a recent prospective randomised trial, aimed at determining optimal maintenance therapy for cytomegalovirus (CMV) retinitis has provided information suggesting that treatment of HHV8 may prevent the development of KS [60]. In this trial, patients were randomised to receive either a ganciclovir retinal implant alone, or the implant with additional systemic ganciclovir. Patients randomised to receive systemic ganciclovir had a statistically decreased risk of developing KS over time. The concept that one could treat lytic HHV8 infection with ganciclovir, and in so doing positively affect the development of a tumour is clearly intriguing, and further work is expected.

14. Interferon-alpha

Interferon-alpha (IFN-α) was the first agent approved for use in AIDS-related KS, and has been shown to have immunomodulatory, antiviral and anti-angiogenic effects. Furthermore, IFN-α also potentially inhibits infection or reactivation by HHV 8 [61]. When used as a single agent, doses as high as 36–50 million units/m^2/day are required, leading to response rates of 30–50% [62–64]. Toxicity is rather significant at these doses, including flu-like symptoms such as malaise, fatigue, myalgia and headache, as well as significant bone marrow suppression. When used together with anti-retroviral agents, the dose of IFN-α may be decreased considerably, ranging from 1 to 10 million units per day, with equal or superior efficacy against KS [65,66]. While effective in disseminated KS, these combinations may require several months for the onset of tumour response, and are thus not advocated for patients with rapid tumour progression.

15. Conclusions

KS is a fascinating disorder, whose pathogenesis is multifactorial, including prior infection by HHV8 and underlying immunosuppression, occurring within the setting of an abnormal milieu of inflammatory cytokines and angiogenic peptides. While various traditional chemotherapeutic approaches may be effective in patients with disseminated KS, newer concepts of therapy are aimed at targeting the factors associated with the pathogenesis of disease. Thus, the use of HAART aimed at the underlying HIV-induced immunosuppression, has been associated with a dramatic decrease in the incidence of KS, and may also be effective in treating known disease. Various anti-angiogenic peptides have been shown to be useful in the therapy of AIDS-related KS, while specific approaches aimed at HHV8 itself are currently under study. The clinical study of KS thus permits an evaluation of pathogenesis-based therapeutic interventions, which may serve as a model for treatment paradigms of the future.

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