Management of AIDS-related Kaposi's sarcoma

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The advent of highly active antiretroviral therapy (HAART) has lead to a substantial reduction in the prevalence, morbidity, and mortality associated with AIDS-related Kaposi's sarcoma. Similarly, concomitant advances in chemotherapy and supportive-care protocols have allowed for Kaposi's sarcoma to be managed more effectively in comparison with the pre-HAART era. Furthermore, developments in our understanding of the pathogenesis of Kaposi's sarcoma have identified several molecular targets that can potentially provide new therapeutic strategies. This Review discusses the role of conventional chemotherapeutic and immunomodulatory agents in the treatment of Kaposi's sarcoma and summarises the current status and future prospects of novel molecularly targeted agents in the treatment of this disease.

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Introduction

Before the advent of highly active antiretroviral therapy (HAART), the prevalence of Kaposi's sarcoma was over 20 000 times higher in patients with AIDS than in the general population.[1] HAART has led to a substantial decline in the prevalence of AIDS-related Kaposi's sarcoma, and patients undergoing HAART show a less aggressive presentation with significantly decreased overall morbidity and mortality.[1–3] This situation contrasts starkly with the situation in certain geographical areas, such as sub-Saharan Africa, where HAART is not readily available. In these regions, Kaposi's sarcoma has reached epidemic proportions, and patients with AIDS-related Kaposi's sarcoma have high tumour burden with rapid disease progression, resulting in a life expectancy of less than 6 months.[4]

The clinical presentation of AIDS-related sarcoma is highly variable, ranging from minimum disease (often presenting as an incidental finding) to explosive growth resulting in significant morbidity and mortality. Skin lesions (the most frequent manifestation of Kaposi's sarcoma) appear most often on the feet, legs, face (especially on the nose), and genitalia. Such lesions are usually papular, ranging from several millimetres to centimetres in diameter. Less commonly, they can be plaque-like, especially on the thighs and soles of the feet (figure 1), or exophytic and fungating with breakdown of the overlying skin. Early lesions (patch stage; figure 2) can develop into more advanced (plaque stage) as the lesional cells proliferate and affect more of the dermis. These lesions can eventually become ulcerating tumours (nodular stage; figure 3).

Lymphedema can be extensive and disproportionate to the extent of the cutaneous disease, especially in the lower extremities, face, and genitalia. Extracutaneous spread is common, especially in patients not undergoing HAART (figure 4). Kaposi's sarcoma in the oral cavity occurs in about a third of patients,[5] and gastrointestinal involvement can be found in about 40% at initial diagnosis (figure 5) and in up to 80% at autopsy, even in the absence of cutaneous disease.[6] Pulmonary Kaposi's sarcoma is also common, and can present as shortness of breath, fever, cough, haemoptysis, chest pain, or as an asymptomatic finding on chest radiograph.[7]

Initial assessment consists of a thorough physical examination with special attention paid to areas typically affected by the disease. Occult blood testing is an excellent screening method for gastrointestinal tract lesions, and endoscopy should be reserved for patients with gastrointestinal symptoms. Pulmonary symptoms or an abnormal chest radiograph should warrant consideration for bronchoscopy. In 1988, the AIDS Clinical Trials Group proposed a staging system that classified patients into

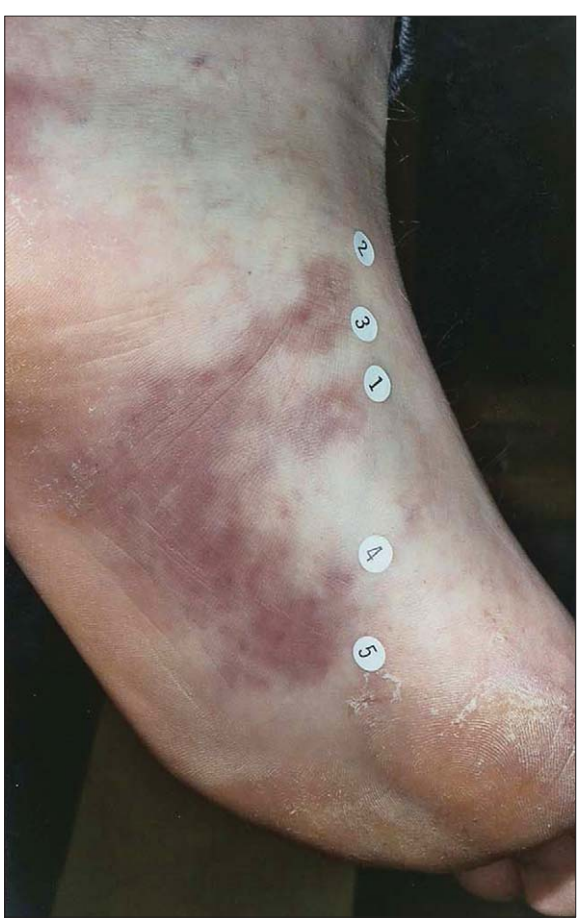

Figure 1: **Cutaneous Kaposi's sarcoma**
Erythematous irregular plaques of the foot (numbers are used to monitor response of individual lesions to treatment). Reproduced with permission from ref 3.

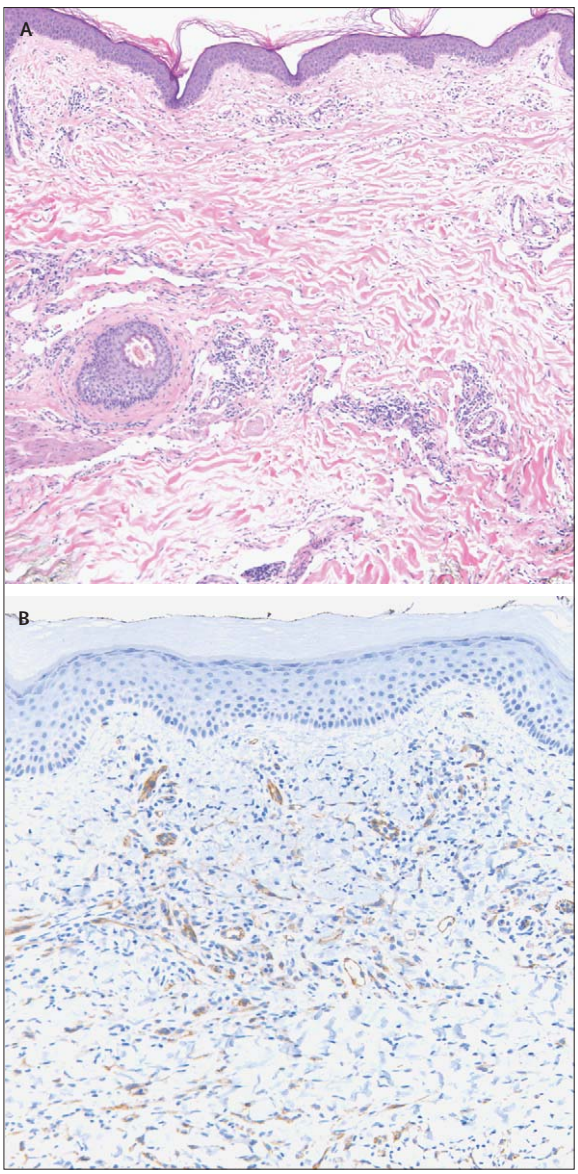

Figure 2: **Photomicrographs of cutaneous Kaposi's sarcoma**
(A) Patch stage cutaneous Kaposi's sarcoma lesion showing dilated dermal vessels and mild chronic inflammation (stained with haematoxylin and eosin, magnification ×100). (B) CD31 immunohistochemical stain shows fine abnormal vessels in a patch stage cutaneous Kaposi's sarcoma (magnification ×200).

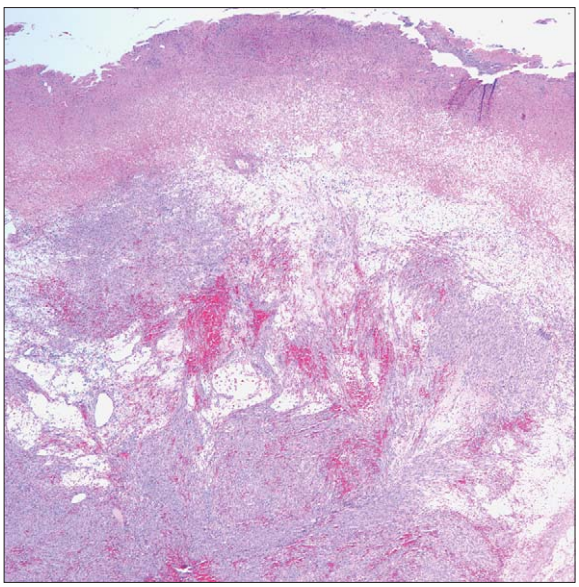

Figure 3: **Nodular Kaposi's sarcoma tumour with overlying oedema and surface ulceration**
(Stained with haematoxylin and eosin, magnification ×40).

good and poor risk categories on the basis of tumour extent (T), severity of immunosuppression as measured by the CD4+ T-lymphocyte count (CD4 count; I), and the presence of any other systemic HIV-associated illness (S).[8] A prospective assessment of this staging system undertaken in the HAART-era (the period of time during which HAART has been readily available) showed that the combination of poor tumour stage (T1) and poor systemic-disease state (S1) adequately identified patients with unfavourable outlooks.[9] The 3-year survival rate of patients with a combination of these adverse prognostic factors (ie, T1S1) was significantly lower (53%) than that of patients without any of these factors (88%) or with only one factor (80% for S1 alone; 81% for T1 alone; p=0·0001).[9]

The major treatment goals for Kaposi's sarcoma include symptom palliation, shrinkage of tumour to alleviate oedema, management of organ compromise and psychological stress, prevention of disease progression, and, perhaps, cure. Treatment decisions depend on the presence and extent of symptomatic and extracutaneous sarcoma, the HIV-1 viral load, and the host status (CD4 count and overall medical condition). A prognostic index for the AIDS-associated disease can be used to help guide therapeutic options.[10] In addition to immune status, measured by CD4 count, other important prognostic factors taken into account when using this prognostic index include patient age, occurrence of the tumour at or after AIDS onset, and the presence of comorbid conditions. This study suggests that patients with Kaposi's sarcoma, with a poor prognostic index, should be treated initially with HAART and systemic chemotherapy, or alternatively be considered for entry into clinical studies with novel agents.[10] However, patients with a favourable prognostic index should initially be treated with HAART alone.

HAART

Most, if not all, patients with Kaposi's sarcoma should receive antiretroviral treatment, assuming access to such treatment is available.[11] Effective antiretroviral regimens are associated with both a reduction in the incidence of AIDS-related sarcoma and a regression in size and number of existing lesions. Histological regression of

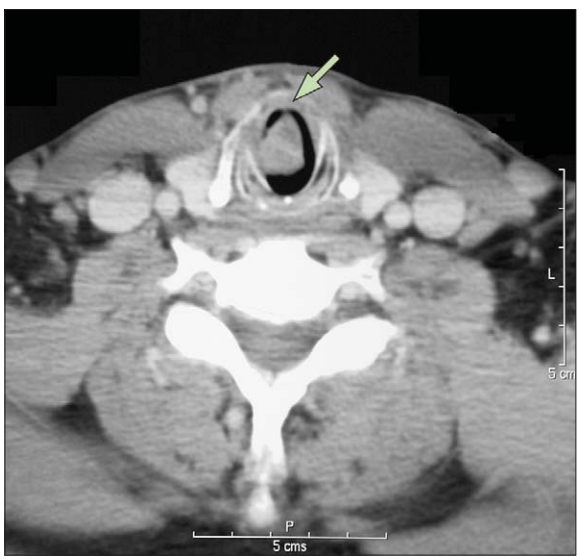

Figure 4: **CT showing exophytic, subglottic, biopsy-proven Kaposi's sarcoma tumour (arrow)**
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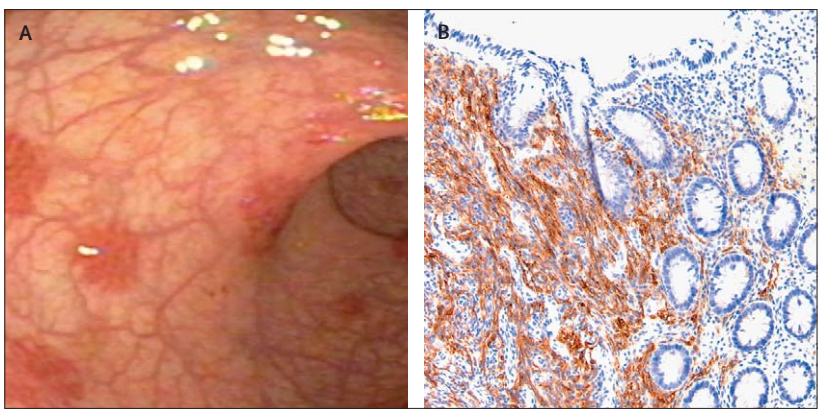

Figure 5: **Kaposi's sarcoma of the colon**
(A) Nodular lesions seen on endoscopy. Reproduced with permission from ref 81. (B) D2-40-positive Kaposi's sarcoma cells infiltrating the colonic lamina propria (magnification ×200). D2-40-immunoreactivity supports a lymphatic endothelial origin for Kaposi's sarcoma cells.

existing lesions has been shown in response to HAART.[12] The effects of HAART on Kaposi's sarcoma are multifactorial and include inhibition of HIV replication, diminished production of HIV-1 transactivating protein Tat, amelioration of immune response against Kaposi's sarcoma herpes virus or human herpes virus 8 (KSHV/HHV8), and possibly direct antiangiogenic activity by inclusion of protease inhibitors.[13–18]

The effect of HAART is shown by a large, Swiss cohort study of patients infected with HIV.[19] In this cohort, the risk of developing Kaposi's sarcoma between 1997 and 1998 (HAART-era) compared with a pre-HAART era between 1992 and 1994 was 0·08 (hazard ratio; 95% CI 0·03–0·22), representing a substantial reduction in this AIDS-defining malignant disease. In another large study,[1] the incidence of various cancers of 375 000 people with AIDS was compared with that of the general population, yielding a standardised incidence ratio. The incidence ratio for Kaposi's sarcoma fell sharply from 22 100 (pre-HAART era; 1990–1995) to 3640 (HAART-era; 1996–2002). Furthermore, both protease inhibitor-based HAART regimens and standard HAART regimens based on non-nucleoside reverse transcriptase inhibitors have been shown to be equally effective in protecting against Kaposi's sarcoma, although their activities in treatment have not been compared prospectively.[20,21] Patients with AIDS and sarcoma treated with HAART sometimes have a longer remission period, reported to last more than 5 years in certain poor-risk individuals.[14] Finally, combination of HAART with other treatment modalities (ie, local treatment, systemic chemotherapy, immunotherapy, biological treatment, and radiotherapy) can increase the period of effectiveness of these treatments.[22]

Immune reconstitution inflammatory syndrome is a well-recognised clinical entity in which paradoxical worsening of stable, opportunistic infections and neoplasms takes place in the setting of HAART-induced recovery of the immune system (ie, rapid decline in HIV-1 viral load and marked increase in CD4 count).[23] In a British cohort of 150 patients who had never received HAART and were subsequently given the regimen to treat HIV infection, ten (7%) patients developed new lesions and had accelerated progression of established lesions during the first 2 months of treatment.[24] This observation is consistent with Kaposi's sarcoma-associated immune reconstitution inflammatory syndrome, which had been described previously.[25]

Local treatment

Regional therapeutic approaches are most useful for the management of localised bulky Kaposi's sarcoma lesions or for cosmesis, but are limited by the fact that they do not affect the development of new lesions in untreated areas.

Radiotherapy can effectively palliate symptomatic disease that is not extensive enough to warrant systemic treatment but is too extensive to be treated with intralesional chemotherapy.[26,27] For some patients with painful, isolated lesions—eg, heavily affected toes—whose poor performance status or hepatic function preclude chemotherapy, radiotherapy might be the only viable option. A retrospective study of patients with AIDS-related sarcoma treated with radiotherapy doses of 8·0 Gy reported an objective response of 74%.[28] In another study of 36 patients with sarcoma of the feet, a schedule of three fractions a week at 3·5 Gy per fraction up to a total dose of 21·0 Gy yielded an overall response in 40 lesions of 91% with a complete response in 35 lesions (80%).[26] Although discomfort from radiotherapy is frequent, it usually resolves without intervention within 2 weeks of completion of treatment. In one series of

576 patients with AIDS-related sarcoma treated with radiotherapy, severe skin reactions—eg, exudative epidermitis and skin ulceration—occurred in 323 (5%) of the 6464 cutaneous lesions.[29] Late radiation sequelae for Kaposi's sarcoma can include skin damage, hypopigmentation, fibrosis, and lymphedema,[30] but are rarely reported in the published work. In a retrospective review of 30 patients with classic Kaposi's sarcoma treated with radiotherapy, seven (23%) had substantially increased oedema, chronic skin breakdown, and severe dermatitis, resulting in the need for multiple surgical corrective procedures in some cases.[31] For patients with mucosal lesions, a high degree of mucositis was often noted after low doses of radiotherapy.[29,32]

The only topical, self-administered treatment approved for the treatment of Kaposi's sarcoma is 0·1% alitretinoin gel. Alitretinoin is a naturally occurring retinoid, which, in a randomised phase III study, was associated with a shorter time to tumour response, and lengthened duration of response and time to disease progression compared with a placebo gel.[33] However, alitretinoin gel can cause dermal irritation and skin lightening at the application site. Responses were noted in patients with a wide variety of CD4 counts and were usually after 4–8 weeks of treatment.

Other local treatments include intralesional chemotherapy, cryotherapy, laser treatment, photodynamic treatment, and excisional surgery, all of which can control local tumour growth. Vinblastine is possibly the most widely used intralesional agent and has a very good response rate of about 70%.[34] Treated lesions usually fade and regress, although they do not usually resolve completely. Intralesional injections of biological agents, such as interferon-alfa, have also shown activity but are now seldom used.

Cryotherapy can be especially effective in the management of local sarcoma lesions. Complete responses were recorded in 80% of lesions treated with cryotherapy, and the duration of response was more than 6 weeks. Of note, greater than 50% cosmetic improvement was reported in that study.[35]

An alternative experimental approach is photodynamic treatment, which is based on activation by light of a photosensitising drug that preferentially accumulates in tumour tissue.[36] In a series of 25 patients with a total of 348 lesions who received photofrin 48 h before light activation, 96% of the lesions responded to treatment (33% complete response, 63% partial response).[37]

Cytotoxic chemotherapy

Systemic cytotoxic chemotherapy is warranted in patients with advanced or rapid progressive disease. The decision to initiate systemic chemotherapy is based not only on the extent of Kaposi's sarcoma, but also on other parameters such as patient performance status, end organ function (especially liver and bone marrow), degree of immunosuppression (CD4 count), and concomitant medications. Typical indications for systemic treatment include: widespread skin involvement (eg, more than 20 lesions); extensive Kaposi's sarcoma of the oral cavity; symptomatic pedal or scrotal oedema; symptomatic visceral involvement; and flare induced by immune reconstitution inflammatory syndrome. The prognostic score can help guide treatment decisions.[10] Although several chemotherapeutic agents—ie, bleomycin, vinblastine, vincristine, doxorubicin, and etoposide—have been shown to be active in the past, liposomal anthracyclines and taxanes constitute the backbone of current systemic cytotoxic treatment against Kaposi's sarcoma. Two liposomal anthracyclines—pegylated liposomal doxorubicin and liposomal daunorubicin—and paclitaxel are the only systemic chemotherapeutic agents approved for treatment of the disease.

Liposomal anthracyclines

Encapsulation of conventional doxorubicin in pegylated liposomes preferentially distributes the drug into tumours that have abnormal blood vessels with high vascular permeability, which helps with the extravasation of liposomes.[38] Moreover, the liposomal formulation of the anthracyclines provides a theoretical advantage of longer plasma half-life and less toxicity in non-target organs compared with conventional anthracycline chemotherapy.

Liposomal anthracyclines are the best chemotherapeutic option for most patients with widely disseminated Kaposi's sarcoma. Two randomised trials, done before the wide availability of HAART, showed that pegylated liposomal doxorubicin was better than both combination of adriamycin, bleomycin, and vincristine (ABV) and combination of bleomycin and vincristine (BV; table 1). In the first study,[40] 258 patients who had not undergone previous chemotherapy were randomly assigned to receive either pegylated liposomal doxorubicin (20 mg/m^2) or ABV given every 2 weeks. The overall response was significantly better with pegylated liposomal doxorubicin than with ABV (46% *vs* 25%, respectively, p<0·001); time to response was shorter with pegylated liposomal doxorubicin than with ABV (39 days *vs* 50 days, respectively, p=0·014), and more patients discontinued ABV because of an adverse event. Neither the median duration of response nor the median overall survival differed between the treatment groups.[39] Moreover, the pegylated liposomal doxorubicin group was associated with a greater improvement in the overall quality of life than the ABV group.[40]

In the second study,[41] 241 patients who had not undergone previous systemic chemotherapy were randomised to receive either pegylated liposomal doxorubicin (20 mg/m^2) or BV. Both regimens were administered every 3 weeks for six cycles. Overall response (complete and partial responses) was significantly higher with pegylated liposomal doxorubicin than with AV (59% *vs* 23%, respectively, p<0·001), as was the end-of-treatment response (39% *vs* 14%, respectively, p<0·001).

Design	Regimen	Patients	Results	Ref
Randomised phase III trial	PLD (20 mg/m^2) *vs* ABV every 2 weeks for 6 cycles	n=258; no previous anthracycline chemotherapy	ORR: 46% (PLD) *vs* 25% (ABV) Similar median response duration and overall survival Less alopecia, neuropathy, nausea, and vomiting in PLD group Greater improvement in quality of life in PLD group	39,40
	PLD (20 mg/m^2) *vs* BV every 3 weeks for 6 cycles	n=241; no previous BV chemotherapy	ORR: 59% (PLD) *vs* 23% (BV) Similar median response duration and overall survival Significantly greater improvements in lesion thickness, nodularity, oedema, colour, pain, and size in PLD group Less neuropathy in PLD group	41
	Liposomal daunorubicin (40 mg/m^2) *vs* ABV every 2 weeks	n=232; no previous systemic chemotherapy	ORR: 25% (liposomal daunorubicin) *vs* 28% (ABV) Similar time to treatment failure and overall survival Less alopecia and neuropathy in liposomal daunorubicin group	42
Phase II trial with dose escalation	Paclitaxel (135–175 mg/m^2) every 3 weeks	n=29; with and without previous systemic chemotherapy	ORR: 71% All patients with pulmonary Kaposi's sarcoma responded (n=5) All patients who had previously received anthracycline treatment responded (n=4)	48
Phase II trial	Paclitaxel (100 mg/m^2) every 2 weeks	n=107; previous failed chemotherapy	ORR: 56% Median duration of response=8·9 months Significant improvements seen in total quality-of-life scores and Karposi's sarcoma-related symptoms, such as facial disease, tumour-associated oedema, and pulmonary involvement	47

PLD=pegylated liposomal doxorubicin. ORR: overall response rate (defined as complete and partial response rate). ABV=adriamycin, bleomycin, and vincristine. BV= bleomycin and vincristine.

Table: **Mature trials of chemotherapeutic agents for the treatment of Kaposi's sarcoma**

Pegylated liposomal doxorubicin produced significantly greater improvements in lesion thickness, nodularity, oedema, colour, pain, and size than did BV. Mortality was similar in the two groups.

The efficacy of liposomal daunorubicin in comparison with ABV was assessed in a randomised phase III trial[42] in which 232 patients randomly received either liposomal daunorubicin (40 mg/m^2) or ABV. Although the overall response was 25% (three complete responses and 26 partial responses) for liposomal daunorubicin and 28% (one complete response and 30 partial responses) for ABV, and, therefore, not significantly different in the two groups, the patients treated with liposomal daunorubicin had less alopecia and neuropathy. Time to treatment failure, and overall survival were similar in both groups. In another small trial,[43] patients were randomly assigned to either pegylated liposomal doxorubicin (20 mg/m^2) or liposomal daunorubicin (40 mg/m^2) every 2 weeks for up to six cycles. Although this study was underpowered statistically, differences in clinical benefit and tumour response tended to favour pegylated liposomal doxorubicin (60 patients) over liposomal daunorubicin (19 patients).

Finally, the safety, tolerability, and efficacy of the combination of pegylated liposomal doxorubicin and HAART have also been assessed in a trial of 54 patients with AIDS-related Kaposi's sarcoma.[44] 44 (82%) of the patients had a complete or partial response within a median of 8 weeks and the combination of pegylated liposomal doxorubicin and HAART was well tolerated.

For treatment, the usual dose of pegylated liposomal doxorubicin is 20 mg/m^2 every 3 weeks and the usual dose of liposomal daunorubicin is 40 mg/m^2 every 2 weeks. Side-effects from these agents are usually mild. Alopecia and neuropathies are unusual with these liposomal agents as opposed to conventional chemotherapy. Even at high cumulative doses these agents do not usually cause the cardiomyopathies that have restricted the use of non-liposomal anthracyclines.[44,45]

Taxanes

Taxanes prevent the growth of neoplastic cells by inhibiting depolymerisation of microtubules. Additionally, taxanes promote apoptosis and downregulate bcl-2 protein expression in sarcoma cells in vitro and in mice. Of importance is the fact that taxanes inhibit angiogenesis, which plays a pivotal role in the pathogenesis of Kaposi's sarcoma.[46]

Paclitaxel, approved in the USA for treatment of Kaposi's sarcoma, has shown striking efficacy, even in patients with anthracycline-resistant disease. Two phase II trials (using paclitaxel at doses of 135–175 mg/m^2 every 3 weeks or 100 mg/m^2 every 2 weeks) showed overall response rates of 71% and 56%, respectively, for patients in whom at least one previous chemotherapeutic regimen had failed.[47,48] The median durations of response were 8·9 and 10·4 months, respectively. The most frequent toxic effect reported in these trials was neutropenia, which generally resolved before the next cycle of treatment. Nevertheless, the high prevalence rates of alopecia, myalgias, arthralgias, and myelosuppression, and the need for a 3-h infusion, make paclitaxel less attractive than pegylated liposomal doxorubicin as initial systemic treatment. Corticosteroid administration to prevent paclitaxel-associated allergic reactions raises concerns over exacerbation of pre-existing lesions or induction of new lesions. Data exist

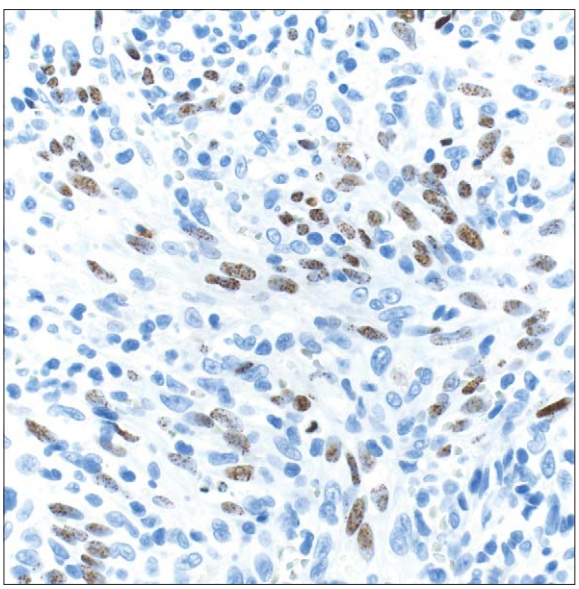

Figure 6: **Human herpesvirus 8 shown by brown, stippled, nuclear immunoreactivity in Kaposi's sarcoma lesional cell nuclei**
(Stained with latent nuclear antigen-1, magnification ×600).

supporting the premise that KSHV/HHV8 is activated in corticosteroid-treated immunocompromised patients.[49] Administration of 20 mg of dexamethasone intravenously 30 min before giving paclitaxel or 10 mg orally 12 and 6 h before paclitaxel administration is recommended.

Notably, there might be a pharmacokinetic interaction between paclitaxel and antiretroviral agents, especially protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Paclitaxel is metabolised extensively by the hepatic P450 microsomal system. Concomitant use of inhibitors and activators of the liver cytochrome P450 CYP3A4 enzyme system can affect paclitaxel metabolism and its subsequent antitumour activity and toxic effects. Protease inhibitors are inhibitors of the P450 CYP3A4 enzyme system, whereas certain non-nucleoside reverse transcriptase inhibitors (eg, delavirdine) are inhibitors, and others (eg, efavirenz, nevirapine) are inducers of this system. In these settings, appropriate dose modifications might be necessary.

Although clinical experience with docetaxel is more limited than that of paclitaxel, small studies suggest that this alternate taxane can produce meaningful responses. A study[50] of low-dose, weekly docetaxel reported a 42% response rate (5 of 12 patients) in those with AIDS-related Kaposi's sarcoma at an advanced stage, although severe neutropenia was frequent. In that trial, docetaxel seemed to have activity even in patients who had failed previous paclitaxel, resulting in a partial response in one of four such patients and stable disease in two. In a small study of patients who had previously not responded well to anthracycline treatment, seven of nine patients treated with docetaxel (60 mg/m^2 every 3 weeks) responded, although, again, severe neutropenia was frequent.[51]

Immunotherapy

The biological response modifier interferon alfa was approved for the treatment of Kaposi's sarcoma many years before the availability of the liposomal anthracyclines and HAART. The response to interferon alfa is much higher in patients with asymptomatic HIV infection and in those with CD4 counts greater than 200 cells/mm^3. Therefore, patients who have attained appropriate immune reconstitution with HAART, and especially those with residual cutaneous Kaposi's sarcoma, can be considered for systemic treatment with interferon alfa.

The AIDS Clinical Trials Group assessed the efficacy and safety of low-dose and high-dose interferon alfa (1 million and 10 million units daily, respectively) combined with didanosine. In a 68-patient study,[52] the response rates of 40% in the low-dose group and 55% in the high-dose group were not significantly different. In another randomised study,[53] 108 patients were treated with zidovudine and interferon alfa (1 million or 8 million units daily). In that study, the higher dose regimen was associated with a higher response rate than the lower dose regimen (31% *vs* 8%, respectively) and longer time to progression (18 *vs* 13 weeks, respectively). In a trial comparing pegylated liposomal doxorubicin with low-dose interferon alfa,[54] 12 patients received 20 mg/m^2 of the liposomal doxorubicin once a month, whereas six patients received 3 million units of interferon alfa three times weekly. Pegylated liposomal doxorubicin was clearly better than interferon alfa in terms of response and toxic effects ($p<0·05$).

Continued treatment for 6 months or more is often needed for a response to interferon alfa. Because the time taken for this response is long (more than 4 months), interferon alfa should not be used in rapid progressive or visceral disease. Furthermore, interferon alfa treatment, especially at higher doses, is often associated with substantial systemic toxic effects, including fever, chills, fatigue, neutropenia, hepatotoxicity, and cognitive impairment. Poor tumour response and higher toxicity is most striking in patients with CD4 counts less than 200/mm^3. For these reason, interferon alfa is not frequently used for the treatment of Kaposi's sarcoma.

Molecularly targeted agents

The pathogenesis of AIDS-related sarcoma is driven by infection of endothelial cells by the gamma herpes-virus KSHV/HHV8 (figure 6).[55] The oncogenic role of KSHV/HHV8 is associated with expression of several viral protein products including those that are homologous to human interleukin-6, interleukin-8 receptor, chemokines of the macrophage inflammatory protein family, cell-cycle regulators of the cyclin family, and antiapoptotic proteins of the bcl-2 family.[56–58] Numerous sequential and parallel cellular signalling pathways are activated by KSHV/HHV8 viral proteins and, ultimately, lead to the creation of an angiogenic-inflammatory state, which is the crucial step in the pathogenesis of Kaposi's sarcoma.[59]

Clarification of the role of the multiple signalling pathways in the pathogenesis has lead to the identification of molecularly targeted treatments for this disease.

Angiogenesis inhibitors

Vascular endothelial growth factor (VEGF) and VEGF-receptor signalling have a central role in the development of the disease. Lesions express VEGF-C and its receptors VEGFR-2 and VEGFR-3.[60–62] Additionally, expression of the human herpesvirus-8 G-protein-coupled receptor, an interleukin-8 receptor analog encoded by KSHV/HHV8, leads to the activation of VEGFR-2 and induction of hypoxia inducible factor-1-alpha-mediated expression of VEGF-A.[62,63] Furthermore, in a murine model, viral interleukin-6, a KSHV/HHV8 encoded human interleukin-6 homolog, upregulates expression of VEGF and is associated with accelerated tumour growth.[64] The prominent role of angiogenesis in the development of lesions has prompted the assessment of several anti-angiogenic agents for the treatment of the disease.

Thalidomide (approved for the treatment of myeloma) has substantial antiangiogenic activity, partly through inhibition of basic fibroblast growth factor-induced angiogenesis. A phase II study[65] of thalidomide in AIDS-related Kaposi's sarcoma showed a partial response in eight of 17 (47%) patients with a median response duration of 7 months. Side-effects included myelosuppression, neuropathy, fatigue, depression, and mucositis. TNP-470, a semisynthetic fumagillin analog, which also inhibits basic fibroblast growth factor, was assessed in a phase I trial.[66] The drug was well tolerated, and seven of 36 (18%) patients responded. In view of the prominent role of VEGF expression, secretion, and related signal transduction in the development of Kaposi's sarcoma, other treatments (eg, bevacizumab, a monoclonal antibody against VEGF) might have a role in treating this disease.

Tyrosine kinase inhibitors

Platelet-derived growth factor (PDGF), platelet-derived growth-factor receptor (PDGFR), stem-cell factor (SCF), and c-kit pathways are important in the pathogenesis of Kaposi's sarcoma.[67] C-kit and PDGFR are members of the type III receptor tyrosine kinase family. Expression of PDGF and PDGFR has been well described, and depletion of PDGF in Kaposi's sarcoma cell cultures inhibits cellular growth.[68] Furthermore, lesions express c-kit, and KSHV-infected endothelial-cell cultures proliferate in response to SCF, the ligand for c-kit.[69]

The importance of the PDGF and c-KIT pathways in Kaposi's sarcoma has been validated in a clinical study of the PDGF-R and c-KIT inhibitor imatinib mesylate (approved for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumour).[70] Ten patients with AIDS-related Kaposi's sarcoma, whose disease progressed despite chemotherapy or HAART, received oral imatinib. Clinical response was established by serial tumour measurements. Biological and histological effects of treatment were identified by skin-lesion biopsies obtained at baseline and after 4 weeks of treatment. Substantial clinical and histological tumour regression was noted, and this regression was correlated with inhibition of PDGFR and its downstream effector, extracellular receptor kinase, a member of the mitogen-activated protein kinase family. On the basis of this favourable outcome, a larger trial using imatinib to treat Kaposi's sarcoma is currently in progress. The activity of the tyrosine kinase inhibitors sorafenib and sunitinib in the disease is unknown, but clinical trials with biological endpoints could help establish their function.

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMP) are a family of zinc-dependent endopeptidases and have a role in the destruction of extracellular matrix proteins. MMP-2 (gelatinase A) and MMP-9 (gelatinase-B) degrade collagen IV, the major component of basement membranes. Overexpression of endothelin-1 in lesions and the HIV-1 transactivating protein Tat upregulate the synthesis and secretion of MMPs from endothelial and inflammatory cells.[71,72] MMPs help tumour invasion, metastasis, and angiogenesis, and are constitutively overexpressed in sarcoma cells.[73]

Col-3, a chemically modified tetracycline, is a matrix metalloproteinase inhibitor that is distinct in its ability to inhibit the activity, activation, and production of MMPs, whereas other inhibitors of MMPs target only the active enzyme.[74] In a phase II study[75] done by the AIDS Malignancy Consortium of the US National Cancer Institute, one of two doses of Col-3 (50 mg and 100 mg) was given orally once a day to 75 patients with AIDS-related Kaposi's sarcoma, whose disease had progressed despite chemotherapy or HAART. Most patients (29 of 37; 79%) gained clinical benefit from low dose Col-3 (two having complete response, 13 partial responsers, and 14 with stable disease). In the 38 patients who received high dose Col-3, there was one with a complete response, ten partial responsers, and 13 with stable disease. Importantly, there were significant declines in MMP-2 and MMP-9 plasma concentrations with treatment (MMP-2, $p<0{\cdot}001$; MMP-9, $p=0{\cdot}001$). These findings support additional assessment of Col-3 either as a single agent or in combination in AIDS-related Kaposi's sarcoma and validate MMP inhibition as an important target in treatment.

Potential of other molecular targets in treatment of AIDS-related Kaposi's sarcoma

The phosphatidylinositol-3 kinase (PI3K) pathway, Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, and mitogen-activated protein kinase (MAPK) pathway, mediate growth and anti-apoptotic, metastatic, invasive, and angiogenic effects, and play a central part in pathogenesis of Kaposi's sarcoma. These pathways are activated by KSHV/HHV8

Search strategy and selection criteria

A systematic review of published papers from January, 1980, to March, 2006, was done using MEDLINE. Electronic searches were limited to the English language using the keywords "Kaposi's sarcoma", "topical therapy", "antiviral therapy", "immunotherapy", "systemic chemotherapy", and "biological drugs". Additionally, abstracts published as official proceedings of international scientific societies were also assessed. Three of the authors (GDL, PAK, BJD) together selected the articles appropriate for this review on the basis of the robustness and generalisability of the data. Priority was given to articles published within the past 5 years.

viral products (including viral G-protein-coupled receptor and viral interleukin-6) and other growth factors (ie, VEGF, PDGF, and SCF), which are expressed at high levels in sarcoma lesions.[76] Accordingly, inhibitors of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, such as the mTOR inhibitors rapamycin and temsirolimus might show potential activity. A report[77] of patients who had regression of their transplant-related tumour when switched to rapamycin indicates that the PI3K/AKT/mTOR pathway is at a juncture of many crucial signalling events.

Finally, treatments that directly target KSHV/HHV8 could, theoretically, be effective against Kaposi's sarcoma. Unfortunately no such treatments are currently available. Specific anti-HHV8 treatment is unlikely to cause regression of lesions, because antiherpes-virus agents inhibit the lytic rather than latent viral replication (in vitro studies have shown that the spindle cells are latently infected by HHV8).[78] Nevertheless, specific anti-HHV8 treatment might have a role in prevention of Kaposi's sarcoma development. Data from a cohort of 935 men with AIDS showed a reduction in the risk of developing the disease by 46% and 60% in patients treated with ganciclovir and foscarnet, respectively, when used systemically to prevent recurrent cytomegalovirus retinitis.[79]

Conclusion

Since the first description of AIDS-related Kaposi's sarcoma in 1981, prevalence, morbidity, mortality, and treatment have changed substantially. Once a psychologically and physically devastating malignant disease, this carrier can now be readily managed with many treatment modalities. The development of cytotoxic chemotherapy, improvement in local approaches, advent of HAART, and development of molecularly targeted treatments have revolutionised the treatment of the disease. Data supporting the beneficial use of chemotherapy, even in patients who are heavily immunocompromised, are encouraging. Most importantly, Kaposi's sarcoma represents an excellent model for simultaneous study of viral-associated carcinogenesis, inflammation, and angiogenesis. Thus, further elucidation of the underlying molecular pathogenesis will not only improve current therapeutic approaches against Kaposi's sarcoma, but will also uncover novel targets, thereby providing a new framework for the treatment of other malignant diseases.

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Conflicts of interest

We declare no conflicts on interest.

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