Kaposi's Sarcoma - An Update of Management

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ABSTRACT

Kaposi's sarcoma is an old but yet new disease. It was first described by Moritz Kaposi in 1872. Though it exists for more than a century, its pathogenesis is only recently revealed. It is now regarded as an angioproliferative disease. Human herpes virus type 8 has been shown to be an important aetiological agent in all types of Kaposi's sarcoma. A complicated network of various types of cytokines participates in the pathogenesis of Kaposi's sarcoma. More researches are being conducted on the pathogenesis and new treatment modalities. The following article will concentrate on the new aspects of management.

Keywords: Kaposi's sarcoma, angioproliferative, human herpes virus type 8

INTRODUCTION

Kaposi's sarcoma (KS) is a multifocal angioproliferative disease characterised by trans-differentiation of human herpes virus type 8 (HHV-8) infected endothelial cells into spindle-shaped cells, followed by cytokine-dependent transformation, proliferation, neovascularisation and inflammatory cell infiltration. Trans-differentiation is the conversion of differentiated cells either morphologically or functionally, or both.

KS was first described by Moritz Kaposi in 1872.[1] Four major distinct epidemiological variants were described in the next century. They are the classic, endemic, iatrogenic immunosuppression-related and epidemic acquired immunodeficiency syndrome-related KS (AIDS-KS). New KS subtypes have been reported in the last decade. A new type of classic KS with different epidemiological features was observed endemic in Greece.[2] Kaposi's sarcoma also developed in HIV-negative homosexual high risk men.[3]

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Pathogenesis

We now have better knowledge of the pathogenesis of KS. Primarily, the KS cells are derived from endothelial cells.[4] A new viral agent was identified to be strongly associated with KS five years ago. This was first called the KS-associated herpes virus (KSHV) and is now known as human herpes virus type 8. HHV-8 DNA sequences are demonstrated in all forms of KS.[5-7] It can be identified in peripheral blood mononuclear cells of half of AIDS-KS patients.[8] Their presence in HIV-positive patients without KS might predict the subsequent development of KS. HHV-8 is postulated to be predominantly sexually transmitted.[9] It is probably a latent infection and the virus may be reactivated under various forms of immunosuppression. It requires the presence of other cofactors for KS to develop. In AIDS patients, human immunodeficiency virus type-1 (HIV-1) infection induces the synthesis of HIV-1 tat protein which works synergistically with other cytokines such as basic fibroblast growth factor (bFGF),[10] interleukin (IL)-1, IL-6, tumour necrosis factor-a (TNF-a)[1] and induces growth of KS. A network of cytokines participates in the pathogenesis. They work in paracrine and autocrine fashions. The main ones include oncostatin-M,[11] IL-6,[12] bFGF,[1,10] transforming growth factor-b,[12] scatter factor,[13] platelet-derived growth factor[12] and CD40.[14] The various cytokines detected in KS such as TNF-a, IL-6 can upregulate viral expression and thus can contribute to reactivation, replication of HHV-8 and subsequent development of KS.

With a clearer picture of its pathogenesis, new treatment modalities directing against different specific steps are developed. The rest of this article will concentrate on the current treatment protocol and recent development of new therapeutic options of KS.

Staging is important in assessing the prognosis and evaluating treatment modalities. The most widely used is the one put forward by New York University (Table 1).[15]

For AIDS-KS, the AIDS Clinical Trial Group (ACTG) staging system is useful. They updated the classification in 1997 and found that a CD4 count of 150/ml was more sensitive in distinguishing between prognostic groups (Table 2).[16] Patients are assigned a disease state of T_x, I_x, S_x where x corresponds to the risk designation (0 or 1) for each risk category.

MANAGEMENT OF KAPOSI'S SARCOMA

There are many modalities of treatment for KS which are divided into two main types, local and systemic (Table 3). The choice of treatment should be individualised according to the subtypes and the stage of KS. A simple guideline employing the CD4 count was suggested (Table 4).[12]

Classic KS usually responds well to local therapies, among which radiotherapy is the treatment of choice.

Table 1. Classification and staging of Kaposi's sarcoma

TUMOUR EXTENT		SYSTEMIC SYMPTOMS
Stage I	Locally indolent cutaneous	
Stage II	Locally aggressive cutaneous±regional lymph nodes	A: asymptomatic B: weight loss (>10%) fever (>38°C)[2]
Stage III	Generalised mucocutaneous[1] and/or lymph node involvement	
Stage IV	Visceral	

1. More than upper or lower limbs alone; include minimal gastrointestinal disease (<5 lesions, <2 mm in combined diameters)

2. Oral temperature (>38°C/>100°F) lasting >2 weeks unrelated to identifiable infection

Table 2. ACTG recommended staging classification of Kaposi's sarcoma

	GOOD RISK (0)[#] (ALL OF THE FOLLOWING)	POOR RISK (1)[#] (ANY OF THE FOLLOWING)
Tumour (T)	Confined to skin and/or lymph nodes and/or minimal oral disease[1]	Tumour-associated oedema or ulceration; Extensive oral KS; Gastrointestinal KS; KS in other non-nodal viscera
Immune system (I)	CD4 cells ³150/ml	CD4 cells <150/ml
Systemic illness (S)	No history of OI* or thrush; No "B" symptoms;[2] Performance status ³70 (Karnowsky)[3]	History of OI* and/or thrush; "B" symptoms; Performance status <70 (Karnowsky);[3] Other HIV-related illness (e.g. neurological disease, lymphoma)

* OI = opportunistic infections

[#] Patients are assigned a disease state of T_x, I_x, S_x where x corresponds to the risk designation (0 or 1) for each risk category.

1. minimal oral disease is non-nodular KS confined to the palate.
2. "B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhoea persisting for >2 weeks.
3. Karnowsky performance status is a score assessing the general health of an individual. The score varies from 10 to 100 with an increment of 10. Score of 100 is normal; score of 10 is moribund and fatal process is rapidly progressing; score of 70 indicates that patient can care for himself but is unable to carry out normal activity or work.

Table 3. Therapies for Kaposi's sarcoma

Local treatments	Camouflage
	Surgical excision
	Cryotherapy
	Radiotherapy
	Laser
	Sclerotherapy
	Photodynamic therapy (PDT)
	Intralesional chemotherapy (vinblastine, vincristine, bleomycin)
	Intralesional IFN-a
	Intralesional IL-2
Systemic treatments	IFN-a
	IFN-a + AZT ± GM-CSF
	Chemotherapy ± AZT ± GM-CSF
	· Single (vinblastine, vincristine, bleomycin, doxorubicin, liposomal doxorubicin or daunorubicin, etoposide)
	· Multiple (vincrisitine + bleomycin ± doxorubicin)
New treatments including Experimental novel treatments*	Paclitaxel
	Retinoids
	b-hCG
	Antiangiogenesis therapy
	· Thalidomide
	· TNP-470
	· SPPG
	· SU5416*
	· Platelet factor 4
	· Pentosan polysulphate
	· MMP inhibitors*
	Cytokine inhibitors*
	· IL-1 receptor antagonist
	· Anti-IL-6 monoclonal antibody
	· Tat antagonist
	· Vesnarinone
	Enediynes*
	Cytotoxin
	· IL-4 receptor directed pseudomonas exotoxin
	Recombinant apolipoprotein E-3*
	Antiviral agents*

AZT: zidovudine; GM-CSF: granulocyte-monocyte colony-stimulating factor; b-hCG: beta-human chorionic gonadotropin; SPPG: sulphated polysaccharide peptidoglycan; MMP: metalloproteinase; IFN: interferon; IL: interleukin

Table 4. Guidelines of therapy according to CD4 count

CD4 COUNT (/ml)	THERAPEUTIC OPTION
³ 500	local only
200-500	interferon + zidovudine ± systemic chemotherapy
< 200	PCP* prophylaxis + antiretroviral therapy + systemic chemotherapy

* Pneumocystis carinii pneumonia

Endemic KS, with the exception of lymphadenopathic variant, responds favourably to systemic treatment. Iatrogenic immunosuppression-related KS normally regresses, without specific therapy, after discontinuing or decreasing the dose of immunosuppressive drugs. There is no definitive treatment for AIDS-KS. Although both local and systemic therapies may be used, they are just palliative and have not been shown to improve survival.[17]

All patients with AIDS-KS should be given antiretroviral therapy (ART) in addition to specific KS therapy.[18] The introduction of highly active antiretroviral therapy (HAART) has revolutionised the management of AIDS. HAART is a combination of nucleoside/non-nucleoside reverse transcriptase inhibitors and protease inhibitors (PI). It is highly effective in suppressing viral replication, increasing CD4 counts and thereby prolonging survival of HIV-positive patients. Significant improvement or stabilisation of KS lesions was observed in patients on HAART or PI only.[19, 20] Nowadays specific treatment for cutaneous KS is no longer recommended for, at least, the first few months after initiation of HAART.[19]

Local therapy

Local treatments are considered as first line therapies for those with localised disease or those with limited number of symptomatic lesions. They produce cosmetic improvement of disfiguring lesions and remove the associated social stigma. They are relatively safe and easily given in outpatient setting. Cosmetic camouflage is useful for asymptomatic KS lesions.

Surgery

Surgical excision may be useful in small, symptomatic lesions but is limited by local recurrence. It needs a wide margin of excision since the actual margin of a KS lesion may be distant from the clinically apparent margin. Koebner's phenomenon may take place.

Radiotherapy

Radiotherapy has been the major treatment modality for cutaneous KS lesions of classic, endemic and epidemic subtypes since KS is exquisitely radiosensitive. The treatment zone should be 0.5cm further away from the lesional margin to reduce local recurrence.[18] Radiotherapy is useful in alleviating symptoms caused by mass effects such as lymphoedema associated with KS since it produces 50% reduction in the size of lesions.[17]

Cryotherapy

Cryotherapy is particularly effective in treating macules and papules of less than 1 cm in diameter with complete or partial response rate of 85% lasting up to 6 months.[21] It is given at 3-week intervals for an average of three treatments per lesion, employing double freeze-thaw cycles with a mean thaw time of 30 seconds per cycle (10 to 20 seconds for macules; 30 to 60 seconds for papules). The treated area should be larger than the clinical lesions to minimise local recurrence. It produces 70% cosmetic improvement but histologically KS cells persist in the deeper reticular dermis. The potential hazard of the HIV particles present in blister fluid after cryotherapy cannot be neglected since it has been demonstrated in a HIV-infected patient with porphyria cutanea tarda.[22]

Laser therapy

Various types of laser used in the treatment of AIDS-KS include argon, carbon dioxide and pulsed dye lasers. They have similar drawbacks of surgical excision like local recurrence and koebnerisation. Another major concern is the potential risk of spreading HIV and other viral particles in the laser plume.[17] It is not a cost-effective method in maintaining long-term remission of AIDS-KS.

Sclerotherapy

Intralesional injection with sclerosing agent, 3% sodium tetradecyl sulphate, has been shown to be an effective treatment of intraoral nodular KS lesions with rapid response.[23] The underlying mechanism is induction of ischaemic necrosis. It can be complicated by pain, scarring, and ulceration. Sclerotherapy is effective, inexpensive and convenient.

Photodynamic therapy

Photodynamic therapy (PDT) has been employed in treating KS with high response rate, but is limited by unsatisfactory cosmetic results including scars and long-standing hyperpigmentation.[24] Furthermore, the occurrence of severe side effects, general and local, has made PDT an unsuitable choice for treating KS. The side effects reported consist of blister, pain, severe oedema, skin necrosis, local temperature increase, malaise, arthralgia, muscle stiffness and photosensitivity.

Intralesional chemotherapy

Intralesional injection with vinblastine or vincristine provides complete or partial response in 60-88% lesions of AIDS-KS and non-AIDS-KS.[20] Forty percent of AIDS-KS recurred in 4 to 6 months.[17] Vinblastine is the most commonly used chemotherapeutic agent. The recommended regimen is 0.1-0.2 mg/cm^2 of vinblastine injected intralesionally with a maximum total dose of 2 mg.[17] It is repeated at 3-week intervals for a total of 2 to 3 cycles. The major side effect is the lesional postinflammatory hyperpigmentation. Transient pain lasting for a few days is common. Other adverse effects include oedema, blister, ulceration, erythema, transient or persistent alopecia in hairy areas. Bleomycin was used to treat AIDS-KS with comparable result without any side effects except hyperpigmentation or hypo-pigmentation.[25]

Intralesional interferon-α

Intralesional interferon-α (IFN-α) has been used successfully in AIDS-KS,[26] and classic KS.[27] One to three megaunits of IFN-α are given three times per week for six to eight weeks. In AIDS-KS, it is administered with oral zidovudine. The proposed mode of action may be due to direct antiproliferative, local antiviral and immunomodulatory properties. Side effects are mild and transient, consisting of flu-like syndrome with fever, chills, fatigue, myalgia and arthralgia. The main limitation is the high cost.

Intralesional recombinant interleukin-2

Intralesional recombinant IL-2 alone was useful in treating a case of classic KS.[28] The mechanism is probably through induction of apoptosis of KS cells via activation of both natural killer cells and lymphokine activated killer cells. Large scale controlled studies are required to confirm the clinical efficacy.

Systemic therapy

Interferon

Interferon has immunomodulatory, anti-proliferative, antiviral and antiangiogenic properties. The antiangiogenic effect is mediated through downregulation of bFGF. These explain its efficacy in the treatment of AIDS-KS. It can be administered subcutaneously, intramuscularly or intravenously. Subcutaneous injection is the commonest route. It is recommended in patients with CD4 count of >200/ml with an initial dose of 3MU three to five times per week.[18] The dose can be increased gradually to 10 to 30MU, if tolerable, to give the best results and reduce acute toxicity. Recurrence is common within six months after cessation of therapy. Low dose recombinant IFN-α 2b (5MU three times a week) has been employed in the treatment of non-AIDS-KS (classic and endemic) with encouraging results.[29]

Interferon and zidovudine (AZT) together can be effective in patients with CD4 count of <200/ml in whom IFN monotherapy is ineffective.[17] The main dose-limiting toxicity is neutropenia which can be alleviated with the use of granulocyte-monocyte colony-stimulating factor (GM-CSF). Hepatotoxicity, anaemia and thrombocytopenia are common.

The major drawbacks of IFN with or without AZT are regular frequent injections, the associated cost and side effects. It should be restricted to a selected group of patients to achieve the best benefit. Patients with primarily cutaneous AIDS-KS and CD4 count >400/ml without history of opportunistic infection should be given IFN monotherapy. IFN and AZT, with or without GM-CSF, is indicated in those with CD4 count <200/ml.

Chemotherapy

Systemic chemotherapy consisting of a single agent or combination should be used for cases of rapidly progressive disease (³10 new lesions/month), pulmonary KS, lymphoedema and widespread symptomatic visceral disease. Because of the serious complications such as neutropenia, immunosuppression and increased risk of opportunistic infection which can compromise the survival of KS patients, chemotherapy should only be used with great caution.

Single agent chemotherapy using vinblastine, vincristine, bleomycin, dacarbazine, doxorubicin, etoposide and actinomycin-D gives moderate response rate. Weekly low dose vinblastine (3.5 to 10 mg) or vincristine (2 mg) intravenous injection given as outpatient treatment is effective for classic and AIDS-KS. The mode of action of vinca alkaloid is depolymerisation of microtubules.

Combination therapy yielded better response rate. Tomlinson et al recommended the use of bleomycin (20 mg/m^2) and vincristine (2 mg) at 3-week intervals for six cycles as the first line treatment.[18] Both agents

are chosen because of their lower myelotoxicity. Doxorubicin is added to the above combination in the United States. Both the UK and USA regimes achieved similar response rates of 65-70%.[18] Clinical response was noted after three cycles of treatment.

Second line therapy, 3-weekly liposomal doxorubicin of 20 mg/m^2 is given after three cycles of first line treatment fail.[18] The alternative is 2-weekly liposomal daunorubicin. This new liposomal formulation delivers the active drug selectively to tumour cells and concentrates in the target cells with enhanced cytotoxicity. It is more effective and less toxic than the traditional anthracyclines. The major side effect is dose-dependent neutropenia.[18] Cardiotoxicity remains the long-term dose limiting adverse effect.

Third line treatment is intravenous infusion of 200 mg etoposide at 4-week intervals or 50 mg orally daily for two weeks every 3 to 6 weeks.[18] It is highly emetogenic and can cause total alopecia.

Careful regular monitoring of clinical symptoms with investigations such as blood tests (including complete blood count, liver and renal tests), lung function test, and echocardiogram are important in the prevention and detection of early complications.

Chemotherapy can be administered together with antiretroviral agents. The combination of vinblastine and bleomycin with a reduced dose of zidovudine is safe.[17] The concomitant use of GM-CSF can reduce the associated myelosuppression.

New treatments

Paclitaxel

Paclitaxel (Taxol) is an anti-microtubule agent which induces irreversible polymerisation of microtubules. It is administered by intravenous infusion over three hours every three weeks. It was reported to achieve 65% partial response in 20 patients who were severely immunocompromised and with advanced KS.[30] All five patients with pulmonary KS responded. There were only 10 weeks of clinical remission. Another preliminary trial demonstrated paclitaxel was effective in advanced KS.[31] The commonest dose limiting adverse effect is neutropenia. Other reported toxicity includes delayed rash, delayed fever, renal failure, cardiomyopathy and eosinophilia.

Retinoids

Retinoids have immunomodulatory and anti-tumour effects via the regulation of cytokines and growth factors which stimulate cellular differentiation. Tretinoin is the most potent inhibitor of KS cell growth in vitro.[32] Oral all-trans retinoic acid induced 17% partial response.[33] The common adverse effects reported were headache, nausea and vomiting, xerosis, alopecia, hypertriglyceridemia, anaemia and neutropenia. New liposomal encapsulated all-trans retinoic acid, offering the same advantages as liposomal anthracyclines, is now under clinical trial.[31]

Antiangiogenesis therapy

Antiangiogenesis therapy is a new potential treatment strategy. Clinical studies are ongoing to evaluate the effectiveness of the following new inhibitors of angiogenesis.

Thalidomide inhibits TNF-a production and HIV replication in addition to its antiangiogenic activity. In a recent small scale phase II study, oral thalidomide 100 mg nightly for 8 weeks induced 35% partial response but was limited by side effects such as rash and nausea.[34] Sedation, peripheral neuropathy and teratogenicity are other well-known toxic effects.

TNP-470 is a synthetic fumagallic analogue derived from *Aspergillus fumigatus* which inhibits bFGF induced endothelial cell growth.[31] Platelet factor 4 (PF4) is a platelet a-granule protein which has induced regression of AIDS-KS when injected intralesionally.[35] Protein kinase C and tyrosine kinase inhibitors, tamoxifen and other antioestrogens are other inhibitors of angiogenesis.[36]

Human chorionic gonadotropin (hCG)

Regression of KS was reported after intramuscular[37] and intralesional hCG.[38] One study demonstrated dose-dependent anti-tumour activity of hCG.[38] The investigators suggested that hCG induces apoptosis of KS tumour cells. The adverse effects include local pain, feeling of perilesional skin retraction, vertigo, dizziness, nausea, headache and fatigue.[37,38]

Experimental novel treatment

SU5416 inhibits vascular endothelial growth factor (VEGF) mediated endothelial cell growth and migration in animal model.[31] It has been demonstrated to suppress KS cell growth in a dose-dependent manner.

Metalloproteinase (MMP) inhibitors are involved in the pathogenesis of KS. Their inhibitors suppress angiogenesis and growth of KS-like cells in vitro.[35]

Since various cytokines are involved in the pathogenesis of KS, **cytokine inhibitors** have become a new potential therapeutic option in KS. Studies are in progress to determine their clinical value.

IL-1 receptor antagonist inhibits AIDS-KS spindle cell growth in a dose-dependent manner by competitive inhibition of the IL-1 receptor.[39] It blocks exogenous IL-1 mediated upregulation of IL-6 and bFGF. ***Vesnarinone*** inhibits TNF and IL-6 synthesis and suppresses growth of AIDS-KS cell growth in vitro.[1] Other cytokine inhibitors include IL-4, anti-IL-6 monoclonal antibody, pentoxifylline, tat antagonist, autologous CD8 cells expanded and reinfused with recombinant IL-2.[1]

Recombinant cytotoxin made of IL-4 fused to Pseudomonas exotoxin has been demonstrated to have in vitro and in vivo activity against AIDS-KS cells, bearing IL-4 receptors, in cell culture and in animal model.[40]

Enediynes has been demonstrated to exert potent antiproliferative and cytotoxic effects on three KS cell lines in vitro.[35] Its clinical application requires further studies to verify.

Antiviral therapy

Antiviral agents against HHV-8 and HIV are being investigated for their therapeutic potential in the management of KS. A retrospective study showed HIV-infected patients who had received foscarnet for reasons other than KS had a significantly reduced chance of developing KS than those who had not received.[41] It was reported that KS improved after foscarnet therapy.

Antiretroviral agents such as PI have been demonstrated effective in inducing regression of AIDS-KS.[20] Adefovir, an acyclic nucleoside phosphonate analogue, is active against HIV and herpesviruses. It blocked replication of HHV-8 DNA in vitro.[42] It may become a therapeutic option for AIDS-KS which targets both HIV and HHV-8. Hydroxyurea was found to inhibit HIV replication in vitro and in vivo which may imply a clinical value.

CONCLUSION

The future trend of KS management will be the use of new biological therapeutic agents with relatively lower toxicity to replace the present regimen of systemic chemotherapy. They target at specific steps of pathogenesis. Different cytotoxins are employed to work against specific receptors or antigens on tumour cell surfaces.

Learning points:
In AIDS patients, highly active antiretroviral therapy (HAART) is now the 'first-line' treatment for Kaposi's sarcoma.

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