THERAPEUTIC UPDATE OF KAPOSI'S SARCOMA A REVIEW

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Kaposi's sarcoma (KS) was originally described by Moritz Kaposi in 1872 as "idiopathic multiple pigmented sarcoma of the skin" [1].

There are at least forty synonyms for this condition. Multiple idiopathic hemorrhagic sarcoma, idiopathic multiple pigmented sarcoma of the skin, cutaneous angioendothelioma, telangiectatic pseudosarcoma, and angioreticulomatosis are among the more commonly used term's [2].

Four forms of Kaposi's sarcoma (KS) have been identified: classic KS (Mediterranean form), endemic African KS, iatrogenic (immunosuppressive treatment-related) KS and epidemic or acquired immunodeficiency syndrome (AIDS)-related KS. These forms differ with respect to their clinical presentation, evolution and immunological characteristics. However, their histologic features are indistinguishable [3].

KS can be divided clinically into six types: patch, plaque, nodular, lymphadenopathic, infiltrative and florid. Rarely, other variants, such as telangiectatic KS are seen. Three new clinical variants have been recently described, KS presenting as generalized lymphedema, ecchymotic KS, and keloidal KS [4].

The cell of origin in KS is unknown. It may be a mesenchymal cell, a pericyte, vascular or lymph endothelium, or a dermal dendrocyte. The most likely possibilities are a pluripotential mesenchymal stem or a more differentiated lymphatic or blood vessel endothelial cell . Several studies have suggested a derivation of KS cells from lymphatic endothelium or a lymphatic endothelium progenitor cell. A central concept is that chronic stimulation of endothelial cells can produce trans-differentiation and permanent conversion of endothelial cells to spindle-shaped cells [5].

These KS spindle-shaped cells are under the control of different cytokines (table 1) [6].

Regardless of its setting, the etiology of KS has remained an enigma over 100 years. It may be multifactorial and there are many factors have been incriminated as genetic, hormonal, environmental, infectious agents, immunosuppressive drugs and impairment of the immune system[7]. Although an infectious

Table 1: Cytokines and Kaposi's Sarcoma Cell Cultures[6]

Growth promoting
Interleukin 1
Interleukin 6
Oncostatin M
Tumor necrosis factor-alpha
Basic fibroblast growth factor
Platelet-derived growth factor
Granulocyte-macrophage colony stimulating factor
Interferon-gamma
VEGF
Growth Inhibitory
Interleukin 2
Interferon-alpha
Interleukin 4

origin for the disease has long been suspected with Human herpes virus 6, Epstein-Barr virus, Cytomegalovirus, HIV, Human papilloma virus and Mycoplasma penetrans ,yet extensive investigations have not proved a causative association between any of these agents and KS[8]. A new human herpervirus type, known as KS-associated herpes virus (KSHV) or human herpes virus 8 (HHV-8) has been identified in KS lesions. However, viral infection per se is not sufficient for the development of malignancy and that one or more additional co-factors are required[9].

A uniform staging system is essential for the classification of patients, one which correlates with overall progonosis and identifies patients likely to benefit from specific treatment modalities. Although several staging system for KS have been proposed, not one has been universally accepted[10,11].

Therapy of Kaposi's Sarcoma:

Although KS is rarely a life-threatening disease, cutaneous lesions can be disfiguring and painful, as well as causing physical and psychological distress. A realistic goal of treatment is to be safe and effective. Since the natural history of KS is variable, it is difficult to assess therapy(6). A number of treatment modalities are available, but an individualized approach must be adopted considering the clinical sitting, the extent of KS, presence of opportunistic infection and the immune state of the patient. Some patients with KS are offered no therapy because their disease is not aggressive and the risks of the therapy outweigh the benefits[12].

Treatment options include[13]

(1) local therapy,
(2) chemotherapy,
(3) biologic response modifiers,
(4) other agents (human chorionic gonadotropin, antiviral agents).

Classic KS

Classic KS usually is limited to the skin and has an indolent course. Patients with this tumor are predisposed to the development of a second primary malignancy and the treating physician should consider this factor when arranging a schedule of follow-up for the patient[14].

1- Local Therapy

Local therapies are easy to perform, relatively safe, and often sufficient, especially in classic KS. They include simple excision, cryotherapy, laser treatment, radiotherapy and intralesional therapy. The basic for these treatments is induction of an inflammatory response that will resolve KS lesions[15].

1- a. Simple Excision

Surgical excision is appropriate for limited disease or to reduce tumour bulk in association with radiotherapy. Local excision is particularly suitable for the elderly patients with one or two nodular lesions which are slowly growing. Recurrent tumour and the emergence of new lesions may follow this form of therapy[14,16].

1-b. Cryotherapy

Cryotherapy leads to more than 70% cosmetic improvement because of camouflaging by superficial scarring, which is important for disfiguring lesions[15]. Advantages of cryotherapy include minimal side effects that are localized to the skin and good-to-excellent results in palliation of lesions, especially small lesions and/or lesions of recent onset. Other advantages of cryotherapy include the short duration of treatment associated pain, the ease and safety of administration, the feasibility of repeated treatments, the potential for combining local treatment with systemic therapy, and, finally, the relative low cost of the treatment. Cryotherapy may improve macular lesions more than papulonodular ones[17]. However, it causes hypopigmentation and can be used for small lesions only[15].

1-c. Laser Therapy

Laser therapy includes argon laser, carbon dioxide laser, and pulsed-dye laser. Argon laser is relatively specific for vascular lesions, but is time consuming[18]. Carbon dioxide laser is faster, but the possible risk of infectious viral particles in the vapor plume has limited its use[19]. Pulsed-dye laser is effective for cutaneous macular lesions, but recurrences are noted within 3 months[15].

1-d. Radiotherapy

Radiotherapy is an important treatment used for many years in classic KS. Lesions of KS are highly radio-sensitive and the treatment is well tolerated and temporarily controls large localized lesion[15]. For solitary lesions or lesions of limited extent, modest doses of radiation applied to the lesions themselves with a limited margin provide excellent control of disease in the treated area. Better cure rates can be achieved, when extended field radiation, is used[14]. Electron beam radiotherapy, which has limited penetration beyond the dermis, is a good modality for treating superficial lesions. Deeper or unresponsive cutaneous disease may be managed by standard non-electron-beam radiation[12]. Various dose regimens have been reported[14]:

Low- voltage (100 kv) photon radiation: 800 to 1,000 cGy as a single or 1,500 to 2,000 cGy over 1 week, for solitary lesions control nearly 100 % of local disease but recurrence in adjacent areas is common.

Electron beam therapy: 400 cGy once weekly for 6 to 8 consecutive weeks with a 4 to 6 Me V electron beam. Ports should include the entire skin surface 15 cm above the lesion.

In one study[20], of 20 patients with KS who received 4Gy of total-skin electron-beam therapy once a week for 6 to 8 consecutive weeks, 85% had complete remissions, which lasted 10 to 92 months. Single application of fractionated dose of 800 cGy had 89% complete response in KS lesions[21]. Side effects inlcude residual hypopigmentation, radiodermatitis and ulceration. Radiotherapy is less effective for mucosal lesions and may cause mucositis and exacerbation of oral infections.

1-e. Intralesional Therapy:

Intralesional cytotoxic chemotherapy (eg.vinblastine), 0.1 ml/0.5 cm2 of KS tumour at a concentration of 0.2 mg/ml, was used for persistent skin nodules[22].

Also, interferon alfa was used intralesionally to treat isolated KS lesions at a dose 3 to 9 million units, 3 time per week for 3-4 weeks[23]. Addition of interleukin-2 resulted in more rapid involution[24].

Intralesional therapy is convenient and has no systemic toxicity, thus providing an attractive alternation to radiation therapy or systemic chemotherapy. The side effects of intralesional therapy include pain, skin irritation, ulceration and post inflammatory hyperpigmentation[25].

2- Systemic or Combination Therapy

2-a. Chemotherapy

Patients with extensive, or recurrent KS or who had lymph node and GI tract involvement can be treated with a combination of surgery, chemotherapy and radiation or with chemotherapy and radiation or with chemotherapy alone. Responses can be obtained with vinblastine, bleomycin, doxorubicin and dacarbazine alone or in combination. Several authors[26,27] have used single-agent vinblastine at a weekly dose of approximately 0.1mg/kg. Almost all patients had good to excellent response. Doses of vinblastine were titrated in individual patients to maintain a WBC count above approximately 3000/cmm.

2-b. Interferon- alpha

Subcutaneous interferon alpha (INF-alpha) [28] is also effective at a dose 3-5 million U, 3-6 times per week for 24 weeks. The exact mode of action of INF-alpha is not yet clear, but the following have in vivo and in vitro evidence of the antiviral, antiproliferative, antiangiogenic or immunoregulatory effects. INF-alpha may enhance a local T-cell-mediated immune response[29].

The advantages of this treatment are[15]:

(1) it is easy to perform.

(2) A response may be obtained even when other treatments have failed.

(3) side effects are transient and do not require cessation of treatment.

(4) remissions are long.

(5) no maintenance treatment is needed.

(6) recurrences are limited, requiring either shorter periods of retreatment or no treatment.

(7) the disease dose not become refractory to treatment.

Its disadvantages are[15]:

(1) regular injections are needed for several months.

(2) relapses may occur during therapy.

(3) it may be not useful for AIDS-KS.

The most common side effects of interferon alpha treatment are influenza-like symptoms (fever, chills, headache and fatigue), weight loss, nausea, depression, anemia and transient neutropenia[15].

2-c. Tumor necrosis factor- alpha

The effect of hyperthermic perfusion (40°C) of the KS affected limb with tumor necrosis factor (alpha) and melphalan for a period of 90 minutes in five patients was evaluated. All five patient had a response in the KS lesions[20].

Endemic KS

Drugs used to treat classic KS have also proved effective for endemic KS. The rate of response is more than 80% with either radiation therapy or chemotherapy[20].

Immunosuppressive treatment-related KS

The KS regresses with the cessation, reduction or modification of immunosuppressive therapy in most patients. A withdrawal or reduction of such therapy in kidney transplant recipients (KTR) leads to the loss of the graft in approximately half of patients. The discontinuation of immunosuppressive therapy led to the resolution of KS in 4 of 5 KTRs(20). There are three treatment options[14]:

1) Discontinue immunosuppressive therapy

This option is critically important in patient who are receiving immunosuppressive drugs as in the case of certain transplant patients but, if this therapy is not critical in the management, its discontinuation is a reasonable first step in these patients.

2) Radiation therapy (for disease limited to the skin)

3) Chemotherapy

Most systemic chemotherapy (single or multiple drugs) trials in classic KS can be effective for immunosuppressive treatment related KS. Combinations of doxorubicin, bleomycin and vincristine were used successfully. Low dose Interferon alpha was used in few selected cases.

Epidemic (AIDS-related) KS

Kaposi's sarcoma is the most common malignancy observed in patients with HIV-1 infection, and causes considerable morbidity and, when the lungs are involved, mortality. Treatment of AIDS-related Kaposi's sarcoma presents several problems and treatment decisions should be based on accurate evaluation of prognostic factors. For this reason there is consensus that KS therapy in patients with AIDS should be individualized. Treatment decisions must take into consideration the extent and the rate of tumour growth, patient symptoms, immune system condition and concurrent complications of AIDS. Since no current therapies have been found to be curative, both delivery of effective anti-Kaposi's sarcoma treatment and maintenance of adequate control of HIV and other infections remain the current goal in the treatment of AIDS-related Kaposi's sarcoma. Recommendations for Kaposi's sarcoma treatment are as follows[13]:

1. *Localised disease: surgical excision; liquid nitrogen cryotherapy ; laser therapy; radiotherapy; local injection with vinblastine, vincristine, bleomycin; interferon-alpha(IFN-alpha).*
2. *Indolent disseminated cutaneous and/or lymphadenopathic disease: immunotherapy + zidovudine ; single-agent chemotherapy; highly active antiretroviral therapy (HAART).*
3. *Aggressive, disseminated disease: dual or multiagent chemotherapy.*

Recently, antiangiogenic factors[30], Apoptosis-inducing agents[31], hormonal therapy[32] and retinoic acids[33] are used.

1-Local Therapy

Localized KS have been treated successfully with surgical excision, laser therapy, liquid nitrogen cryotherapy, radiotherapy

and intralesional therapy. With any local modality, there is generally residual evidence of the disease process, whether it be a scar associated with laser therapy or cryotherapy, or residual pigmentation after irradiation or intralesional injection. The modality chosen depends mainly upon the expected adverse effects of the intervention[13].

1-1. Radiotherapy

Radiotherapy, which has been frequently employed in the treatment of classical Kaposi's sarcoma, has become the most important therapy in the local treatment of AIDS-related Kaposi's sarcoma. Whole body electron beam therapy, fractionated focal x-ray therapy in doses up to 4500 cGy, and single dose treatments of 800 cGy produced complete remissions in 50 to 80% of patients. Patients with HIV infection tend to have more radiation-related complications for any given dose than non-HIV-infected patients. Postradiation hyperpigmentation, mucositis, lymphoedema and local recurrence are reported. Late complications of radiotherapy include fibrosis, ulceration and superinfections[34].

Different regimens can be used 800 cGy in a single fraction, 20 Gy in 10 fractions, or 40Gy in 20 fractions. Complete response rate and duration of disease control were superior in the two higher dose arms than in the single fraction arm. However, radiotherapy is less effective for mucosal lesions. In general, a single dose of 800cGy has been effective in reducing symptoms associated with Kaposi's sarcoma in patients with advanced HIV disease, while a fractionated course is more suitable in patients with more extensive disease and a longer life expectancy[35].

1-2. Intralesional Therapy

Only isolated lesions of epidemic KS can be treated by the intralesional injections. It can be used adjuvent to other systemic therapy. Vinblastine, vincristine, bleomycin and IFN-alpha have been reported to be effective treatments[36,37]. The only adverse effect was local pain, skin irritation, ulceration and post inflammatory hyperpigmentation.

Injection of sclerosing agents (3% sodium tetradecyl sulfate) cleared all (15) oral lesions of 12 patients with AIDS-KS and 14 oral lesions of an additional 12 patients decreased in size by 80% within 14 to 21 days with complete clearing in four patients. The mode of action is induction of ischemic necrosis. This treatment is effective, inexpensive, and convenient (one treatment is enough) and it includes fast responses and long remissions. Its disadvantages are pain, scarring and ulceration[38].

Another promising treatment is intralesional recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF).[39] Its possible mode of action is provocation of inflammation which includes local necrosis.

Recently, intralesional injection of ß-human chorionic gonadotropin (ß-hCG) has three time a week for two weeks, has been shown to be effective in KS. It's effect was dose dependent, with superior response with a dose of 2000 IU per lesion[40].

1-3. Topical Therapy

Topical use of dimethyl sulfoxide (DMSO) has the ability to cross biological membranes carrying with it substances unable to penetrate the membrane spontaneously. Thus bleomycin-DMSO was used with some effect in epidemic KS[41].

A topical preparation, Aliretinoid, has been approved recently by the FDA for the treatmetn of KS. Aliretinoid is a naturally occurring endogenous retinoid (9-cis-retinoid acid) found to inhibit the growth of KS cells in vitro. Aliretinoid binds to and activates all six known intracellular retinoid receptors. Once the receptors have been activated, they serve as transcription factors, regulating the expression of genes involved in the control of cell differentiation and proliferation, both in normal and neoplastic cells. Clinical benefit was found mainly for patients who received the medication in a gel form and applied it twice a day for 4-6 months. Toxicities related to topical treatment of aliretinoid were almost exclusively limited to the site of medication included rash, pain and paresthesia. Severe skin irritation may become treatment-limiting, with intense erythema, edema and vesiculation at the site of gel application[42].

Iontophoresis is another experimental noninvasive method and successful vinblastine iontophoresis was noted in 31 patients with epidemic KS[43].

1-4. Lasers and Surgical Therapies

Carbon dioxide laser and photodynamic therapy (indocyanine green as photosensitizer in combination with a diod laser) have been succfessfully used to treat large oral lesions.[44,45] However, the potential exposure of the laser operator to HIV and other viruses is a concern. Pulsed-dye laser therapy is effective for cutaneous macular lesions, but lesions typically recur within 12 weeks[46]. Local excision can be of benefit for particularly troublesome lesions at carefully selected sites (e.g. oral, eyelid, penile shaft).

2-Systemic Therapy

2-1. Cytotoxic Chemotherapy

Cytotoxic therapy should be considered for patients with rapidly progressive disease (10 or more new cutaneous lesions/ month), lymphedema, pulmonary KS and wide spread symptomatic visceral disease. Great caution should be used

in choosing the cytotoxic agent, either as a single-agent or in combination (table 2). The use of aggressive treatments can lead to serious pancytopenia and immunosuppression that are associated, in most cases, with a poor out-come[42].

Table 2: Most commonly used Cytotoxic therapies in acquired immunodeficiancy syndrome- related Kaposi's Sarcoma[42].

Agent	Dose	Schedule	Response Rate (%)
Vinblastine	4-6 mg IV	q. 1 w	50
Vincristine	2 mg IV	q. 1-2 w	61
Etoposide	150 mg/m² x 3d	q. 28 days	76
	150-450 mg	q. 1 w	36
Bleomycin	5 mg/d	q. 2 w	74
	20 mg/m²/d civ x 3 d	q. 3 w	41-65
Paclitaxel	135-175 mg/m²	q. 2 w	65
	100 mg/m²	q. 2 w	59
Lip. Daunorubicin	40 mg/m²	q. 2 w	28
Lip. Doxorubicin	20 mg/m²	q. 3 w	32-80
Combination ABV regimen:			
Adriamycin	20 mg/m²	q. 2 w	50-88
Bleomycin	10 U/m²		
Vincristine	2 mg		

IV = intravenous; civ = continuous intravenous; w = week; Lip = liposomal; q.= every; U = units

2-1-1. Single Agent Chemotherapy

Several single agent therapies had been reported to be active in AIDS-related Kaposi's sarcoma and include the vinca alkaloids (e.g.vincristine & vinblastine), anthracyclines (e.g.doxorubicin & Daunorubicin), epipodophyllotoxins (e.g.etopiside & teniposide) and bleomycin (table 2). Although clinical trials with single agent chemotherapy showed significant overall response rates, responses were short-lived and the occurrence of opportunistic infections was a major problem. In general, for patients who are leucopenic and require chemotherapy, vincristine and bleomycin are the single agents used most widely. Myelosuppression, neurotoxicity, pulmonary toxicity or gastrointestinal toxicity may be observed[13].

2-1-2. Dual Agent Chemotherapy

With the aim of improving objective responses and duration of clinical benefits without increasing adverse events, especially myelosuppression, small studies using a combination of vincristine-bleomycin, vinblastine-methotrexate, vinblastine alternating weekly with vincristine or bleomycin have also been conducted[47].

Bleomycin-vincristine chemotherapy was relatively well tolerated and resulted in a high response rate (57 to 72%) in patients presenting with disseminated Kaposi's sarcoma and severe peripheral blood cytopenias. Unfortunately, responses were short lived and the occurrence of opportunistic infections was a major problem[47,48].

2-1-3. Multiagent chemotherapy

Multiagent chemotherapy employs various combinations of drugs that have been found to be effective as single agents, and they are generally administered to patients with advanced disease and visceral involvement. First multichemotherapeutic regimens specifically devised for AIDS-related Kaposi's sarcoma were a combination of doxorubicin, bleomycin and vincristine (or vinblastine). Gill et al[49] reported a multicentre, randomised clinical trial comparing low dosage doxorubicin (adriamycin) 20 mg/m² alone (n=31) or doxorubicin 20 mg/m2, bleomycin 10 mg/m² and vincristine 1.4 mg/m² (ABV) [n=30] every 2 weeks. Complete and partial tumour remissions were significantly higher with ABV (88%) than with doxorubicin alone (48%) [p=0.004]. The median survival was 9 months in both groups. Adverse effects were similar in both groups and the regimens were well tolerated. Treatment-related adverse effects consisted of nausea and vomiting, hair loss, mucositis, peripheral sensory neuropathy and granulocytopenia. Neutropenia occurred in 34% of patients receiving doxorubicin alone and in 52% of patients receiving ABV.

The majority of patients with advanced KS are severely immunocompromised and eventually die from opportunistic infections rather than KS. Therefore, a major concern was whether the use of chemotherapy would aggravate the immune dysfunction and predispose patients with AIDS to more opportunistic infections. It is also of interest whether concurrent use of antiretroviral therapies (zidovudine 100mg/day orally every 4 hours) would prevent the occurrence of opportunistic infections[50]. The use of recombinant haematopoietic growth factors GM-CSF 250 μg/m²/day to support patients undergoing chemotherapy has been evaluated in some studies as a means of preventing bacterial infectious complications[51].

2-1-4. New Chemotherapy Agents

a. Liposomal Anthracyclines

In the last few years, new cytotoxic treatmetns (liposomal anthracyclines) have become widely used in KS. To reduce toxicities and to increase the potential for antitumor activity, both doxorubicin and daunorubicin have been used in preparations in which the cytotoxic agent is liposomally encapsulated. This clever chemical intervention produces a dramatic change in drug kinetics with a prolonged half-life. Liposomal daunorubicin has a half-life of 8 hours, and liposomal doxorubicin has a half-life of 30 hours. The marked difference in half-life between the two liposomal preparations is caused by the addition of polyethylene glycol (PEG) to the liposome, which diminishes the reticulo-endothelial drug uptake[52]. Furthermore, because liposomal preparations tend to accumulate in KS lesions and in tumor cells in general, at higher

concentrations, they deliver a higher toxicity to the targeted cells. The concentration of liposomal preparations is 5- to 50-fold greater in KS lesions than in healthy surrounding tissue[53].

To compare the safety and efficacy of liposomal daunorubicin with that of the reference regimen of ABV as primary therapy in advanced AIDS-related KS, 232 patients were randomised to receive liposomal daunorubicin 40 mg/m^2 or a combination regimen of doxorubicin 10 mg/m^2, bleomycin 15 U and vincristine 1 mg, administered intravenously every 2 weeks. Liposomal daunorubicin had comparable efficacy to ABV, was associated with significantly less alopecia and neuropathy and produced no evidence of cardiac adverse effects. Patients on liposomal daunorubicin experienced more neutropenia and had a higher incidence of opportunistic infections. The authors concluded that liposomal daunorubicin can be recommended as a well tolerated and effective primary therapy for advanced AIDS-related KS[54].

Recently. Stewart et al.[55] conducted a randomised study that compared PEG-coated liposomal doxorubicin 20 mg/m^2 with a combination of bleomycin 15 U/m^2 and vincristine 2 mg in 241 patients with advanced stage KS. Both regimens were administered by intravenous infusion every 3 weeks for 6 cycles. The response to PEG-coated liposomal doxorubicin was superior to BV:58.7% vs 23.3% ($p<0.001$). Adverse effects such as alopecia, neuropathy, nausea and vomiting occurred less frequently in patients who received liposomal doxorubicin. Although better tolerated by patients, PEG-coated liposomal doxorubicin is significantly more myelotoxic compared with the BV regimen and this is associated with an increased incidence of infections. Concomitant use of both antiretroviral therapy and haematological growth factors is needed, with the aim of reducing opportunistic infections and myelotoxicity.

Toremifene, a well-tolerated oral triphenylethylene derivative similar to tamoxifen, has been reported to inhibit multidrug resistance-1 (MDR-1) activity in vitro and to reverse doxorubicin resistance at concentrations that can be achieved in humans with oral dosing[56].

b. Paclitaxel

Paclitaxel, a novel cytotoxin agent with preliminary evidence of anti-tumour efficacy, has antiangiogenic effect and stabilizes microtubules in patients with Kaposi's sarcoma. Neutropenia has been the primary dose-limiting adverse effect of paclitaxel. Peripheral neuropathy may also be severe, and occasionally dose-limiting. Hypersensitivity reactions, dyspnoea, hypotension and angioedema have also occurred[13]. In one study[57] paclitaxel was administered at a dose of 100 mg/m^2 IV over 3 hours every 2 weeks. Visceral disease was present in 35% of patients and median CD4+ count was 20/ µl. There was one complete response and 32 partial responses (complete remission + partial responses =59%). Major response was not different between the treatment subgroups (55% for patients receiving prior systemic therapy versus 69% in all others). Neutropenia was the most common adverse event occurring in 62% of patients. Anaemia or thrombocytopenia was less common. Severe nonhaematological adverse effects were uncommon, occurring in less than 15% of patients.

c. Vinorelbine

Vinorelbine is a cytotoxic agent with preliminary evidence of anti-tumour activity in patients with KS. It has been shown to be active against various tumour types and is relatively safe and well tolerated[58]. Vinorelbine 30 mg/m^2 was given intravenously every 2 weeks. Complete remission occurred in 3 of 22 evaluable patients (14%) and partial remission in 8 patients (38%). Because of its favourable adverse effect profile predominantly of mild myelosuppression. This agent may be an excellent choice for palliative treatment of patients who may be unable to tolerate more toxic therapies.

2-2. Biologic response modifiers

2-2-1. Interferon-alpha

IFNs are proteins and glycoproteins with antiviral, immunomodulatory and antiproliferative activities. IFN-alpha is the only immunomodulating agent known to play a role in the treatment of AIDS-related KS[59]. Clinical trials using high doses (>20MU) of IFN-alpha have given response rates of 18 to 46%[60,61]. The first sign of tumour regression is usually noted within 4 to 8 weeks, but maximal responses generally require 6 or more months of treatment. The factors associated with a poor response to IFN therapy include prior or present opportunistic infections, systemic symptoms and CD4+ counts <200 cells/ mm^3 [62]. Adverse effects generally consist of myelosuppression, hepatic abnormalities, influenza-like symptoms (fever, chills, myalgias, anorexia) and occasional hypotension. To some degree these adverse effects can be avoided by initiating treatment with low doses of IFN and gradually escalating to full dose. However, these high doses of INF-alpha led to an impaired quality of life and to reversible cardiomyopathy[42].

Combination Therapy with Interferon-alpha

In vitro studies have shown that zidovudine and IFN-alpha act synergistically to inhibit the replication of HIV in peripheral mononuclear cells at concentrations achievable in patients[63]. Several studies have been conducted to evaluate this drug in AIDS-related Kaposi's sarcoma .

Krown et al.[64] administered IFN-alpha 4.5,9 or 18 MU/ day and zidovudine 100 or 200 mg every 4 hours to 41 patients with AIDS-related Kaposi's sarcoma. Of the 37 evaluable patients, 17 (46%) showed complete or partial tumour regression. Anti-tumour effects occurred more frequently in

patients with baseline CD4+ counts >200 cells/mm^3 (65%) than in patients with lower baseline counts (30%).

Fischl et al. [65] evaluated 63 patients with IFN-alpha (18 MU/day) and zidovudine (600 mg/day). Although this trial included patients with low CD4+ counts, therapy resulted in tumour regressions in 40% of patients and the median duration of response was 22.4 weeks. The major adverse effects included anaemia (16%), neutropenia (27%) and elevated serum transaminase levels (16%).

The addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) to the combination regimen of zidovudine and IFN-alpha has been tried to ameliorate the myelosuppression seen with co-administration of these agents[66].

On the other hand, the result have been disappointing in other studies and there has been no evidence that this combination adds anything to response rates. Furthermore, in most cases, combination therapy has led to increased toxicity, although survival and incidence of opportunistic infection were similar[12].

2-2-2. Antiangiogenic Factors

A new generation of anti-KS agents has been developed based on the new under-standing of AIDS-KS pathogenesis. Most of these new agents target the neoangiogenesis characteristic of the KS lesions. It is well known that KS cells produce many inducers of endothelial cell proliferation and migration[24,6] including angiogenic factors such as interleukin-8(IL-8), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), and cytokines, such as interleukin 1 (IL-1), interleukin 6 (IL-6), and oncostatin-M. Drug research has also focused on the endothelial cell receptor induced tyrosine kinases, known to be involved in angiogenesis, in particular, FLK-1 and FLt-1, the receptors for VEGF(42,67).

IM 862 (a dipeptide isolated from the soluble fractions of the thymus) has been found to have antitumor activity without any direct toxicity to the tumor cells. It has shown to inhibit angiogenesis in vivo using the chicken allantoid membrane assay (CAM). IM 862 was studied in an open-label trial at a dose of 5 mg, given as a nasal solution, to assess with AIDS-KS(68). The total response rate was 37%. The onset of a major response occurred at 6 weeks, and the median duration of response was longer than 28 weeks. The medication was well tolerated with minor side effects, mainly headaches, elevated liver enzymes, fatigue, moodiness, and ear congestion. There was no bone marrow toxicity.

The TNP-470 molecule is an analog of fumagillin, an antineoplastic agent extracted from Aspergillus fumagatus fresensius, that inhibits bFGF-induced endothelial cell proliferation. This substance has proven to be more active and less toxic than fumagillin. TNP-470 was given every week as a 1-hour infusion. Although it was a phase I clinical trial, responses were seen in 18% of the patients; the mean duration of the response was 11 weeks[69].

SU 5416 is a small molecule that inhibits phosphorilation and activation of FIK-1, the signaling receptor for VEGF homodimer and heterodimer. VEGF is produced by KS cells and used for their own growth. SU 5416 has potent and specific inhibitory effects on VEGF-induced proliferation of endothelial cells and subcutaneous tumor growth. This orally bioavailable compound has been shown to inhibit the growth of established tumors and the regrowth of tumors following adjuvant chemotherapy[42].

Tecogalan is a small compound isolated from the cell membrane of the Arthobacter species AT-25. It has been shown to inhibit growth of both endothelial and KS spindle cells in vitro. In mice, tecogalan also has inhibitory effects on KS-cell-induced capillary permeability. A phase I clinical trial was conducted[70] based on available in vitro and in vivo data. Patients received tecogalan intravenously once a week for 4 weeks. Although no objective responses were noticed, a reduction in tumor-associated edema was observed.

Thalidomide, a popular medication in the 1960's that was removed from the market because of its teratogenic effects, has recently been shown to inhibit angiogenesis, block tumor necrosis factor-alpha (TNF-alpha), inhibit intercellular adhesion molecules, and inhibit basement membrane formation. It is now believed that the teratogenic effects of thalidomide result from its antiangiogenic properties. Side effects, which included neutropenia, skin rash, fever, myositis and depression[71].

Angiostatin was discovered following the clinical observation that, after surgical removal of primary tumors, the metastatic disease tended to progress very rapidly. Presence of factors produced by the primary tumor that inhibit the growth of the metastatic tumor was found in the urine of tumor-bearing mice. Subsequently, a protein was isolated and purified that shares sequence homology with a fragment of plasminogen. In vivo studies in mice using recombinant protein have shown that angiostatin inhibits tumor growth without any direct effect on the tumor cells[72].

Endostatin is another protein with antiangiogenic effects isolated from the supernatants of a hemangio-endothelioma. Further purification and sequencing of this protein showed that it represents a fragment of collagen XVIII. Endostatin inhibits cell proliferation tumor cell growth in vivo by blocking angiogenesis[73].

Interleukin 12 (IL-12) has been shown to be a potent inhibitors of angiogenic activity through the induction of interferon-gamma (IFN-y), which in turn induces protein-10 (IP-10). Three patients had objective partial response at the 300 ng/kg doses, and 1 patient at the 500 ng/kg dose. Seven patients continue to receive IL-12 without progressive disease. Reversible hepatotoxicity was noted in one patient[74].

Sulfated polysaccharide dextrin 2-sulfate has antiangiogenic effect; its delivery through the intraperitoneal route to the lymphatic circulation resulted in a clinically significant improvement in KS[75].

Some experimental studies observed that Captopril[76] and Tamoxifen[31] have in-vitro antiangiogenic effect and are thus potential candidate for development in treatment of KS.

2-2-3. Cytokine Inhibitors

Other potential therapeutic approaches aim at the inhibition of the action of cytokine responsible for the growth of KS. A therapeutic role may exist for the use of IL-1 receptor antagonist (IL-1ra). This naturally occurring compound was recently found to inhibit proliferation of AIDS-associated KS cells that produce and secrete IL-1 by competitively inhibiting the cytokine's receptor in a dose-dependent manner. IL-1ra can block the effects of exogenous IL-1 on AIDS-associated KS cells as well as IL-1-mediated upregulation of IL-6 and bFGF[77].

Masood et al.[78] studied the fusion toxin DAB38a-IL-6 targeted specifically to IL-6 receptors in AIDS-associated KS cells and found inhibition of cell protein synthesis as well as cell viability. Also, IL-2 receptor-targeted fusion toxin (IL-2 and cytotoxic diphtheria toxin fragments) can be used[6].

Vesnarinone inhibits tumor necrosis factor and IL-6 production in some cell culture systems. It was also found to inhibit AIDS-associated KS cells in culture at pharmacologically achievable concentrations and may be useful clinically[5].

2-2-4. Apoptosis-inducing agents

Cytotoxic T lymphocytes or natural killer cells play a central role in immune survelliance. The Fas system has been involved in the mechanism of target cells lysis by these killer cells via transduction of an apoptotic signal into susceptible cells. Fas is a receptor protein belonging to the tumor necrosis factor/nerve growth factor receptor superfamily. One recent study showed that AIDS-KS cells are resistant to Fas-mediated apoptosis. This finding suggests that the sensitization of AIDS-KS cells to Fas-mediated cytotoxicity in vivo might provide a new therapeutic approach in the treatment of AIDS-KS. It appears that agents capable of selectively incuding apoptosis of KS cells may have therapeutic potential for treatment of this disease[31].

2-3. Other Therapy

2-3-1. Retinoic acids

Retinoic acids have important biological properties affecting cell differentiation, inhibition of cell proliferation and regulation of morphogenesis. Retinoic acids exert their activity after binding to their cognate nuclear receptors. Their biological effects are mediated by regulating cellular genes, in particular mediators of immune response, such as IL-1 and IL-6. Retinoids have been found to be active in studies of patients with clinical KS. The main biological effect or retinoic acids is to inhibit KS cell proliferation , in part by inhibiting IL-6 production[79].

A liposomal encapsulated preparation of trans-retinoid acid has been tested in clinical trials to avoid the drop in plasma levels seen with systemic use of retinoid acid after initiation of therapy. Another advantage of a liposomal preparation is that the medication tends to accumulate in the tumor tissue. A multicenter trial of 81 patients with AIDS-KS was conducted with escalating doses (60, 90 and 120 mg/m^2) given intravenously either weekly or three times a week. The overall response rate was 23%. The toxicity profile included headaches (88%) and dry skin (58%). The study concluded that liposomal encapsulation of trans-retinoid acid is rasonably tolerated when given intravenously three times a week and can stabilize disease progression[80].

2-3-2. Hormonal Therapy

One of the interesting epidermiologic features of KS is that nearly all affected patients are men. This male predominance is more than can be explained by patterns of KSHV infection and it suggests that there may be some hormonal effect on the disease pathogenesis. Also,there is an observation that the KS cell line (KS Y-1) failed to grow in pregnant mice[32].

Recently, there is a factor in the urine of pregnant women blocked the growth of a KS-derived cell line. This factor was initially thought to be human chorionic gonadotropin (HCG), but subsequent investigation has suggested that it is a related urinary protein that is found in certain preparations of HCG and which could induce regressions in KS. Associated clinical findings included increased CD4 cell count, reduced HIV viral load, and weight gain[81,82].

2-3-3. Antiviral therapy

a- Highly Active Antiretroviral Therapy (HAART)

There are some evidence of a link between KS growth and HIV replication, so antiretroviral therapies can be used in KS. Protinase inhibitors (ritonavir, indinavir) are highly selective and potent inhibitors of HIV replication. Clinical studies have demonstrated a marked reduction in plasma viral load, sustained improvement in immune function and prevention of AID-related complications in HIV-infected patients[83].

Conant et al. [84] described 5 patients with KS treated with ritonavir 600mg twice daily, who experienced improvement or resolution of KS lesions.

KS regression is linked to decreased HIV replication with an associated decrease of cytokine levels and to the restoration of immune function. HAART might be a useful alternative both to immune response-modifiers during less aggressive stages of KS and to systemic cytotoxic drugs in the long-term maintenance therapy of advanced KS. The management of KS with HAART is very interesting as it targets both tumor cells and the underlying HIV infection. The likelihood of long term treatment with agents with low adverse effect profiles makes this approach attractive[13].

b- HIV-tat Inhibitors

HIV-tat protein has been shown to bind to KS cells and to induce a mitogenic response. Tat protein induces the expression of many cellular genes, such as IL-6, that may participate in the development of KS. Transgenic mice expressing tat protein develop hyperplasia of the dermis, followed, in male mice only, by the development of vascular tumors[34]. The HIV-tat protein receptor on KS is also a VEGF receptor. The recent introduction of the protease inhibitors has altered the natural course of HIV infection in a remarkable way. Effective antiretroviral therapies appear to have altered the natural history of KS. It is not known whether new KS lesions will appear if patients develop resistance to these new antiretroviral treatments[85].

c- Antiherpes Therapy

With the discovery of the KSHV/HHV-8, there has been increasing interest in the potential use of antiherpes agents, but it is not proved that the ongoing KSHV/HHV-8 replication is important for continued KS growth. The preliminary evidence suggests that antiherpes drugs as acyclovir, foscarnet, cidofovir and ganciclovir have variable response rates[6,86].

2-3-4. Gene Therapy

Another promising area of research is the human genome project, which may identify genes relevant for KS, since there is a genetic predisposition for KS. Gene therapy is an exciting experimental field. Clinical trials are being conducted in AIDS, aiming at preventing HIV replication by such technologies as antisense oligonucleotide, ribozymes to genomic RNA, and transdominant negative HIV proteins. The effect on KS may be a byproduct of these efforts[15].

Summary

KS remain a challenge to clinicians and investigators more than a century after its initial description. Debate continues as to the cell of origin, as well as whether or not it is a true cancer. KS appears to be an opportunistic neoplasm, which in its earliest phase retains some features of a benign hyperproliferative process, but in its late stages behaves like an aggressive malignancy. Pathogenesis seems to involve a predisposed individual (genetically susceptible or immunologically compromised) who comes into contact with an infectious agent, most likely a virus. Cytokines papers to play a major role in the growth of the tumor.

A number of treatment modalities for KS are available, but an individualized approach must be adopted considering the clinical sitting, the extent of KS, presence of opportunistic infection and the immune state of the patient.

Classic and endemic KS

1- Localized KS

Local therapy (surgical excision, laser therapy, cryotherapy, radiotherapy and intralesional therapy) is suitable for patients with few lesions.

2- Extensive or progressive KS

Systemic cytotoxic chemotherapy or combination of surgery, chemotherapy and radiation or with chemotherapy and radiation or with chemotherapy alone can be used.

Immunosuppressive treatment-related KS

Cessation, reduction or modification of immunosuppressive therapies led to the resolution of KS in most patients but, in some situations radiotherapy or chemotherapy can be used.

Epidemic (AIDS-related) KS

1. Stable or slowly progressive cutaneous KS

Local therapy (radiotherapy, intralesional therapy, topical therapy , cryotherapy, laser and surgical therapy) is suitable for patients with few lesions.

2. Moderately extensive cutaneous or mucosal KS

Immunotherapy, anti retroviral drugs and the new chemotherapy agents are indicated. Recently, antiangiogenic factors, Apoptosis-inducing agents, hormonal therapy and retinoic acids are used.

3. Aggressive and extensive mucocutaneous or visceral KS

Systemic cytotoxic chemotherapy alone or with anti retroviral drugs can be used.

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