AIDS-Related Kaposi’s Sarcoma: Current Treatment Options, Future Trends

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Kaposi’s sarcoma (KS) is the most common malignancy associated with the acquired immunodeficiency syndrome (AIDS). Recent years have witnessed a decline in the overall incidence of AIDS-related KS, as well as a greater

Introduction

Kaposi’s sarcoma (KS) is a tumor of vascular origin that manifests in four different population groups: (1) classic KS affects mostly elderly men of Mediterranean, East European, or Ashkenazi Jewish heritage; (2) African-endemic KS is confined to young adults and children in sub-Saharan Africa; (3) iatrogenic, immunosuppression-induced KS develops primarily in transplant recipients; and (4) KS associated with the acquired immunodeficiency syndrome (AIDS) primarily affects homosexual males.

Kaposi’s sarcoma is the most common malignancy associated with AIDS, and arises more frequently in homosexual and bisexual men than in any other group infected with the human immunodeficiency virus (HIV).[1,2] Although KS occurred rarely in the United States prior to 1980, its incidence established KS as an AIDS-defining malignancy during the early years of the AIDS epidemic.[3,4] Over the past decade, the epidemiology of KS has changed dramatically, with a significant decline observed in the number of newly diagnosed AIDS patients presenting with KS.[2] The decline in the incidence of AIDS-related KS most likely reflects the greater awareness among the gay community of the need to prevent sexual transmission of HIV infection, resulting in a trend toward more consistent safe-sex practices among homosexual males.[5]

To a somewhat lesser extent, the more frequent use of highly active antiretroviral therapy (HAART) may also have contributed to the overall decline in the incidence of AIDS-related KS in the developed world.[6] However, the prolonged effects of HAART on suppressing HIV infections and thereby influencing the development of AIDS-related KS remain uncertain because of long-term problems, including multidrug resistance, treatment-limiting toxicities, and treatment noncompliance with often complex regimens. Indeed, patients continue to present with KS despite the use of HAART.[6] Recognition of KS as a serious manifestation of AIDS has been neglected in recent years, notwithstanding the extensive morbidity and increasing mortality associated with KS involvement of the lungs, gastrointestinal tract, and other visceral organs.[7]

The characteristic, unsightly cutaneous lesions of AIDS-related KS severely compromise physical appearance and often lead to social stigmatization because of the association of this disease with HIV infection. Diverse clinical presentations of AIDS-related KS pose numerous challenges for the clinician, and treatment approaches must be individualized, taking into account the patient’s overall clinical condition, immune status, psychological status, and other concurrent medical problems and therapies.

There is no known cure for KS. Traditional treatment options, both local and systemic, have been palliative in intent. This fact underscores the need for therapies that not only are safe, efficacious, and convenient but also minimize the risk of drug interactions and toxicities when administered concurrently with any other medications that patients may be taking.

Etiology and Pathogenesis

Although the epidemiologic pattern of AIDS-related KS suggests a virus as the infectious agent,[8] a number of factors are thought to contribute to the development of this disease. The fact that KS occurs at a relatively high rate in homosexual males who are HIV negative,[4,9-11] as well as those who are HIV positive, lends credibility to the argument for an infectious, sexually transmitted etiology.
**Kaposi’s Sarcoma Herpesvirus**

The agent thought to be responsible for KS tumor formation has been designated Kaposi’s sarcoma herpesvirus (KSHV) or human herpesvirus type 8 (HHV-8). This novel human gamma herpesvirus is transmitted by sexual contact or the blood-borne route.[12-15]

Using representational difference analysis, Chang and colleagues[12] identified a novel herpesvirus-like viral DNA sequence in patients with AIDS-related KS, suggesting that a unique virus may be the underlying cause of this type of KS. In additional studies evaluating these DNA sequences in both immunocompromised and immunocompetent KS patients, evidence of HHV-8 was found in 95% of all tissue samples from patients with AIDS-related KS, in HIV-seronegative homosexual males with KS, and in patients with classic KS.[16]

Further characterization of HHV-8 isolated from various KS tumors will be necessary to define more clearly the exact role of this virus in the pathogenesis of KS.

**Role of Cytokines**

The role of cytokines in the regulation of growth of KS cells has received much attention in an attempt to determine the etiology of KS. Cells infected with HIV and KS cells themselves are known to actively secrete high levels of angiogenic growth factors and cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-6, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and oncostatin-M (Onco-M), and to express receptors with a high affinity for several cytokines.[17-19] These cytokines have autocrine (ie, supporting their own growth) and paracrine (supporting the growth of other cells) characteristics that induce the development of lesions with features similar to KS.[20]

It appears that multiple cytokines may act in concert to stimulate the formation and growth of KS cells.[17,21-23] These cytokines activate the expression of several HIV-1 genes, which, in turn, can increase the proliferation of KS cells. Various cytokines may enhance the expression of HIV-tat, the HIV-1 transactivating gene that has been implicated in KS cell growth.[22,24]

The role played by cytokines in AIDS-related KS is further supported by the identification of increased production of certain cytokines in HIV-infected patients. Several cytokines may act locally and over a long period to stimulate the development of endothelial cells into tumor cells.[19,25-27] High levels of cytokines (TNF-alpha, IL-1-alpha, and IL-6) have also been identified in HIV-infected patients following opportunistic infections—a fact that may help explain the development and rapid growth of KS tumors after such infections.[20]

**Role of Hormones**

Since KS occurs predominantly in men both with and without HIV infection, and is rare in women, the possibility that hormonal events may influence the development of KS seems plausible. Findings from HIV-tat transgenic mice indicate that KS-like vascular tumors develop in the skin of male mice only.[28] In a human case study, Bouscarat et al[29] observed proliferative effects of androgen therapy on cutaneous KS lesions in an HIV-infected male. The lesions stabilized and regressed following the discontinuation of androgen therapy.

Epidemiologic data collected over a 10-year span during the pre-AIDS period indicate a male-female incidence ratio of about 4:1 for this tumor.[3,30] However, further study is necessary to confirm the exact role of sex hormones in the etiology of AIDS-related KS.

**Epidemiology**

Although the etiology of AIDS-related KS is complex, certain unique epidemiologic characteristics may offer clues to its origin. These characteristics include a much higher prevalence in males than females,[31] the association of AIDS-related KS with sexually transmitted HIV and HHV-8 infection,[14,32,33] and the recent decrease in the incidence of this disease in male homosexuals.[34,35]

An analysis of KS data (independent of KS type) performed by Beral et al[36] indicated that the geographic distribution of KS varies according to gender and sexual contact, race, age, country of origin, and method of HIV infection. The risk of developing KS is substantially greater among the male homosexual and bisexual populations, and KS is more common among those who acquire HIV by sexual contact vs parenteral drug exposure.[36,37]

Women who develop KS are far more likely to have had sexual contact with bisexual men than with heterosexual men or intravenous drug users, suggesting the possibility of a sexually transmitted cofactor in the development of AIDS-related KS.[36] Beral and colleagues also found that, among adults with heterosexually acquired HIV, a higher prevalence of KS was observed in those from Caribbean countries, Central America, or Africa than in those from North America.[36]
The overall risk of KS occurring in a person with AIDS is more than 20,000 times that of other immunosuppressed persons.[36] Approximately 90% of AIDS-related KS cases in the United States occur in homosexual males, with far fewer cases observed in heterosexual males, women, or intravenous drug users.[19]

The prevalence of HHV-8 infection is high among homosexual men, correlates with the number of homosexual partners, and is temporally and independently associated with AIDS-related KS.[32] These observations strongly support an etiologic role for HHV-8 in AIDS-related KS, and suggest that this virus is sexually transmitted among men.[32]

**Recent Decline in KS as a Presenting AIDS Illness**

The surprising decline in the number of HIV-infected patients presenting with KS in recent years is an enigmatic phenomenon. Jones et al.[38] reported a decline of 10% per year in the incidence of AIDS-related KS (4.8/100 person-years in 1990 to 1.5/100 person-years in 1997). Jacobson and colleagues[39] observed a similar decline in the incidence of KS as a presenting AIDS illness, from 2.6/100 person-years in the early 1990s to 0.75/100 person-years in 1996 through 1997. Results of studies by Rabkin et al.[40] and Buchbinder and coworkers[41] were consistent with these findings. Numerous hypotheses to explain this curious epidemiologic trend have been proposed. These include: a reporting artifact, a shorter incubation period for the development of AIDS-related KS than for opportunistic infections, the failure to report KS as a secondary AIDS diagnosis, the presence of a genetic or environmental cofactor for the development of AIDS-related KS, the transmission of KS as a second sexually transmitted disease (for example, via HHV-8 infection) distinct from HIV, and the use of antiretroviral therapies protecting against the development of KS.[14,38-40,42]

**Clinical Features**

Kaposi’s sarcoma may occur at any stage of HIV infection, although its presentation is usually associated with more severely compromised immune function.[42] The clinical spectrum of AIDS-related KS is diverse. The skin is usually the initial site of involvement, although extracutaneous involvement of the oral cavity and viscera (gastrointestinal tract, lungs) is not uncommon.

Skin lesions typically begin as small, reddish, vascular-appearing macular and papular lesions and progress to large, multiple, pigmented cutaneous nodules and plaques that are firm and palpable and may appear on any body surface.[43,44] Lesions may range in color from pink to purple or brownish-black, tend to have a predilection for the upper body and head and neck areas, and may involve the face, scalp, periorbital skin, and conjunctiva.[44,45] The lesions frequently appear in a symmetric distribution and may follow the creases of the skin.

Oral lesions are the first clinical manifestation of KS in approximately 22% of patients.[45] These lesions are also diverse in appearance and presentation, ranging from asymptomatic purple plaques to large, ulcerated nodules that affect the soft palate and gingiva. Oral lesions may interfere with eating and speaking and bleed easily, causing the patient much physical and emotional discomfort.[43]

The gastrointestinal tract is the most common site of visceral involvement of AIDS-related KS, involving sites from the mouth to the rectum.[45] Other organs that may be affected, particularly during the latter stages of the disease, are the lung, liver, pancreas, and spleen. Visceral involvement is responsible for death in approximately 10% to 20% of patients with AIDS-related KS.[46]

Pulmonary KS is considered to be the most life-threatening form of this disease. Clinically, pulmonary KS may be difficult to distinguish from pulmonary opportunistic infections with respect to symptoms, physical findings, chest x-rays, and arterial blood gases.[47] Initially, patients may present with dyspnea, cough, fever, and, in some cases, hemoptysis.[48] Radiologic findings may show lesions as isolated or diffuse nodules or as diffuse reticular-nodular infiltrates.[43]

Despite the characteristic appearance of endobronchial KS, biopsy of such lesions is often nondiagnostic. Open lung biopsy is performed infrequently because the bronchoscopic appearance of KS is adequate to make a presumptive diagnosis of pulmonary KS in most cases.[49] Recent reports indicated that thallium and technetium-99m scanning can help differentiate KS from other pulmonary lesions.[50]

**Disease Progression**

The clinical course of AIDS-related KS is highly variable and usually correlates with the patient’s overall immune status. Just as the clinical presentation of AIDS-related KS is diverse, the overall pattern and progression of this disease is difficult to predict. It may be indolent and progress slowly with limited organ involvement, or behave aggressively and result in significant morbidity and
Assessing the prognosis of AIDS-related KS based on initial presentation or stage has proven challenging. However, certain data have suggested a possible inverse correlation between the overall health and immune status of patients with AIDS-related KS and disease progression. In a prospective analysis, Vadhan-Raj et al.[52] investigated pretreatment immunologic variables (eg, lymphocyte count, natural killer cell activity, serum immunoglobulins) that might predict therapeutic response, subsequent development of opportunistic infection, and survival in a group of 70 patients with AIDS-related KS treated with interferon-alfa. Their findings suggested that immunologic parameters may be useful in characterizing patients with AIDS-related KS who are most likely to respond to interferon-alfa therapy, and in determining certain treatment strategies.

**Diagnosis**

Clinically suspected AIDS-related KS should be confirmed via biopsy and histologic examination of a skin lesion, lymph node, or other tumor-involved tissue.[44] Biopsies are important for excluding other diseases that may mimic the appearance of KS, including bacillary angiomatosis, vasculitides, or other angiopathic lesions.

**Staging**

Development of a uniform staging system for classifying patients with AIDS-related KS has been difficult. This disease, unlike other cancers, is largely affected by the underlying HIV infection, which influences its growth as well as overall outcome. Thus, AIDS-related KS presents as a disease within a disease.[53]

Comparative assessments of the efficacy of different treatment regimens were historically affected by the lack of established criteria for classifying extent of disease, tumor stage, and response to treatment. In 1989, the AIDS Clinical Trials Group (ACTG) developed a system for classifying AIDS-related KS in order to categorize patients more effectively for clinical trial participation and subsequent evaluation.[54] Classifying patients into good- or poor-risk groups, this three-tiered staging system categorizes disease severity according to the TIS system: clinical extent of tumor (T), immunologic status (I), and evaluation of HIV-related systemic illness (S).[54]

More recently, Krown et al.[53] conducted a prospective validation of the original TIS staging classification developed by the ACTG in order to reflect its impact on patient survival.[53] Table 1 illustrates the recommended staging classification according to these criteria.

**Psychosocial Factors**

The debilitating physical manifestations associated with AIDS-related KS, including severe edema, pain, secondary infection, difficulty in eating and speaking (with oral lesions), and difficulty in walking (with plantar lesions), are compounded by the psychological impact of this disease. The disfiguring cutaneous lesions serve as a constant reminder of the chronicity of the illness to both patients and the people with whom they come in contact. The lesions contribute to social isolation and rejection, and this tremendous psychosocial burden must be taken into consideration when evaluating treatment options.

**Treatment Issues**

Since no cure for KS is currently available, treatment has generally been palliative. Current therapeutic goals for AIDS-related KS are to reduce morbidity by removing or shrinking cutaneous and oral lesions, alleviating pain and edema associated with lymphadenopathy or extensive cutaneous disease, slowing the progression of systemic disease, and maximizing quality of life through control of disfiguring lesions.

Treatment must be individualized based on prognosis and the desired outcome of therapy. In particular, clinical aspects of the underlying HIV disease (eg, extent of immunosuppression, opportunistic infections, neutropenia) are major determinants of the treatment approach for patients with AIDS-related KS.[42] For patients with early-stage disease confined to cutaneous lesions, local therapy generally is indicated, whereas patients with advanced-stage disease (extensive cutaneous disease, visceral disease, lymphedema) tend to respond best to systemic agents.[55]

The decision regarding when to initiate treatment of AIDS-related KS remains controversial. Patients should be informed about treatment options for the various stages of the disease. Treating a patient with asymptomatic lesions may be appropriate in order to elicit a positive psychological effect and prevent disease progression. Treatment of patients with isolated cutaneous lesions and no visceral involvement with a topical therapy is also appropriate, given the potential psychosocial benefits. For patients with minimal cutaneous KS, many physicians institute local treatment (eg, cryotherapy, intralesional therapy, radiation therapy) or use low-dose chemotherapy or interferon-alfa. Visceral KS usually requires chemotherapy. Clearly, there is a clinical need for a topical treatment for patients whose KS is not sufficiently extensive or debilitating to warrant treatment with potentially toxic
systemic therapy.
The treatment algorithm shown in Figure 1 is intended as a general guide for weighing treatment choices against the extent of disease and rate of disease progression.

**Local Therapy**

**Radiotherapy**
Radiation therapy has been the mainstay of palliative local treatment for AIDS-related KS because it is often effective.[56-60] Radiotherapy has been particularly useful in treating tumors of the face and eyelids, benefiting patients both cosmetically and with respect to visual function.[43] In addition, inguinal lymph nodes with confluent KS plaques, oropharyngeal lesions, and plantar lesions may respond well to radiotherapy.[43]

Some controversy exists regarding the use of this therapeutic modality, since irradiating oral lesions can result in significant mucositis. Some investigators contend that radiotherapy should be implemented only for symptomatic oral lesions because of the severe mucositis that may follow.[42] However, Nisce and colleagues[61] have demonstrated good success with radiotherapy for oral lesions, with minimal side effects. Other complications of radiotherapy include loss of facial hair and hyperpigmentation.[59]

**Cryotherapy**
Cryotherapy (liquid nitrogen) has been used for the palliative treatment of minor, cosmetically unacceptable lesions of the face, neck, and hands, primarily by dermatologists.[43] The complete or partial clinical response rate reported for this method of treatment is 85%, using ACTG response criteria.[42] A clinical response to cryotherapy may result despite a lack of penetration to the dermis; this lack of penetration, however, may be responsible for frequent tumor recurrences observed following this therapy.[62]

Hypopigmentation, or "white scarring," is a consequence of cryotherapy that may make this treatment choice unacceptable to patients.[63] Thus, patients should be evaluated carefully, according to skin tone, before initiating cryotherapy. Also, cryotherapy is sometimes painful and often requires multiple office visits to complete a course of therapy.

**Intralesional Therapy**
The most common form of this topical therapy involves intralesional injections of low-concentrations of vinca alkaloids; such injections produce relatively high response rates in the treatment of cutaneous lesions.[64-66] In one study of 11 men with KS, complete or partial clinical responses were observed in 88% of vinblastine-treated KS lesions.[65] In a group of six KS patients who had received no prior or concomitant systemic chemotherapy, complete regression was observed in 70% of cutaneous lesions following only one or two injections of intralesional vincristine.[64]

Intralesional chemotherapy may also be useful for treating symptomatic oral lesions, although residual KS has been known to be present following treatment.[42] Disadvantages of intralesional chemotherapy include the need for multiple office visits, postinjection pain, postinflammatory hyperpigmentation (especially in light-skinned patients), flu-like syndrome, and edema. In addition, exposure of patients and health-care workers to the toxic chemotherapeutic agents required for intralesional therapy may be of concern.

Several biological agents have been evaluated for intralesional therapy in KS patients. These include interferon-alfa,[67] myeloid colony-stimulating factors,[68] and human chorionic gonadotropin (hCG).[69] Although these treatments have been reported to induce regression of KS lesions, they are used less widely than intralesional vinblastine and remain investigational.

**Photodynamic Therapy**
Photodynamic therapy is a relatively new oncologic treatment that has emerged during the last decade. It has been used with some success in the treatment of AIDS-related KS. Photodynamic therapy is based on the reaction of a bound chemical photosensitizer (drugs in tumor tissues) to laser light. This reaction produces chemicals that destroy tumor cells.[70]

Varied outcomes have been reported using photodynamic therapy for AIDS-related KS.[70-72] One patient was treated successfully with pulsed-dye laser therapy for KS facial plaques, with no evidence of lesion recurrence after 12 months.[72] In contrast, the results of a study using pulsed-dye laser therapy for 15 patients with AIDS-related KS demonstrated recurrence of KS lesions within 12 weeks after treatment.[71]

Advantages of photodynamic therapy include minimal pain, a reduced risk of wound infection and bleeding, the ability to treat multiple lesions in one sitting, and the potential for retreatment of tumors that respond only partially. Disadvantages of this treatment modality include local side effects and the requirement for specialized equipment.
effects of pain, edema, and skin necrosis, short-lived cosmetic improvement, and the risk of lesion recurrence.[71]

**Surgical Excision**

Local excision of isolated AIDS-related KS lesions present at certain sites (i.e., oral mucosa, eyelid, penile shaft) may be beneficial to patients.[42] Early recurrence at the site of surgical excision is very common, however. Since KS is a systemic disease, local surgical excision should be reserved for single problematic local lesions in individuals who refuse other local or systemic treatment options.

**Systemic Therapy**

**Single-Agent Chemotherapy**

When KS is extensive or is disseminated to the visceral organs, (i.e., gastrointestinal tract, lungs, lymph nodes), systemic chemotherapy is the treatment of choice. Various single chemotherapeutic agents, including the vinca alkaloids,[73,74] topoisomerase inhibitors,[75,76] and anthracyclines,[77,78] have been evaluated as systemic therapies for KS.

**Liposomal Anthracyclines**

More recently, liposomally encapsulated anthracyclines (doxorubicin [Doxil] and daunorubicin [DaunoXome]) have been used effectively for the treatment of patients with advanced AIDS-related KS. Currently, these agents are considered to be the initial chemotherapeutic agents of choice for extensive, but otherwise uncomplicated, cutaneous KS.[79] The design of anthracycline encapsulation in liposomes results in a longer plasma half-life, greater drug concentration in KS tissue, and less organ toxicity.[80,81] Response rates for liposomal anthracycline therapy in patients with advanced-staged KS have ranged from 25% to 81%. The median duration of response to liposomal anthracyclines in clinical studies for advanced KS has ranged from 4 to 35 weeks.[75,77,82,83] Side effects of these agents include myelosuppression, skin rashes, and erythema of the palms and soles.

**Taxanes**

Paclitaxel (Taxol) has demonstrated significant single-agent activity against advanced AIDS-related KS. Three recent clinical studies of paclitaxel included KS patients with visceral involvement who had received prior anti-KS therapies.

At an initial dose of 135 mg/m² administered over 3 hours every 3 weeks, paclitaxel produced response rates of 65%[84] and 71.4%. At a paclitaxel dose of 100 mg/m² administered every 2 weeks, a complete or partial response was achieved in 59% of patients. The median duration of response was 10.4 months.[86] The most frequent dose-limiting toxicities associated with paclitaxel therapy were neutropenia, anemia, thrombocytopenia, and alopecia.[84,85,86]

Paclitaxel may be the agent of choice for the treatment of patients with refractory, advanced KS.[75]

**Combination Chemotherapy**

The two principal combination chemotherapy regimens for treatment of AIDS-related KS are ABV (Adriamycin, 10 to 20 mg/m²; bleomycin, 10 to 15 U/m²; and vincristine, 1 to 2 mg) administered as an intravenous push every 2 weeks, and BV (bleomycin, 10 to 15 U/m²; and vincristine, 1 to 2 mg) administered as an intravenous push every 2 to 4 weeks. Reported response rates range from 25% to 88% with ABV and from 23% to 72% with BV. The median duration of response to ABV and BV therapies in clinical studies varied from 2 to 9 months.[75] Compared with single-agent Adriamycin (doxorubicin), treatment with the ABV combination regimen may result in higher incidences of neutropenia and peripheral neuropathy but appears to significantly extend the median time to patient relapse.[75]

**Interferon-alfa**

Because of its immunomodulatory, antiviral, and antiangiogenic effects, interferon-alfa has been used extensively for the treatment of patients with AIDS-related KS since early in the disease epidemic.[87-89] The typical dose of interferon-alfa is 1 million to 10 million IU/d. The dose is considerably lower (1 million to 5 million IU/d) when interferon-alfa is used in combination with antiretroviral therapy than when used as monotherapy. Although higher dose levels (50 million IU/m²/d) have been associated with response rates as high as 30% to 50%, side effects, such as flu-like symptoms, thrombocytopenia, neutropenia, neuropathy, hepatic enzyme abnormalities, and mental confusion, preclude administration of interferon-alfa at this high dose.

In patients with AIDS-related KS taking effective antiretroviral therapy, it has been observed that lower doses of interferon-alfa given alone or after induction chemotherapy with anthracyclines or paclitaxel appear to extend the benefit of chemotherapy. The most promising responses have been observed when interferon-alfa is used in patients with CD4+ counts greater than 200 cells/mm³.[90-93]

**Retinoids**
Retinoids, synthetic and natural analogs of retinoic acid, are biological modulators that exert a variety of effects, including cell growth inhibition, induction of normal cellular differentiation, and initiation of apoptosis (programmed cell death).[94] These compounds exert their effects by binding to specific intracellular retinoic acid receptors (ie, RAR-alpha, RAR-beta, RAR-gamma) and retinoid X receptors (RXR-alpha, RXR-beta, RXR-gamma).[95] The stereoisomers all-trans-retinoic acid (tretinoin [Vesanoid]) and 13-cis retinoic acid (isotretinoin [Accutane]) interact primarily with the RAR subgroup of retinoid receptors,[96] whereas 9-cis-retinoic acid (alitretinoin [Panretin]) interacts with both the RAR and RXR receptor subgroups.[97]

The demonstration of the antiproliferative effects of retinoids on KS cells in vitro[1,98,99] provided the rationale for the evaluation of their antitumor effects in human clinical trials. Moreover, the affinity of alitretinoin for both the RAR and RXR receptor subgroups suggested that it may produce clinical benefits distinct from those observed with other retinoid preparations.[100-103]

The results of clinical trials using retinoids for the treatment of AIDS-related KS have varied.[104-106] Treatment with oral tretinoin has shown clinical benefit in patients with AIDS-related KS,[7,106,107] but use of the topical formulation of this retinoid has produced weaker clinical responses.[108] Isotretinoin was found to elicit little cosmetic benefit and considerable toxicity in patients with AIDS-related KS.[109] Thus, despite the promising in vitro findings supporting the use of retinoid therapy for AIDS-related KS, results from clinical studies with tretinoin and isotretinoin have been equivocal and somewhat disappointing.

The only currently approved topical retinoid for self-treatment of cutaneous AIDS-related KS is alitretinoin gel. It has been shown to be efficacious in several patient populations, including treatment-naive patients, patients having had one or more prior anti-KS therapies, and treatment-refractory patients. Phase I/II clinical trials showed alitretinoin gel to be superior in efficacy to no treatment.

Two randomized, double-blind, phase III trials demonstrated significant improvement in the cutaneous lesions of patients with AIDS-related KS who self-applied alitretinoin gel, as compared with those who used vehicle gel, with minimal adverse events. The treatment benefit in these trials was maintained after a wide range of factors were considered; these included extent of disease, immune status, and concurrent antiretroviral therapy.

**Emerging Therapies**

New treatment approaches are emerging for the management of AIDS-related KS. As a better understanding of the pathogenesis of this disease is gained, several new treatment approaches are being designed to more directly intervene in the pathogenesis of AIDS-related KS.

Classes of emerging investigational therapies include antiangiogenesis compounds, cytokine inhibitors, signal transduction inhibitors, and anti-HHV8 agents. Dosages for these compounds have not been established, and all of these agents should be considered experimental and should be utilized only in the clinical trial setting. Furthermore, each of these agents has a known toxicity profile, and unexpected toxicities may emerge as more clinical trial data are accumulated.

**Antiangiogenesis Compounds**

Antiangiogenesis compounds are designed to control vascular proliferation, a major component of KS lesions. Both vascular endothelial growth factor (VEGF) and bFGF have been found in great abundance in KS tissue. Vascular endothelial growth factor is an angiogenesis growth factor, and is thought to be associated with the vascular permeability found in KS tumor tissue. An investigational intravenously administered VEGF inhibitor, SU5416, currently being evaluated in phase I/II studies, has demonstrated some activity in decreasing tumor growth in AIDS-related KS.[110]

Thalidomide (Thalomid), which is well known for its teratogenic effects, has been found to inhibit blood vessel formation, showing promise as an antitumor agent when given as a single drug (dose range, 200 to 1,000 mg/d) to patients with AIDS-related KS.[111]

Another compound, IM862, which is self-administered intranasally, is being studied in phase I/II clinical trials. This agent has elicited objective responses, including responses in patients who were treated previously with chemotherapy.[117]

Still another angiogenesis inhibitor, TNP-470, an analog of flumagillin, has demonstrated antitumor activity in some patients with cutaneous AIDS-related KS when administered as a once-weekly 1-hour infusion.[112]

**Cytokine Inhibitors**

The principal cytokine targets being evaluated for potential modulation include IL-6 and bFGF, both of which stimulate growth of KS cells. Approaches to IL-6 modulation have included an IL-6
monoclonal antibody; IL-4, which downregulates IL-6 production; and retinoid compounds, such as alitretinoin and tretinoin. Modulators of bFGF include interferon-alpha, which reduces bFGF production, and platelet factor 4, which inhibits angiogenesis via an attenuation of growth factor-stimulated endothelial cell proliferation.[113]

**Anti-HHV-8 Agents**

Inhibition of HHV-8 may be desirable for both the prevention and treatment of AIDS-related KS. Studies have shown that virus-inhibiting antibiotics, such as cidofovir (Vistide) prevent HHV-8 replication in infected cell lines.[114] In vitro antiviral drug assays showed that HHV-8 is very sensitive to cidofovir, moderately sensitive to ganciclovir (Cytovene) and foscarnet (Foscavir), and weakly sensitive to acyclovir.[115] A separate sensitivity analysis showed HHV-8 to be insensitive to acyclovir.[114]

Data collected by the Centers for Disease Control and Prevention (CDC) on more than 30,000 HIV-infected persons indicated that treatment with foscarnet, but not ganciclovir or acyclovir, was independently associated with a decreased risk for developing KS.[37] A recent retrospective study of patients with previously diagnosed KS who were treated with foscarnet or ganciclovir for CMV infection showed a longer time to progression among foscarnet-treated patients, as compared with ganciclovir recipients.[116]

**Conclusions**

Kaposi’s sarcoma is the most common tumor associated with HIV and is recognized as an AIDS-defining diagnosis. Although the incidence of AIDS-related KS has declined in the United States in recent years, possibly signaling a changing epidemiologic trend, KS continues to occur in a substantial number of patients with AIDS.

Clues to the etiology of KS suggest major roles for HHV-8 and various cytokines or growth factors. Treatment of this disease and its complications poses many challenges for patients and clinicians. The availability of a self-administered topical gel may provide a desirable alternative for patients whose KS is not extensive or debilitating enough to require systemic therapy or is not responding to other modalities. Other investigational approaches to the treatment of AIDS-related KS reflect significant advances in the understanding of the viral origins and immunopathogenesis of KS. These new approaches may ultimately lead to more effective control or prevention of this difficult and stigmatizing disease.

**References:**


