ELSEVIER

Kaposi's Sarcoma

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Before the first clinical descriptions of the acquired immunodeficiency syndrome (AIDS), Kaposi's sarcoma (KS) was a rare tumor among Western populations, occurring in only 0.02% to 0.06% per 100,000 people.[1] In a typical dermatology practice, it was unusual for a busy practitioner to see more than one such case every 5 years. By June and July of 1981, however, reports from California and New York described large numbers of homosexual men who were afflicted with pigmented skin lesions of KS, either as an initial manifestation of a compromised immune system or following opportunistic infections such as oral candidiasis and *Pneumocystis carinii* pneumonia.[2–4] Since then, approximately 15% to 25% of men infected with human immunodeficiency virus (HIV) in the United States have been diagnosed with KS.[5] Typically, these tumors involve skin and lymph nodes and, less frequently, visceral organs.

Although visceral KS can cause life-threatening symptoms, it is usually the dermatologic manifestations that lead patients to their physician's office. The characteristic, unsightly cutaneous lesions of AIDS-related KS severely compromise physical appearance and often lead to social stigmatization. In response to these concerns and because of the diverse clinical presentations of KS, physicians must individualize treatment approaches, taking into account the patient's overall clinical condition, immune status, psychological status, and other concurrent medical problems and therapies.

The natural history of AIDS-related KS has changed with the widespread use of highly active antiretroviral therapy (HAART). Recent declines in morbidity and mortality due to AIDS have been attributed to the use of these three-drug or four-drug combination antiretroviral regimens, which generally include nucleoside analog reverse transcriptase inhibitors and either protease inhibitors or nonnucleoside reverse transcriptase inhibitors. As patients with HIV and KS live longer due to the beneficial effects of HAART, a renewed interest in the development of therapies that are not only safe, efficacious, and convenient but also minimize the risk of drug interactions and toxicities takes on greater importance.[6]

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This article will briefly review the changing epidemiology of KS in the HAART era and discuss the pathology and pathogenesis of KS. Recent advances in the treatment of HIV-associated KS, including the potential to modulate the natural history of this tumor with HAART, will also be discussed in conjunction with newer and more specific targeted therapies.

Epidemiology

Classical Kaposi's Sarcoma

The first cases of KS were described by Moritz Kaposi in 1872.[7] He detailed the clinical course of 5 men with aggressive "idiopathic multiple pigmented sarcomas of the skin." One patient died of gastrointestinal bleeding 15 months after the initial appearance of the skin lesions, and an autopsy showed visceral lesions in the lung and the gastrointestinal tract. Classical KS, as it is now called, was later characterized as a slowly progressive disease involving the cutaneous surfaces of the lower extremities. The condition has been found to be more common among elderly (Jewish) men from Eastern Europe or Mediterranean countries.

Endemic African Kaposi's Sarcoma

As early as 1971, KS accounted for roughly 3% to 9% of all reported malignancies in Uganda.[8] Four clinically distinct forms of endemic African KS have been described (Table 1). Benign nodular endemic African KS most commonly appears as papules or nodules on the extremities of men in their 40s. Aggressive endemic KS is also seen more commonly among men, but differs from classical KS in that it may affect a younger population and is more likely to spread to visceral organs and lymphatics.[9] In addition to the usual number of patients with typical endemic KS, an increasing number of patients with an aggressive (florid) variant that responds poorly to conventional treatment has been reported.[9] Lymphadenopathic KS may also affect African children in particular. In Eastern and Southern Africa, KS makes up to 25% to 50% of soft tissue sarcomas in children and 2% to 10% of all cancers in children.[10] It generally grows rapidly and contributes to death within 1 to 2 years.

While HIV is also endemic to equatorial Africa, African endemic KS is not related to HIV infection and is a clinical entity distinct from AIDS-KS in Africa. KS in HIV-seronegative and HIV-seropositive patients is now the most

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Table 1. Epidemiology and Clinical Characteristics of Kaposi's Sarcoma Variants

Type	*Epidemiology*	*Occurrence*	*Lesions*
Classical	Mediterranean or Ashkenazic descent; 40–70 years of age; male:female ratio of 10–15:1	0.2% of cancers in US	Some patches, mostly plaques and nodules (usually rounded)
Endemic African	Blacks in equatorial Africa; middle-aged adults and children; male:female ration, 17:1 (adults) and 3:1 (children)	9% of all malignant tumors in equatorial Africa	
1. Benign nodular			Papules and nodules
2. Aggressive			Large exophytic nodules and fungating tumor
3. Florid			Nodules
4. Lymph–adenopathic			Rarely manifests lesions
Iatrogenic/transplant immunosuppression	Immunosuppressive therapy; any age; male:female ration, 2.3:1	400% greater incidence than in the population at large	Patches, plaques, and nodules
Epidemic			
1. HIV-associated	Homosexual males and intravenous drug users; 20–50 years of age; male: female ratio, 106:1	15% of 35% of AIDS patients in early years of the epidemic	Patches, plaques, nodules; often fusiform and irregular; small nodules, patches or plaques
2. HIV-negative	Homosexuals	Currently unknown	

common tumor in central Africa, accounting for 50% of tumors reported in certain central African countries.[11,12]

Iatrogenic or Transplant-Related Kaposi's Sarcoma

Iatrogenic or transplant-related KS affects patients receiving chronic immunosuppressive therapy such as azathioprine, cyclosporine, or corticosteroids to prevent organ rejection or a variety of other medical conditions.[13] It tends to be aggressive, involving lymph nodes, mucosa, and visceral organs in about half of patients, sometimes in the absence of skin lesion.[14] This form of KS predominates in men, although less dramatically classical KS does. The Cincinnati Transplant Tumor Registry contains data collected during the past 30 years on almost 11,000 recipients of solid-organ transplants, many of whom later developed various malignancies.[14] These data indicate that KS constitutes a negligible percentage of all cancers among the general population but constitutes approximately 6% of all cancers in solid-organ transplant recipients, appearing a median of 12 months (average 21 months) after transplantation.

In men of European, Semitic, or African ancestry, the rate of KS after renal transplantation is 500-fold greater than in other populations.[3,14] KS constitutes approximately 80% of all tumors among Saudi Arabian solid-organ transplant recipients.[15]

Given the link between iatrogenic or transplant-related KS and immune status, the use of new targeted immunomodulating therapies, which may cause less systemic immunosuppression, may contribute to a reduced incidence of this disease. However, as the number of solid-organ transplants continues to increase, the absolute number of transplant-related KS also may increase.[16]

Epidemic (AIDS-Related) Kaposi's Sarcoma

Until recently, among patients infected with HIV, the rate of epidemic KS was 100,000-fold greater than that of the general population. This risk appeared most strongly concentrated in men who acquired HIV infection through unprotected sex with men.[17] Specifically, KS is 20 times more prevalent in men who have sex with men than among heterosexual HIV-infected hemophiliacs. The disparity between the sexes is reflected by a male to female ratio of greater than 20:1 among HIV transmission groups.[18]

Explanations for the higher incidence of KS among certain HIV transmission groups have long attracted the attention of dermatologists, epidemiologists, and other members of the medical community. Investigators have speculated on the role that different sexual practices, exposure to various viruses, hormonal milieu, and class II human lymphocyte antigen-DR 5 antigens might have in promoting KS growth.[18,19] More recently, a newly identified herpes virus, termed human herpesvirus-8, or KS-associated herpesvirus (KSHV) has been noted in KS tissues.[20] In contrast to other viruses previously linked to KS pathogenesis (including Epstein-Barr virus, cytomegalovirus, and human papillomavirus), KSHV has been consistently detected in all forms of KS.[21–23] In addition, KSHV DNA is present in the lymphoid system, peripheral blood mononuclear cells, saliva, and semen of patients with KS.[24–26] In HIV-infected individuals the presence of antibodies to this virus is predictive of KS development.[27,28]

Table 1. Continued

Distribution	*Lymph Nodes*	*Visceral*	*Behavior*
Usually confined to lower extremities; disseminated lesions late in course of disease	Rare	Sometimes	Indolent: gradual increase in number of lesions often associated with lymphedems; visceral lesions occur late, often discovered at autopsy; survival 10 to 15 years
Multiple localized tumors, most commonly seen on lower extremities	Rare	Rare	Indolent, resembles classical type disease; survival; 8 to 10 years
Most often located on the extremities	Rare	Sometimes	Progressive development of multiple lessions with invasion and destruction of underlying subcutaneous tissue and bone; survival: 5 to 8 years; Rapidly progressive; locally aggressive and invasive, early visceral involvement; survival: 3 to 5 years; Rapidly progressive; survival: 2 to 3 years
Widely disseminated	Sometimes	Sometimes	
Minimal	Always	Frequent	
Usually localized to the extremities; rarely disseminated	Rare	Sometimes	Variable; tumor may regress after immunosuppressive therapy is discontinued
Multifocal, widely disseminated, often symmetric; frequent oral lesions; Multifocal, often on extremities	Frequent	Frequent	Rapidly progressive; survival: 2 months to 5 years (median, 18 months) with visceral disease; cutaneous disease may be indolent or progress geradually; Indolent, appears to be more benign than classical type
	Rare	Rare	

In the United States, up to 40% of homosexual men who received an AIDS diagnosis in the early 1980s presented with KS at the time of their initial AIDS diagnosis. Ten years later, the percentage of people with HIV infection who had KS as their initial AIDS-defining illness had decreased to approximately 10% to 20%.[18] Factors that may have contributed to this phenomenon that antedated the HAART era include expansion of the AIDS case definition to encompass conditions that may be diagnosed earlier than KS, a decrease in identification or reporting of relatively minor KS lesions, and a decline in exposure to environmental factors associated with KS. In particular, the adoption of "safer" sex practices, which theoretically have reduced the rate of transmission of the putative KS infectious agent, KSHV, is considered to be an important modifier of incidence.[18,19]

The decline in KS incidence has been even more marked during the HAART era, which began in late 1995 and early 1996. In a prospective study of 6,704 men who had sex with men, Buchbinder and colleagues evaluated the relationship between the rate of new cases of AIDS in general and the incidence of AIDS-defining malignancies.[29] Index of AIDS diagnoses per 100,000 patients years fell dramatically from 17.6/100 per year in 1993 to 1.7/100 per year in 1996. Likewise, the risk of death declined dramatically in the same period. A significant decrease in the incidence of KS was reported from 3/100 per year (1993 to 1997) to 0/100 per year in 1996 ($P = 0.06$).

Data collected from a large multistate observational cohort study, the Adult/Adolescent Spectrum of HIV Disease (ASD) project, indicates that the incidence of KS declined 8.8% per year between 1990 (observed incidence, 4.1/100 per year) and 1998 (observed incidence, 0.7/100 per year).[30] The ASD data analysis shows that the use of antiretroviral therapy is associated with reduced risk for the development of AIDS-KS ranging from a 13% reduction with monotherapy or dual therapy to a 59% reduction with triple therapy (Table 2). Improvements in HAART result in prolongation of the duration of HIV infection before the development of

Table 2. Effect of Antiretroviral Therapy on the Risk of Development of AIDS-KS[30]

Antiretroviral Therapy	*Number of Patients*	*Relative Risk (95% CI)*
Mono or dual therapy	21,080	0.87 (0.78–0.97)
Triple therapy	802	0.41 (0.35–0.98)

profound immunosuppression, which is one of the pathogenic factors in the development of KS.[31,32]

Pathology

Although the clinical expression of disease may vary, KS histopathology does not differ among the various risk groups.[33] KS is an angioproliferative tumor that is characterized by slitlike neovascular processes and the presence of proliferating endothelial cells, fibroblasts, infiltrating leukocytes, and a population of spindle-shaped tumor cells.[34] In the very early stages, cutaneous KS is characterized by inflammatory cell infiltration, extravasation of red blood cells, endothelial cell activation, and angiogenesis. This is followed by the appearance of the typical spindle-shaped cells that represent a heterogeneous population dominated by activated endothelial cells mixed with macrophages and dendritic cells.[35,36] In advancing lesions, spindle cells tend to become the predominant cell type, although angiogenesis always remains a prominent feature.[37]

Pathogenesis

Important advances in our understanding of the factors that contribute to KS initiation and growth occurred when investigators perfected laboratory techniques to sustain the growth of a large number of KS cells in culture.[38] Subsequent studies demonstrated that cultured spindle cells from KS lesions were abnormally responsive to a variety of growth factors and that transformed culture media promoted normal endothelial cells to acquire the features of the KS phenotype.[39] These factors, which include Oncostatin M, gamma interferon, interleukin (IL) -1, IL-6, and IL-8, tumor necrosis factor (TNF), granulocyte macrophage-colony stimulating factor (GM-CSF), plateletderived growth factor, basic fibroblast growth factor (BFGF), and vascular endothelial growth factor (VEGF), are also found in the inflammatory cell infiltrates of KS lesions.[40–42] The fact that this inflammatory infiltrate can promote KS growth was elegantly illustrated in experiments in which nude mice were inoculated with KS cells and the media used to support growth of the cells; the mice subsequently developed cutaneous KS-like lesions.[43]

In its early stages, KS behaves more like a hyperplastic proliferative disease than a true cancer.[43,44] BFGF and VEGF mediate spindle-cell growth, angiogenesis, and edema of KS. The abnormal cytokine milieu of HIV infection and the mitogenic effects of HIV-*tat* protein may further act synergistically to stimulate KS spindle-cell growth through autocrine and paracrine loops, leading to an increased frequency and aggressiveness of KS.[43,45–48] However, the recognition that KS lesions are clonal and that KS-like cells can be detected in the peripheral blood of patients with AIDS-associated KS provides evidence for the malignant potential of KS spindlecell proliferation.[49–51]

The role that KSHV plays in stimulating KS growth remains uncertain, but a number of clues are emerging. The genetic sequence of KSHV has largely been determined and portions of its genome are analogous to DNA sequences believed to have oncogenic potential.[52] For example, the bcl-2 family of proteins is known for its ability to modulate apoptosis and KSHV DNA codes for a functional bcl-2 homologue.[53] Dysregulation of bcl-2 may contribute to neoplastic cell expansion via an antiapoptotic effect that enhances cell survival rather than by accelerating rates of cellular proliferation. The KSHV-encoded G-protein coupled receptor (GPCR) may also act as a viral oncogene. In conjunction with VEGF, it appears capable of inducing angiogenesis in transformed mouse kidney cells containing the KSHV-GPCR gene.[54] In nude mice, the introduction of KSHV-GPCR transformed kidney cells results in tumor formation. KSHV may also code for proteins that mimic human cytokine and cytokine response pathways (including IL-6 and macrophage inhibitory protein-1) or stimulate supporting cells to produce angiogenesis factors.[55,56]

Mesri has proposed a model by which multiple factors contribute to the creation of an inflammatory-angiogenic environment (Fig 1).[57] According to this model, circulating KS progenitors and cells latently infected with KSHV migrate to inflammatory sites. Exposure to various inflammatory cytokines results in dedifferentiation of these latently infected cells into KS-like spindle cells and induces KSHV reactivation. Reactivation of KSHV leads to the expression of pathogenic early genes, including viral IL-6, which can activate VEGF and induce angiogenesis. Viral lytic replication in the same cells activates inflammation, which may also stimulate angiogenesis. The HIV-1 Tat protein enhances this inflammatory-angiogenic state by increasing the angiogenic activities of VEGF, bFGF, and gamma interferon, and by increasing the expression of matrix metalloproteinases.[58]

Clinical Manifestations

The clinical features of epidemic KS differ markedly from those seen in classical and endemic African forms (Table 1).[59,60] AIDS-KS tends to be multicentric, often involving mucous membranes along the entire gastrointestinal tract and occurring in atypical locations. Patients may have small, innocuous-looking skin blemishes that are easily overlooked. Alternatively, large and complex skin lesions may be scattered over the body, manifested as red, purple, or brown patches, plaques, or nodules. In some patients, only a few skin lesions are apparent and the lesions may remain unchanged for several years; in others, lesions appear

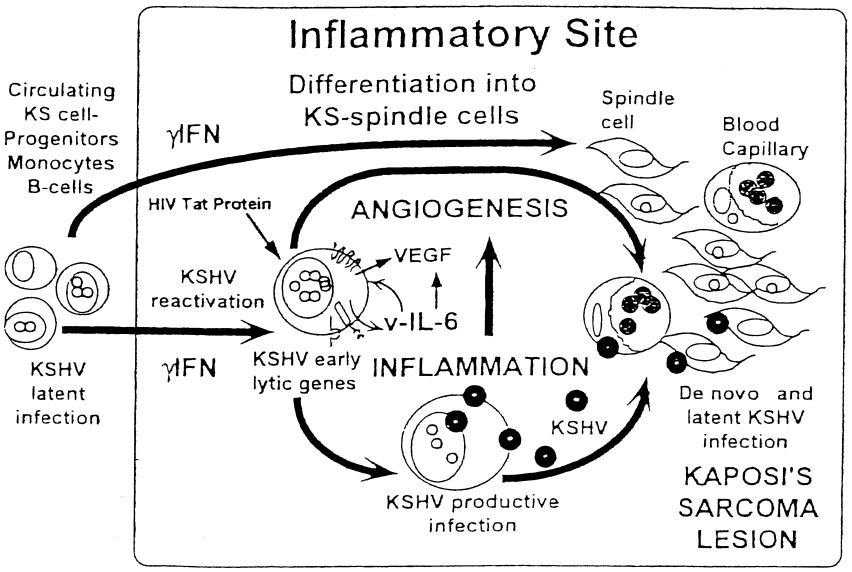

Figure 1. *The creation of an inflammatory and angiogenic milieu. Reprinted with permission.*

rapidly, particularly during a period of heightened immunosuppression or illness. In most patients, new lesions appear gradually during a period of several weeks to months.

KS often involves the head and neck, including the tip of the nose and the retroauricular and periorbital areas. KS involving the eyelid or conjunctiva can interfere with vision.[61] Careful examination of the oropharynx may uncover clinically silent hard and soft palate lesions; if allowed to grow, these lesions can interfere with eating and, rarely, cause airway obstruction. Lymphatic involvement may produce debilitating and cosmetically unacceptable edema, particularly in the periorbital areas, genitalia, and lower extremities. Edema may be complicated by skin breakdown and cellulitis. Foot lesions are common.

Involvement of the tracheobronchial tree, pulmonary parenchyma, and pleura are late and serious KS complications. Patients may have dyspnea, hemorrhagic pleural effusions, and fever. Even in the absence of symptoms, the presence of hilar adenopathy, diffuse interstitial infiltrates, or prominent parenchymal nodularity on chest roentgenogram should heighten clinical suspicion.[62]

Approximately 30% to 50% of patients with cutaneous KS also have gastrointestinal involvement. These tumors may be a source of dysphagia, gastrointestinal blood loss, or obstipation. Finally, KS may involve almost all organs, but central nervous system growth has only rarely been described.

Clinical Evaluation

Initial evaluation of a patient with KS includes a physical examination with particular attention given to the skin and rectal and oral cavities. Clinically suspected AIDS-related KS should be confirmed by biopsy and histologic examination of a skin lesion, lymph node, or other tumor-involved tissue. Biopsies are important for excluding other diseases that may mimic the appearance of KS, including bacillary angiomatosis, cellulitis, vasculitis, or other angiopathic lesions.[63,64] Bacillary angiomatosis *Bartonella* organisms can be identified by Warthin-Starry silver staining. A chest roentgenogram and routine blood tests, including CBC, serum albumin, cholesterol, CD4+ T-lymphocyte cell count, and HIV viral load, may help stratify patients into good- or poor-prognosis groups. Bronchoscopy to establish a diagnosis of pulmonary KS is indicated for patients with abnormal chest roentgenograms, and for whom documentation of lung involvement would result in a change in treatment recommendations.[62] Because the bronchoscopic appearance of pulmonary KS is characteristic, biopsy is rarely needed, and the risk of bleeding at biopsy can be avoided. Additional studies (such as upper and lower gastrointestinal tract evaluation, and computerized tomography scans) are sometimes necessary to exclude other conditions but are rarely necessary as part of a routine staging evaluation. Symptomatic gastrointestinal involvement is best evaluated with endoscopy because barium contrast studies often produce false-negative findings.[65]

Monitoring the growth of KS lesions can be challenging.[66] Bidirectional measurements of several clearly demarcated sentinel lesions may be the easiest to follow, but in patients with more than 25 tumors or with substantial confluence of tumors, photographs of the lesions are helpful. Newer techniques that capitalize on

advances in ultrasound and infrared imaging are also under investigation.[67]

The 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 growth as well as overall outcome. Comparative assessment of the efficacy of different treatment regimens was historically compromised by the lack of established criteria for classifying extent of disease, tumor stage, and response to treatment. In 1989, the National Institutes of Health-sponsored AIDS Clinical Trials Group (ACTG) developed a system for classifying AIDS-related KS to categorize patients more effectively for clinical trial participation and subsequent evaluation.[68] Stratifying patients into good or poor-risk groups, this three-tiered staging system characterized disease severity according to the TIS system: clinical extent of tumor (T), immunologic status (I), and evaluation of HIV-related systemic illness (S). More recently, Krown et al. conducted a prospective validation of the original TIS staging classification developed by the ACTG to reflect its impact on patient survival.[69] The analysis demonstrated that patients with KS confined to the skin and/or lymph nodes who possess minimal oral KS lived significantly longer than patients with visceral KS, bulky oral KS, or tumor-associated edema (27 months versus 15; $p < 0.001$). A change in CD4+ count from 200 to 150 cells/μL was the only modification needed to distinguish between the good and poor immune system categories. Patients with a CD4+ count of >150 cells/μL had a median survival of 39 months; those with <150 cells/μL survived a median of only 12 months ($p < 0.001$). Table 3 illustrates the recommended staging classification according to these criteria.

*Table 3. Revised ACTG Staging Classification for Kaposi's Sarcoma**

Staging	*Good Risk (0) (All of the following)*	*Poor Risk (1) (Any of the following)*
Tumor (T)	Confined to skin and/or lymph nodes and/or nodular oral disease confined to the palate	Tumor-associated edema or ulceration
		Extensive oral KS
		Gastrointestinal KS
		KS in other nonnodal viscera
Immune System (I)	CD4 cells > 150/mL	CD cells <150/mL
Systemic Illness (S)	No history of opportunistic infection or thrush	History of opportunistic infections and/or thrush
	No "B" symptoms (unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea) persisting more than 2 weeks	"B" symptoms present
	Performance status[3] 70 (Karnofsky)	Performance status <70
		Other HIV-related illness (e.g., neurologic disease, lymphoma)

** From Krown, et al.[69] The revised CD4+ cutoff of 150 cells/mL is lower than the original proposal of 200 cells/mL. Example of staging: A patient with KS restricted to the skin, CD4+ count of 10 cells/mL, and a history of Pneumocystis carinii pneumonia would be $T_0I_1S_1$.*

General Treatment Issues

No therapy consistently results in shrinkage of all KS tumors; hence, treatment has generally been palliative. Therapeutic goals for all patients with KS are to reduce morbidity by removing or shrinking cutaneous and oral lesions; alleviating pain, edema, and ulceration associated with lymphadenopathic or extensive cutaneous disease; and slowing the progression of systemic disease while maintaining or improving the quality of life through control of disconcerting lesions.[6]

Treatment is individualized according to prognosis and the desired outcome of therapy. Associated medical conditions also affect the treatment decision. In patients with transplant-related KS, concern regarding allograft rejection generally would preclude reducing the dose of the immunosuppressant therapy as a treatment option for localized cutaneous disease. Another consideration regarding the reduction of immunosuppression in a patient with transplant-related KS is the transplanted organ; in the case of heart or liver transplant, allograft rejection may mean the death of the patient. For patients with underlying HIV disease, extensive immunosuppression, opportunistic infections, and neutropenia are major determinants of the treatment approach.[6] In contrast, in developing countries where endemic KS is prevalent, the largest determinants of care are the limited economic resources of the state.[70]

The decision regarding when to initiate KS treatment remains as much art as science. Although Figure 2 provides an algorithm for the treatment of AIDS-associated KS, this is not to imply that one single approach is best. Patients should be educated about treatment options for the various stages of the disease. For patients with few cutaneous or oral lesions that are neither emotionally nor physically distressing nor progressive, the patient and physician may choose to wait before initiating therapy (expectant observation). During expectant observation, cutaneous lesions may be camou-

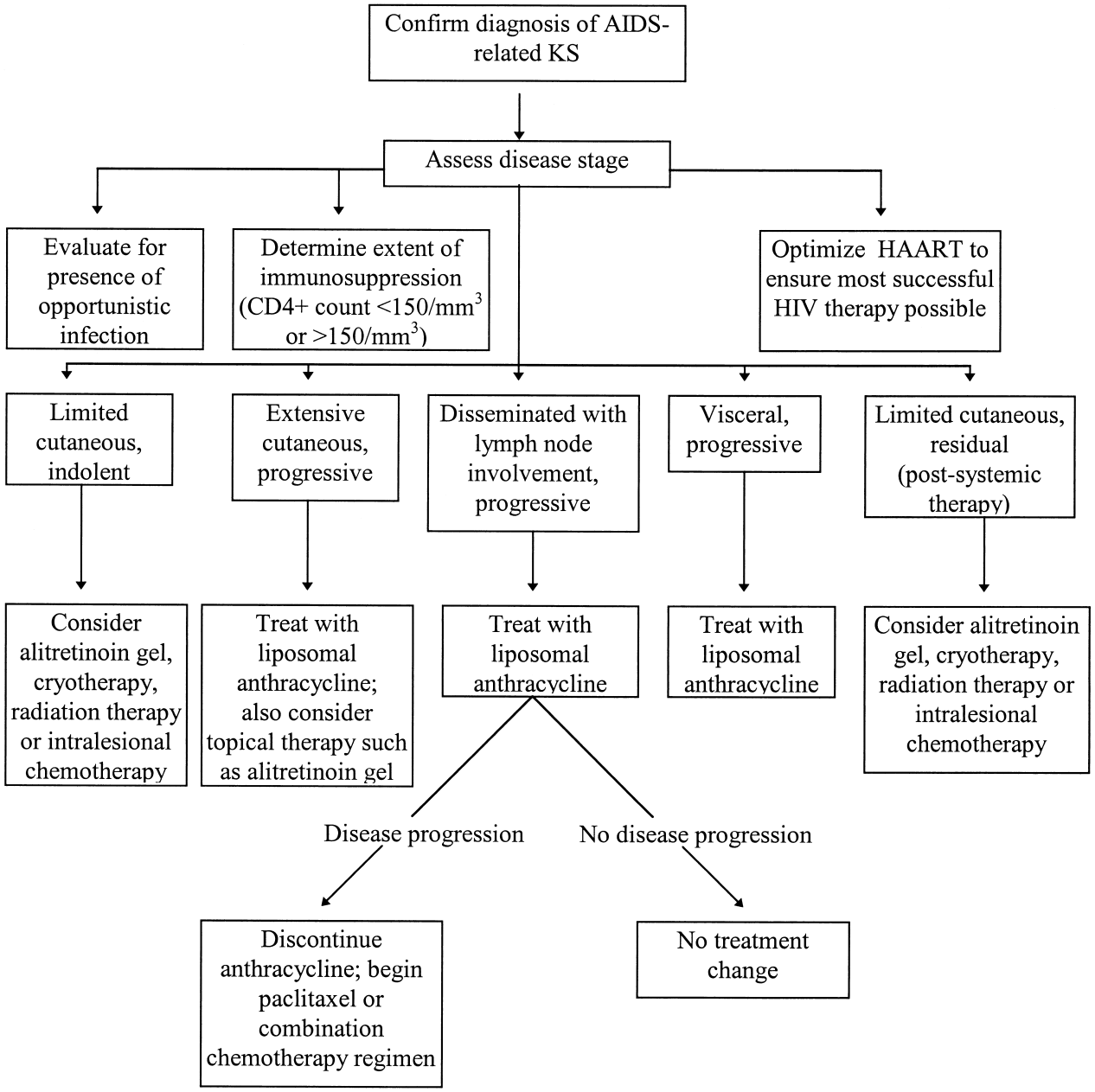

Figure 2. *Treatment of AIDS-related Kaposi's sarcoma.*

flaged with cosmetic cream concealers. On the other hand, treating a patient with asymptomatic lesions may help elicit a positive psychological effect and prevent disease progression.

For patients with minimal cutaneous KS, many physicians institute local treatment (e.g., intralesional therapy, radiation therapy, cryotherapy, or application of topical retinoid gels) or low-dose chemotherapy or, less frequently, interferon-alFa. Visceral KS usually requires chemotherapy to prevent tumor-related complications, decrease pain and discomfort, and prolong survival.[6]

Treatment

Classical Kaposi's Sarcoma

Treatments were first developed for the classical form of KS, and descriptions of such treatment have chiefly appeared in reports of small studies at single institutions or in case reports.[11] Typically, the disease is multifocal and recurs despite treatment. In one series of 129 patients, only 30% were disease-free at 10 years, but only 1 had died of KS.[71]

For patients with single lesions, excisional biopsy often provides adequate treatment. Simple excision is also appropriate for resectable recurrences. Of 52 patients who underwent surgery as the primary treatment, 29 (56%) had no recurrences for 1 to 162 months (median, 15 months).[71]

Once the diagnosis is established, observation is appropriate for immunocompetent, asymptomatic patients with little progression of disease over a long period. Of 39 such patients, 15 (38%) remained progression-free for 1 to 83 months (median, 4).[71] In a multivariate analysis, immunosuppression was the only statistically significant independent factor affecting time to progression. A conservative approach to therapy is underscored by the finding that the disease may regress spontaneously and may not recur for long periods.[11]

Patients with limited disease may be treated with single-dose extended field radiation therapy. Symptomatic and objective response rates on the order of 60%–95% are generally obtained.[72] Megavoltage electron therapy, whole-body-surface electron irradiation, and total-skin electron-beam therapy given once a week for 6 to 8 consecutive weeks have also resulted in high response rates.[72,73] Altough residual pigmentation may be present post-radiation treatment, biopsy rarely reveals active KS.

Patients with extensive or recurrent KS can be treated with a combination of surgery, chemotherapy, and radiation, or with chemotherapy alone. Complete remissions of disseminated disease can occur with chemotherapy and radiation or with radiation therapy and can last for years. Chemotherapies useful for AIDS-associated KS are effective in this group with response rates varying between 50% to 80% and include α-interferon, vinblastine, bleomycin, doxorubicin, vincristine, and etoposide.[11]

Iatrogenic or Transplant-Related Kaposi's Sarcoma

The chemotherapy agents used for classic and AIDS-associated KS are also effective for treatment of immunosuppression-associated KS. Five patients whose tumors did not shrink following a reduction or discontinuation of immunosuppression therapy or local radiation therapy received a combination of doxorubicin, bleomycin, and vincristine.[74] Two patients had complete responses, and 2 had partial responses. The median duration of response was more than 13 months (range, 8 to 45).

Modifying the dose of immunosuppressive drugs may be more problematic in the case of recipients of heart or liver transplants. Discontinuation of immunosuppressive therapy is an option in renal-transplant recipients since dialysis is available.[74,75] Cincinnati Tumor Transplant Registry data revealed that 38% of solid-organ transplant recipients experiencing a complete remission of KS were treated with a reduction or cessation of immunosuppressive therapy; patients with nonvisceral disease had a higher remission rate (53%) than those with visceral disease (27%).[14] However, among renal allograft recipients whose KS was successfully treated with reduction or cessation of immunosuppressive therapy, 59% lost their allograft and another 6% had permanently impaired function.[76]

Endemic KS

Strategies used to treat classical KS have also proven effective for endemic KS in a few published series.[11] Of 10 Zambian men (mean age, 41 years) who presented with typical endemic KS, all had a prompt response to a combination of dactinomycin and vincristine.[9] Of 47 HIV-seronegative South African patients who were treated between 1980 and 1990, the objective rate of response was more than 80% with either radiation therapy or chemotherapy.[10]

AIDS-Associated KS

Highly Active Antiretroviral Therapy

Recent studies indicate that patients who respond to HAART have decreased plasma levels of HIV, decreased incidence of opportunistic infections, increased circulating CD4+ T-cells, and decreased short-term mortality.[31,77–79] Reports further suggest that conditions previously deemed intractable, such as cytomegalovirus retinitis, progressive multifocal leukoencephalopathy, azole-resistant mucocutaneous oral candidiasis, and intestinal cryptosporidiosis and microsporidiosis may stabilize or even diminish after increases in CD4+ cell counts or significant reductions in HIV plasma viral RNA loads.[80,81] KS can also be added to this list.

The mechanisms by which HAART influences growth of KS lesions remain incompletely understood. The antiviral drugs that are typically utilized in HIV-drug regimens appear to have little if any intrinsic inhibitory activity against KSHV. Rather, by downregulating HIV expression while promoting some component of immune reconstitution it appears that HAART may play an active role in regression of KS tumors.[82]

Support for the assertion that effective suppression of HIV replication has important clinical implications comes from a preliminary report involving 13 patients with AIDS-related KS.[83] Before initiation of HAART, these patients received one or more systemic therapies for severe KS for a median of 8 months. After the initiation of effective antiretroviral therapy, their median HIV viral load was reduced from 43,000 copies/mL to nondetectable levels and their median CD4+ cell count increased from 79/mm^3 to 180/mm^3. None of the 13 patients experienced progression of KS despite discontinuing systemic KS therapy for a median of 10 weeks (range 0 to 41 weeks). Similar results were re-

ported among eight patients with KSHV antibodies and documented KS. The initiation of HAART led to tumor shrinkage and a decline in KSHV viral loads.[84] Effective suppression of HIV viral RNA levels among patients with previously treated cutaneous and visceral KS considerably prolonged time to treatment failure.[85,86] Such an approach suggests that HAART alone may be an effective maintenance therapy for patients with KS. However, because the response of KS to HAART is unpredictable, specific localized or systemic treatment is often instituted as well.[11,87]

Although preliminary clinical reports concerning the impact of HAART on modifying both the incidence and clinical expression of KS are encouraging,[88] enthusiasm must be tempered by several mitigating factors: our uncertain knowledge of the length of time that HAART can effectively suppress viral replication; the inability of antiviral therapies to restore completely impaired immunity; and our imperfect knowledge of how best to maintain patient compliance in a setting in which medications must be taken multiple times a day, have unpleasant side effects, and interact unpredictably with numerous other medications.[89,90]

Local Therapy

For patients with localized disease, photodynamic therapy using intravenously administered Photofrin 48 h before exposure to 100 to 300 J/cm^2 of 630-nm light resulted in a 68% partial response.[91] This therapeutic approach is still considered investigational but may be useful for small, cosmetically unsightly lesions.[92,93]

A more common modality employed for the treatment of localized KS is externally applied electron-beam therapy. Electron-beam therapy is highly effective in relieving facial and eyelid edema. It has also been used to shrink inguinal lymphadenopathy and plantar lesions but is usually not a first-line treatment for control of lower extremity edema or oral lesions because of the potential to worsen lymphedema and skin compliance when applied to the legs and to cause mucositis when used to treat oral lesions.[94,95] Other complications of radiotherapy include loss of facial hair, hyperpigmentation, and fibrosis.[92]

Cryotherapy (liquid nitrogen) has been used successfully, primarily by dermatologists, for the treatment of disconcerting lesions of the face, neck, and hands.[6] Using ACTG response criteria, this modality has yielded a complete and partial response rate of 85%.[94] A clinical response to cryotherapy may be achieved despite a lack of penetration to the dermis; this lack of penetration, however, may be a reason that frequent tumor recurrences occur with this modality. Cryotherapy is sometimes painful and some patients will need repeated applications of liquid nitrogen. Therapy may also cause hypopigmentation. Consequently, patients should be evaluated carefully before this modality is recommended.[6,96]

Small cutaneous and oral KS lesions can be treated by intralesional injections of 0.1 mg of vinblastine and 0.1 ml sterile water using a tuberculin syringe. Treated lesions will usually fade and complete and partial remissions between 70% and 88% have been reported after one or two injections of intralesional therapy.[97,98] Disadvantages of intralesional chemotherapy include the frequent need for repeated treatments, pain at the injection site, postinflammatory hyperpigmentation, flulike syndrome, and edema.[6]

Several biological agents have also been injected intralesionally for the control of KS. These include interferon-alpha,[99] GM-CSF,[100] and human chorionic gonadotropin (hCG).[101] Although these agents have been reported to induce regression of KS lesions, experience with them is largely anecdotal and they are rarely utilized outside the context of clinical investigation. This is underscored by experience with hCG. Although intralesional administration of this agent led to tumor regression in selected patients, highly purified hCG was inactive in vitro, suggesting that either a copurified molecule or degraded product of hCG was responsible for antitumor activity.

Alitretinoin gel 0.1% (Panretin; Ligand Pharmaceuticals, San Diego, CA) is the only topical, patient-administered therapy approved by the Food and Drug Administration for the treatment of KS. Alitretinoin is a retinoid receptor panagonist. It is presumably this unique receptor-binding profile that gives alitretinoin its efficacy in the topical treatment of KS. It has been shown to be effective in several patient populations, including treatment-naïve patients, patients having one or more prior anti-KS therapies, and treatment-refractory patients.[102] Most patients require 4 to 8 weeks of treatment before responses are noted. Dermal irritation is common at the site of application of the gel and, because minimal drug is absorbed systemically, the gel would not be expected to affect the growth of new lesions in untreated areas.[103]

Systemic Chemotherapy

A number of cytotoxic chemotherapeutic agents have also been shown to have systemic activity in AIDS-KS, including bleomycin,[104] vinca alkaloids,[105,106] etoposide,[107] and anthracyclines.[108] For patients with extensive or advanced disease, combination regimens containing bleomycin and vincristine,[109] or doxorubicin, bleomycin and vincristine/vinblastine (ABV)[107,110–112] have produced response rates as high as 60% to 88% but with appreciable toxicity. Liposomal preparations of doxorubicin and daunorubicin are also frequently employed for KS treatment in part because of their lower toxicity profile.[111,113–116] In randomized multicenter trials, each of these liposomal agents has been found to be

Table 4. Pathogenesis-based Therapies

Agent	*Dose and Schedule*	*Response Rates*
Antiangiogenic compounds		
TNP-470	10–70 mg/m^2 weekly IV	18%
Tecogalan	30–240 mg/m^2 weekly IV	0%
Thalidomide	200–1,000 mg daily orally	47%
IM862	5 mg daily or every other day intranasally	53%
SU-5416	45 mg/m^2 twice weekly IV	*
Angiostatin	Not yet defined	
Hormonal agents		
Liposomal all-*trans*-retinoic acid	60–100 mg three times weekly	23%
9-*cis*-retinoic acid	60–100 mg daily orally	37%
Human chorionic gonadotropin	5,000–10,000 IU daily SC	33%

** Study in progress; IV, intravenous; SC, subcutaneous.*

superior to conventional chemotherapy (bleomycin and vincristine with or without nonliposomal doxorubicin) in terms of response rate and toxicity profiles. At a dose of 20 mg/m^2 every 3 weeks for liposomal doxorubicin, and 40 mg/m^2 every 2 weeks for liposomal daunorubicin, side effects, including alopecia, neuropathy, and cardiomyopathy are rare. For advanced KS unresponsive to first- and second-line options, infusions of low-to-moderate dose paclitaxel are associated with response rates of 53% to 65%.[117,118] An NIH-sponsored AIDS-Malignancy Consortium (AMC) study is currently randomizing patients with KS to receive either liposomal doxorubicin or paclitaxel. The results of this study will likely determine whether the potential side effects of paclitaxel, such as leukopenia, hair loss, and peripheral neuropathy, are sufficiently burdensome to limit its use only to patients with advanced or refractory disease.

Interferon-Alpha

Interferon-alFa was among the first agents studied for the treatment of epidemic KS. It was viewed as a particularly attractive option for patients with CD4+ T-lymphocyte counts >100 cells/mm^3 because of its immunomodulatory, antiviral, and anti-angiogenic effects.[119] As a single agent at a dose of 50 million IU/m^2/d, response rates of 30% to 50% have been achieved but with unacceptable toxicity. More commonly, interferon-alfa is given at a dose between 1 million to 5 million IU/d in conjunction with HAART.[120] Flulike symptoms, neuropathy, hepatic enzyme elevations, mental confusion, and inconvenience associated with daily subcutaneous injections have limited the utility of this therapeutic modality now that liposomal anthracyclines can be given with fewer side effects and greater efficacy.[121]

Retinoids

Several clinical trials have examined the role of retinoids as a systemic therapy for AIDS-related KS 13-*cis*-retinoic acid has shown limited value and considerable toxicity in the treatment of poor-risk patients.[122–124] All-*trans*-retinoic acid yielded inconsistent results in five clinical trials, eliciting objective response rates for the intent-to-treat patients ranging from 0%[125,126] to 40%.[127] In contrast, 9-*cis*-retinoic acid binds not only to the three RARs but also to the three RXRs, so it may provide clinical benefit distinct from other retinoids.[128] Two recent studies enrolled a total of 123 patients to receive 60–100 mg/day of oral 9-*cis*-retinoic acid.[129,130] Partial and complete response rates of 37% were achieved in both trials. Treatment-related toxicity included headache, fatigue, dry skin, alopecia and elevations in triglycerides. The vast majority of patients also received HAART. The influence of anti-HIV therapy thus cannot be clearly ascertained.

Future Directions

Pathogenic-based therapies have become an important area for the development of anti-KS therapies.[131] Factors critical for the growth and spread of KS have been identified for therapeutic development. A number of antiangiogenic compounds and hormonal therapies have been evaluated in limited-phase I/II studies (Table 4). Inhibitors of metalloproteinases and antiviral substances that may have activity against HIV or KSHV are also under investigation (Table 5).[132]

Among the antiangiogenesis compounds, IM-862 is one of the most interesting. This dipeptide was identified from the soluble fractions of the thymus and found to promote sheep red blood cell rosetting. In vivo it possesses antiangiogenic effects when tested in the chicken allantoic membrane assay, and antitumor effects in murine tumor models, in syngeneic mice bearing various tumor types, and in human tumor xenograft models. A randomized phase–II trial in KS was recently completed.[133] The drug was administered intranasally either every other day or daily for 5 consecutive days, followed by 5 days off drug. Patients in this trial had a median CD4+ cell

Table 5. Novel Targeted Therapies of AIDS-associated Kaposi's Sarcoma

Target	*Drugs*
Matrix metalloproteinase inhibitors	Col-3
	Bay-1
	TIMPs
	IL-12
VGEF-inhibitors	Anti-sense VGEF
	PTK 878/ZK
bFGF-inhibitors	Anti-sense bFGF
IFN-β	IL-12
KSHV	IL-12
	INF-α
	ganciclovir
	foscarnet
	lobucavir
HIV Tat protein	HAART
	IFN-α

VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; IFN, interferon; TIMPs, tissue inhibitors of metalloproteinases; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.

count of 162/mm^3, and more than half had been treated previously with chemotherapy. Major responses were documented in 16 (36%) of 44 treated patients. Encouragingly, no significant toxicities were reported. A phase–III AMC study comparing IM-862 with placebo in patients on stable HAART regimens is currently accruing patients.

Thalidomide is another interesting drug that is well known for its teratogenic effects. It not only inhibits angiogenesis but also blocks TNF-α production and inhibits basement membrane formation and intercellular adhesion molecules. In one study, 20 patients with AIDS-KS received between 200 and 1,000 mg/day of thalidomide, based on individual tolerance.[134] A partial response was achieved in 8 (47%) of 17 assessable patients, and the median time to progression was 7.3 months. Toxicities have included fever, rash, peripheral neuropathy, and depression.

Other antiangiogenic compounds have been clinically evaluated for AIDS-KS and include TNP-470,[135] SU-5416,[136] and tecogalan,[137] but their role in the treatment of AIDS-KS appears limited. TNP-470 is an analog of fumagillin, a substance previously identified to inhibit bFGF-induced endothelial cell proliferation. SU-5416 is a novel compound that inhibits phosphorylation and activation of Flk-1, the signaling-receptor for VEGF. SU-5416 also inhibits VEGF-induced endothelial cell proliferation and migration. Tecogalan inhibits endothelial cell and KS spindle-cell growth in vitro, and KS cell-induced capillary permeability in the murine model. Unfortunately, TNP-470 and SU-5416 have been associated with erratic and sometimes severe toxicities, including ocular and pulmonary hemorrhage; in a phase-I study of patients with AIDS-KS, tecogalan was not associated with a single response.[137]

Other new classes of antiangiogenic compounds include matrix metalloproteinase inhibitors (MMPIs).[132,138] MMPIs block tumor growth and metastases by inhibiting enzymes that degrade matrix proteins such as collagen, gelatin, and fibronectin. Col-3 is one such agent that the AMC is poised to evaluate in a phase-II study. PTK787-ZK, which acts as an inhibitor of VEGF, is another agent that is currently being investigated for the treatment of KS.

Inhibitors of other targeted molecules such as IL-6, IL-8, and TNF are at various stages of development.[132] IL-12 also appears to have angiogenic inhibitory activity that may be mediated via induction of interferon-δ with resulting decrease in VGEF production and matrix metalloproteinase activity.[139] Anecdotal reports of KS regression after treatment with foscarnet[140] and several studies indicating a diminished incidence of KS treated with anti-herpes agents[141] suggest that, under some circumstances, inhibition of KSHV may also be of value. Because KSHV latently infects endothelial cells, the benefit of such drugs may best be to prevent primary infection.

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