MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

Kaposi sarcoma: review and medical management update

Mahnaz Fatahzadeh, DMD, MSD, Newark, NJ
NEW JERSEY DENTAL SCHOOL-UMDNJ

Despite recent advances in our understanding of pathogenic mechanisms involved, the true nature of Kaposi sarcoma remains an enigma. Four clinical variants have been described for the disease, differing in natural history, site of predilection, and prognosis. All forms of Kaposi sarcoma may manifest in the oral cavity and Kaposi sarcoma–associated virus appears essential to development of all clinical variants. The spectrum of therapeutic strategies is broad and selection of appropriate intervention mandates a thorough understanding of disease spread and the patient's symptomatology, as well as risks and benefits of therapy. This article provides an overview of epidemiology, subtypes, clinical course, pathogenesis, and management strategies for Kaposi sarcoma. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:2-16)

Kaposi sarcoma (KS) is a multifocal angioproliferative disorder of vascular endothelium, primarily affecting mucocutaneous tissues with the potential to involve viscera.[1] Four clinical variants of classic, endemic, iatrogenic, and epidemic KS[2,3] are described for the disease, each with its own natural history, site of predilection, and prognosis.[4,5] In the absence of therapy, the clinical course of KS varies from innocuous lesions seen in the classic variant to rapidly progressive and fatal lesions of epidemic KS.[6,7]

Classic KS is a rare and mild form of the disease first described by the Hungarian dermatologist Moritz Kaposi in the 19th century as a vascular tumor affecting the lower extremities of elderly men from the Mediterranean region.[8,9] Although primarily detected in the Eastern European and Mediterranean basin,[10,11] pockets of this variant in other geographic regions have also been reported.[5,12] The male-to-female ratio for classic KS is 17:1[13] and lesions primarily present as multiple purplish-red pigmented plaques on the skin of arms, legs, and trunk of men older than 50 years in the endemic areas.[5,11,14] Lesions tend to start on the extremities, progressively enlarge, and spread to more proximal sites.[14] Classic KS has an indolent course, often spares viscera, and does not require aggressive therapy.[11,15] There is evidence that some patients with classic KS may be at a greater risk for development of solid or hematopoeitic neoplasms.[10]

Iatrogenic KS refers to the form associated with the use of steroids, immunosuppressive agents, and drugs with antitumor necrosis factor (TNF) activity in patients with autoimmune disorders, inflammatory conditions, or solid organ transplantation.[16-20] Interestingly, the incidence of KS following bone marrow (BM) or peripheral blood stem cell (PBSC) transplantation is low with only a few cases reported in the literature.[21-23] Iatrogenic KS has a 3:1 male predilection[13]; may involve mucocutaneous tissues, lymph nodes, or viscera[2,24]; and tends to affect liver transplant patients more often than recipients of kidney or heart allografts.[25] Although no clear association between dose or duration of immunosuppressive therapy and development of iatrogenic KS has been reported,[19] discontinuation of therapy appears to improve iatrogenic KS.[2,3,4,19]

African or endemic KS is a variant of disease affecting human immunodeficiency virus (HIV)-seronegative children and young adults in sub-Saharan Africa.[9,26] Following the HIV epidemic, the incidence of this variant has increased significantly, particularly in the pediatric population, in the African subcontinent.[13,27-30] The clinical course of endemic KS is variable and includes indolent skin disease, locally infiltrative lesions of extremities, and aggressive visceral involvement with potentially fatal sequela.[5,9,11,31] Generalized lymphadenopathy is a common feature of endemic KS,[9,32] and oral mucosa is infrequently affected.[33]

Epidemic or acquired immunodeficiency syndrome (AIDS)-associated KS (AIDS-KS) is the most common variant and a more aggressive form of this disorder.[9,11] It is also the second-most frequent tumor affecting HIV patients worldwide,[34] known to have an unfavorable prognosis in the absence of therapy.[9,31,35] The incidence of epidemic KS is correlated with the mode of HIV acquisition[36-38] and in the western hemisphere, HIV-seropositive male ho-

Fig. 1. Clinical presentation of an irregular pink patch at the tip of the nose of an HIV-positive male.

Fig. 2. Clinical presentation of an irregular light purple patch on the upper thigh of an HIV-positive male.

mosexuals are 5 to 10 times more at risk for KS compared with other groups with high-risk behaviors.[34] This is in stark contrast with Africa, where AIDS-KS affects younger age groups and both genders, albeit unequally.[39]

Although epidemic KS may develop throughout the entire spectrum of HIV disease, it is more likely to occur in the context of advanced immunosuppression,[6] and could represent the first manifestation of HIV infection in some patients.[15] Lesions of AIDS-KS tend to enlarge, multiply in number, become more nodular, or coalesce in association with immune deterioration and drop in CD4 count.[40] Epidemic KS often affects mucocutaneous tissues as multifocal plaques, patches, and nodules with a predilection for the face and lower extremities (Figs. 1 and 2).[1,6,41,42]

More than half of patients with AIDS-KS may have visceral involvement.[34] Manifestation of AIDS-KS in the gastrointestinal tract may occur independent of skin disease and lead to abdominal pain, diarrhea, weight loss, bleeding, and vomiting when symptomatic.[1,34] Pulmonary KS, the second-most common site of extracutaneous KS, is a late and potentially fatal complication presenting with cough, dyspnea, and hemoptysis in symptomatic patients.[1,43,44] Asymptomatic pulmonary KS may manifest with abnormal radiographic findings on chest x-ray, which could be differentiated from opportunistic infections by gallium and thallium scans.[34,45] Lymphedema, a complication resulting from obstruction of lymphatics, frequently affects the lower extremities and periorbital region of HIV patients.[15,41] It may develop before or concurrent with diagnosis or progression of KS[26] and, in the context of AIDS-KS, indicates advanced disease and poor prognosis.[6,32,46,47]

MANIFESTATION OF KS IN THE ORAL CAVITY

All forms of KS may present in the oral cavity; however, oral lesions are more likely to occur with the epidemic variant of the disease.[5,9,11,36,48,49] The oral cavity is the first clinical site of disease in 22% of patients with KS,[5,36,50-52] and up to 71% of HIV patients may develop oral KS concurrent with cutaneous and visceral involvement.[5,36] Oral KS may also be the initial indication of undiagnosed HIV infection.[9,15,36] The most frequently affected oral sites include hard palate, gingival, and dorsal tongue (Figs. 3 and 4).[7,15,36] Oral KS may present as solitary, mutifocal, or multicentric macules, plaques, or nodules of different sizes, varying in color from deep red to bluish-purple. Multifocal lesions may gradually coalesce into confluent, exophytic masses affecting oral mucosa.[36,53] Resorption of alveolar bone underlying KS and tooth mobility,[54,55] primary intraosseous KS of the jaw bones,[52] and involvement of major salivary glands have also been documented.[54,56] Oral KS may cause local tissue destruction, pain, bleeding, difficulty with mastication, or interference with wearing of oral prosthesis.[5,7] Development of KS in the oral cavity also has prognostic implications for untreated HIV patients,[15,57] who are found to have higher death rates than patients affected only by cutaneous disease.[57,58]

ROLE OF KSHV IN KS PATHOGENESIS

The pathogenesis of KS involves infection with human herpes virus type 8 (HHV-8), also known as Kaposi sarcoma–associated herpes virus (KSHV).[31] KSHV is a DNA virus first isolated by Chang et al.[59] from the KS lesion of an AIDS patient in 1994. It is believed to be the infectious agent necessary for development of all clinical subtypes of KS irrespective of

Fig. 3. Clinical presentation of a bluish-purple mass affecting the palatal aspect of maxilla in an HIV-positive male.

Fig. 4. Clinical presentation of purplish-blue gingival enlargement affecting anterior and right buccal maxillary arch in an HIV-positive male.

differences in presentation, natural history, or prognosis.[4,9,31,46] The finding that KSHV induces angiogenic and inflammatory cytokines, as well as gene products implicated in angiogenesis, may suggest a direct role for this virus in KS pathogenesis.[60] Also, viral load of KSHV in lesions positively correlates with clinical progression of KS from patch/plaque to the nodular stage.[46] The etiologic role for KSHV is further supported by higher risk of KS development in KSHV-infected solid organ transplant recipients and HIV-seropositive patients.[10,49] In addition, the rarity of KS occurrence following stem cell transplantation (SCT) has been attributed to elimination of latent KSHV reservoir from the body by total body irradiation before transplantation.[23] Of interest is also the rare development of nonmalignant illness, including fever, cutaneous rash, splenomegaly, hepatitis, bone marrow failure, and plasmacytosis coincident with primary infection or reactiva-

tion of KSHV in solid organ or peripheral blood stem cell (PBSC)/BM transplant recipients,[61,62] development of which appears related to the patient's immunosuppressed state.[23] Some investigators recommend pretransplant screening of donors and recipients for KSHV, as well as prophylactic measures and close follow-up for KSHV-seropositive patients in highly endemic regions.[23]

Although necessary, KSHV may not be sufficient for initiation and progression of KS.[4,7,31,36] This may explain why despite high prevalence of KSHV in the endemic regions and in high-risk populations, KSHV infection is frequently asymptomatic and does not lead to KS.[15,46,63,64] Regression of iatrogenic KS with the cessation of immunosuppressive therapy also indicates KSHV may be an essential but insufficient cofactor in KS pathogenesis.[65]

In HIV-seropositive patients, detection of KSHV DNA in peripheral blood and in mononuclear cells of peripheral blood is shown to predict onset of KS.[66,67] In men coinfected with both HIV and KSHV, the KS hazards appear to increase by 60% for each year of infection with HIV[68] and KS pathogenesis probably involves a synergistic action between these viruses.[46] It is postulated that HIV-mediated immune suppression/dysregulation promotes T-helper type-1 cytokines, such as TNF-alpha, interleukin-1b (IL-1b), and IL-6.[15,46,69] Production and release of HIV-Tat protein from HIV-infected cells further contribute to release of proinflammatory cytokines, vascular endothelial growth factors (VEGFs), and matrix metalloproteinases (MMPs), facilitating proliferation of endothelial cells and development of KS.[15,46,70] HIV-Tat protein and chronic state of inflammation also mediate reactivation and replication of latent KSHV, promoting expression of viral gene products implicated in angiogenesis.[15,36,70] In this postulate, coinfection with HIV and KSHV in the presence of a chronic inflammatory state is conducive to initiation and progression of KS.[46] This model is, however, incomplete, as KS also develops in HIV-seronegative patients, indicating that contribution of HIV gene products is not critical in all variants of KS.[36,63]

KSHV SEROPREVALENCE AND MODE OF TRANSMISSION

Seroprevalence of KSHV among the general population varies geographically and its precise mode of transmission is not clearly understood.[13] KSHV has been detected in a variety of body fluids and potential routes of transmission include vertical, horizontal through sex or oral shedding, blood transfusion, and injection drug use, as well as solid organ or BM transplantation.[71-74] The pathogenesis of iatrogenic

KS may involve transmission of KSHV from the infected graft or reactivation of KSHV in seropositive recipients in the context of immunosuppression.[49,72]

In regions where KSHV infection is endemic, infection is probably acquired in childhood from seropositive family members and seroprevalence rates increase with age reaching as high as 80%.[71,75-77] The drop in the mean age of onset and loss of male predilection for AIDS-KS in the African subcontinent have been attributed to high KSHV seroprevalence among HIV-seronegative residents of sub-Saharan Africa and superimposition of AIDS-KS on the preexisting risk of endemic KS in these regions.[13,34,38,77,78] In view of both spread of the HIV epidemic in Africa and poor access to highly active antiretroviral therapy (HAART), infected patients often develop rapidly progressive KS with life expectancy of fewer than 6 months.[34,79]

Several studies suggest mode of transmission may affect risk of KSHV infection.[80,81] In a cohort of HIV-seronegative males from Brazil, KSHV seroprevalence was higher among men who have sex with men (MSM) compared with males with an intravenous drug use habit, suggesting a sexual route for KSHV transmission.[82] Smith and coworkers[81] identified homosexual/bisexual but not heterosexual behavior as the independent risk factor for KSHV seropositivity among 2718 patients attending a sexually transmitted diseases clinic. Distribution pattern of KSHV seropositivity also mirrors that of sexually transmitted pathogens and HIV-infected homosexuals have higher prevalence of KSHV antibodies compared with HIV-seronegative MSM.[38,82,83]

Despite the evidence in support of a sexual route of transmission for HHV-8,[80,81] a number of studies support a role for saliva and saliva-contaminated objects for transmission of KSHV between immunocompetent MSM.[84,85] For instance, KSHV has been detected more frequently and at a higher viral load in saliva compared with genital and anal specimens collected from a group of homosexual males.[84] Also, higher copy numbers of KSHV in saliva compared with semen have been found in patients with and without KS and independent of HIV status.[86] Moreover, saliva samples from HIV-infected Kenyan women more often tested positive for KSHV DNA than plasma or vaginal swabs.[87] It is possible that oropharyngeal epithelial cells harbor KSHV and facilitate its replication and shedding into saliva, contributing to viral transmission.[84,88,89]

KS HISTOLOGY AND DIAGNOSIS

KS lesions clinically resemble vascular entities and vary in color from pink to reddish-purple.[32] Although
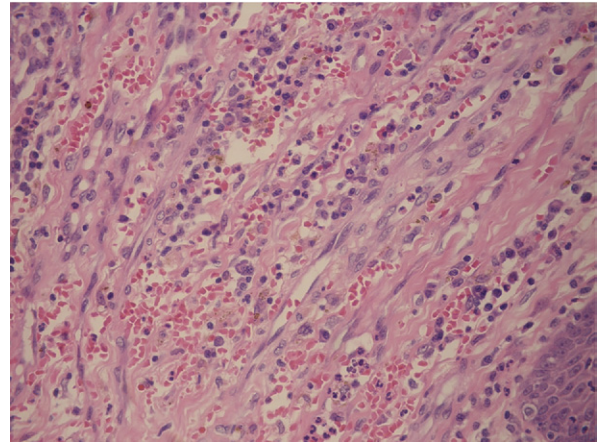

Fig. 5. Histopathological photomicrograph of an oral KS lesion illustrating fascicles of pleomorphic spindle cells compressing extravasated erythrocytes with release of hemosiderin seen as black-brown granules (hematoxylin and eosin, magnification ×400).

mucocutaneous discoloration is a classic feature of KS, isolated nonpigmented oral lesions have been documented.[90,91] Differential diagnosis of clinical mucocutaneous lesions includes nevi, pyogenic granuloma, bacillary angiomatosis, hemangioma, angiosarcoma, and, when affecting bone-bearing oral tissues, also melanoma, leukemia, and lymphoma, as well as inflammatory or fibrotic gingival enlargements,[5,7,92-95] necessitating histopathological tissue evaluation for definitive diagnosis.[4,5]

Microscopic features of KS are diagnostic and shared by all variants of the disease (Fig. 5).[96] They include an abundance of proliferating mononuclear inflammatory and spindle cells, ill-defined vascular channels, hemorrhage, and edema.[9,60] Hemorrhage may result from the absence of smooth muscle cells known as pericytes in the newly formed blood vessels, causing leakage and erythrocyte extravasation.[60] Histopathological features of KS become more prominent with clinical progression from the early patch to plaque and more advanced nodular form of the disease.[7,33] Microscopically, this is manifested as a transition from focally proliferative miniature vessels to tumorlike fascicles mainly composed of spindle cells and vascular network, as well as atypical and extravasated erythrocytes.[64,92]

In early lesions, the spindle cell component may be sparse, leading to misdiagnosis of KS as a benign vascular lesion.[5] In addition, bacillary angiomatosis (BA) caused by *Bartonella henselae*, shares similar clinical and microscopic features with early KS.[1,4] Demonstration of the etiologic agent by Warthin-Starry silver stain or a positive therapeutic response to doxycycline, however, help exclude this infectious entity.[1,97] Identification of KSHV DNA by polymerase

chain reaction (PCR) or immunohistochemistry and detection of KSHV latency-associated nuclear antigen (LANA) have been proposed for differentiation of KS from clinically similar lesions.[7,98]

Diagnosis of KS in a patient with unknown HIV status mandates evaluation for the presence of coexisting HIV infection.[9,11] HIV-seropositive patients with lesions suggestive of KS should receive a diagnostic biopsy for confirmation.[6] Initial workup for staging AIDS-KS involves a complete physical examination that includes evaluation of skin, oral cavity, and rectum, as well as a chest x-ray.[6] When pulmonary or gastrointestinal disease is suspected, lesions may be visualized by bronchoscopy or endoscopy, respectively.[6] Presence of additional symptoms or physical and laboratory findings may necessitate other diagnostic workup.[6] Clinical features of lesions, such as color, surface features, and, in particular, presence of nodularity and KS-associated edema should also be documented at each visit.[6]

PATHOGENESIS OF KS

Lesions of KS are composed of a heterogeneous population of cells expressing a variety of antigenic profiles.[7,24,26,31,99] For example, the endothelial cells of KS express both lymphatic and vascular immunophenotypes.[7] KS lesions test positive for CD-34, a glycoprotein expressed on blood vascular endothelium,[100] and C-kit, expressed on both vascular and lymphatic endothelium.[101] The evidence for lymphatic expression of endothelial cells includes positivity for D2-40,[102-104] a highly sensitive and specific marker of podoplanin glycoprotein that is not expressed on vascular endothelium.[105] The current opinion suggests that infection of endothelial cell precursors by KSHV may lead to a cascade of intracellular events conducive to a hyperinflammatory state, angiogenesis, and lymphatic differentiation.[35,102] The pathogenesis of lymphedema in AIDS-KS may involve cytokine-driven local inflammation, KSHV-induced proliferation of lymphatic endothelial cells, obstruction of lymphatic channels, and enlargement of affected lymph nodes.[106]

There is no consensus on whether KS represents a true malignant neoplasm derived from monoclonal expansion of a single neoplastic progenitor cell; a multicentric, reactive, polyclonal, angioproliferative disorder; or both.[10,33,107] Although the monoclonal nature of advanced nodular lesions arising in different body parts has been demonstrated by several investigators,[108,109] a number of questions remain unresolved. These include variable course of KS lesions, the absence of classic features of malignancy,[7] rarity of metastasis or anaplastic transforma-

tion, absence of cytogenetic abnormalities even with established monoclonality,[110,111] and the potential for spontaneous regression,[15,32] particularly with the start of HAART,[112-114] all of which point to a reactive virus-induced angioproliferative pathogenesis.[115]

Proponents of this concept argue that disseminated KS probably results from multicentric proliferation of KSHV-infected endothelial cells at different sites rather than true metastatic spread as expected from a malignant process.[15,108] Although early lesions may result from reactive polyclonal hyperplasia driven by inflammatory mediators,[31,46,60,63] persistent cellular proliferation also increases the risk of mutations leading to dysregulated growth.[69] Clinically aggressive KS could potentially represent malignant transformation of a subset of monoclonal cells within advanced lesions.[31,46,109] Future studies will help clarify whether KS represents a malignant neoplasia or an inflammatory hyperplasia.[99]

MANAGEMENT STRATEGIES

Selection of therapeutic interventions for KS depends on the location and variant of KS; the rate of progression and distribution of lesions; the presence, absence, or severity of symptoms; the efficacy and potential side effects of therapy; the presence or absence of HIV infection and comorbidities; the degree of host immune competence; and the prognosis and preference of the patient.[2,3,4,6,34,116] Therapy for KS aims to palliate symptoms, reduce tumor-associated edema, and improve esthetics and function.[32,36,41,42,106] Therapeutic approaches for classic KS range from no treatment to surgical excision, local interventions, and radiotherapy.[11,33] Management of iatrogenic KS often involves reduction or elimination of immunosuppressive therapy with or without local measures,[3,4,32,117] whereas endemic KS is frequently responsive to systemic chemotherapy.[3,32] Management of epidemic KS, in contrast, is not aimed at a cure but palliation and control of KS progression with HAART is considered an essential component of this process.[6,34,106,116]

AIDS-KS AND HAART

There is evidence that epidemic KS often regresses with HAART[112-114,118] and that HIV patients undergoing antiretroviral therapy have a less severe form of the disease compared with those naive to HAART at the time of KS diagnosis.[57,58,119] Potent antiretroviral medications have, in fact, led to a dramatic decline in the incidence of KS among patients infected with HIV.[6,120] The criteria for staging epidemic KS, with the advent of HAART, have also been modified.[1] The current prognostic indicators for staging of AIDS-KS, proposed by Nasti et al.,[121]

Table I. Post-HAART prognostic criteria in staging epidemic Kaposi sarcoma

Prognostic indicators[a]	Definition[b]
Tumor extension (T)	T_0 = restriction of lesions to skin and/or lymph nodes and/or minimal oral disease[c]
	T_1 = presence of tumor associated edema or ulceration, extensive oral disease, or visceral involvement
Systemic disease (S)	S_0 = no history of opportunistic infections, "B" symptoms,[d] Karnofsky Performance Status ≥ 70
	$S1$ = history of opportunistic infections, "B" symptoms,[d] other HIV-related illnesses, Karnofsky Performance Status <70

Based on references 1, 34, 42, 121, 122.
[a] and [b]Initially described by ACTG Oncology Committee for staging AIDS-KS.
[c]Non-nodular solitary Kaposi restricted to palate.
[d]Unexplained fever, night sweats, >10% involuntary weight loss or diarrhea >2 weeks.

include tumor extension (T) and HIV-related systemic illness (S) resulting in good and poor survival risk categories depending on the combination of prognostic markers (Table I). In this modified classification, severity of immunosuppression reflected in CD4 count is not an independent prognostic indicator for staging AIDS-KS as initially put forth by the AIDS Clinical Trials Group (ACTG) Oncology Committee.[121,122] In the post-HAART study by Nasti et al.,[121] treated HIV-positive patients with the combination of poor tumor stage (e.g., tumor-associated edema) and constitutional symptoms (T_1S_1) were found to have an unfavorable prognosis with a 3-year survival rate of 53%. In contrast, HIV patients on HAART with none or only 1 prognostic criteria (T_0S_0, T_0S_1, T_1S_0) were found to have a good prognosis with 3-year survival rates of 88%, 80%, and 81%, respectively.[121] In addition, within the T_1 risk category, pulmonary involvement was predictive of poorest survival.[121]

Suppression of viral replication and restoration of immunity by HAART has proven efficacious in control of disease in most patients considered to have good prognosis (T_0S_0, T_0S_1, T_1S_0).[1,34,78,112,123] Based on review of 9 prospective studies, Krown[124] found that institution of antiretroviral therapy alone led to resolution of early lesions of epidemic KS in 80% of patients. Initiation of HAART in newly diagnosed patients or intensification of medical therapy in those resistant to or incompliant with antiretroviral therapy is, therefore, indispensable to treatment of HIV-KS.[6,34,106] Nevertheless, some clinicians advocate watchful waiting or consideration of CD4 cell count, viral load, and active opportunistic infections prior to HAART initiation for asympromatic KS (T_0S_0, T_1S_0).[1,124,125] Despite these observations, HAART alone is not sufficient for advanced epidemic KS with poor prognostic index (T_1S_1), which requires additional interventions.[1,34,124,126-128] When tolerable, AIDS-KS with unfavorable prognosis (e.g., pulmonary involvement or rapidly progressive disease) is best managed with a combination of HAART and systemic chemotherapy.[34,35,41,106,113,129] Although protease inhibitors are thought to have specific antiangiogenic effects, the choice of HAART regimen does not appear to influence protection against epidemic KS.[6,35,126,130,131]

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME—ASSOCIATED KS

In contrast to the general drop in the incidence and severity of AIDS-KS with HAART, some HIV-infected patients are at risk of developing KS within a few weeks of HAART initiation.[15,34,132] This paradoxical exacerbation of opportunistic infections, such as KS, despite immunologic recovery and favorable virological response with HAART is known as immune reconstitution inflammatory syndrome (IRIS).[34] This phenomenon typically affects younger individuals who are profoundly immunosuppressed (CD4 < 100 cells/mm^3) at the time of HAART introduction.[133,134]

IRIS may represent a pathogen-specific immune reconstitution in the presence of a dysregulated hyperinflammatory state and high antigenic burden.[15] Although acute IRIS occurs in response to a subclinical infection within the first 3 months of HAART initiation, delayed IRIS often develops against antigenic components of dead pathogens anytime after the first 3 months of therapy.[15,132] To reduce the risk of IRIS, severely immunosuppressed patients naive to therapy should be screened for preexisting opportunistic infections, educated about the potential risk of IRIS with HAART initiation, and monitored closely.[15,134] The potential risk of IRIS with HAART initiation in patients with advanced immunosuppression supports early institution of antiretroviral therapy to improve CD4 count and reduce viral load.[135,136] Management of IRIS-associated KS generally does not involve interruption of HAART but may necessitate additional modes of therapy.[15] Tables II and III, respectively, provide an overview of the management strategies and the spectrum of therapeutic modalities for epidemic Kaposi sarcoma. The 5 drugs currently approved by the Food and Drug Administration (FDA) for treatment of HIV-KS include 0.1% alitretinoin gel for topical therapy and daunorubicin citrate liposome (DNX), pegylated li-

Table II. Potential management strategies for epidemic Kaposi sarcoma based on disease severity

Severity of AIDS-KS	Management approach
• T_0S_0 (focal disease in the absence of systemic illness)[1,34]	
• T_0S_1 (early but mildly symptomatic KS, e.g., minimal cutaneous disease)[1,34]	HAART ± local therapy[1,34]
• T_1S_0 (slowly progressive AIDS-KS)[34]	HAART[34]
• Extensive disfiguring skin lesions[1]	
• Widespread, symptomatic cutaneous AIDS-KS + edema[1]	
• Rapidly progressive AIDS-KS[1,34]	
• Symptomatic visceral involvement[1,34]	
• Obstructive or painful oropharyngeal AIDS-KS[1]	
• Inadequate response to HAART alone[1]	
• IRIS-associated KS[34]	

Based on reference 34. *AIDS,* acquired immunodeficiency syndrome; *HAART,* highly active antiretroviral therapy; *IRIS,* immune reconstitution inflammatory syndrome; *KS,* Kaposi sarcoma.

Table III. Spectrum of therapeutic modalities for epidemic Kaposi sarcoma

Local/regional therapy
- surgical excision[11,15,137]
- cryotherapy[148]
- sclerotherapy[149,150]
- intralesional vinca-alkaloids,[137,144,145,149] bleomycin,[146] interferon-alpha[147]
- topical 0.1% alitretinoin,[151,152,*] imiquimod 5% cream[153]
- radiotherapy[138-141]
- laser therapy[142,143]

Systemic therapy
  HAART
  - NNRT-based therapy[130]
  - PI-based therapy[130,131]
  Chemotherapy
  - Liposomal anthracyclins[154,155,*]
  - Paclitaxel[156,*]
  - Oral etoposide[157-159,*]
  - Combination agent ABV[154,155,160] or ABVb[159]
  - Single agent vincristine,[161] vinblastine,[162] vinorebline,[163] bleomycin[164]
  Immune modulators
  - Interferon-alpha 2b[165-167,*]

Experimental & targeted therapies
- Antiherpes therapy[168-170]
- Angiogenic inhibitors (e.g., thalidomide)[171,172]
- VEGF inhibitors[173]
- Tyrosine kinase inhibitors[174]
- Matrix metalloproteinases[175]

ABV, doxorubicin, bleomycin, vincristine; *ABVb,* doxorubicin, bleomycin, vinblastine; *HAART,* highly active antiretroviral therapy; *NNRT,* non-nucleoside reverse transcriptase; *PI,* protease inhibitor; *VEGF,* vascular endothelial growth factor.
*Drugs approved by the US Food and Drug Administration for epidemic Kaposi sarcoma.

posomal doxorubicin (PLD), taxane paclitaxel, and interferon alpha-2b for systemic therapy.[33,176,177]

LOCAL THERAPY

Local therapy is safe, easy to administer, and efficacious for limited, asymptomatic mucocutaneous lesions of AIDS-KS.[1,34,126] It may also be considered when HAART is unavailable, response to HAART is less than optimal, or as a palliative measure in patients with rapidly progressive mucocutaneous lesions causing pain, esthetic concerns, or interference with oral function.[34,36] In addition, local therapy may prevent pain, ulceration, and bleeding in indolent lesions of classic KS.[137] Local delivery of chemotherapeutics to a large, solitary nodular lesion of classic KS may also provide additional benefit to ongoing systemic therapy.[34,126,137] In spite of these benefits, the local approach is often costly and frequently unsuccessful in controlling the onset of new lesions.[1]

Radiotherapy is highly effective for management of local or regional KS causing pain, bleeding, or edema and remission rates in excess of more than 90% for AIDS-KS have been documented.[1,34,116,138] Radiotherapy has also been effectively used to treat solitary or widespread lesions of classic KS, achieving response rates higher than 80%.[5,11,139] Although generally well-tolerated,[126] potential drawbacks of radiotherapy include risk of radiodermatitis with repeated cutaneous exposure, disease relapse because of radiation-induced fibrosis, and hyperpigmentation.[34,137,178,179] Although oral KS is highly responsive to radiotherapy,[126,179] adverse effects, such as severe mucositis, hyposalivation, and dysguesia have been reported with total doses as low as 7.5 Gy delivered in multiple fractions.[116,178-181] Oral toxicities are often transient and develop early in the course of therapy, necessitating close patient follow-up and institution of palliative measures as needed.[140,179,180] Effective doses range from 8 Gy as a single fraction to 30 Gy delivered over 10 fractions, and it is appropriate to individualize radiotherapy based on a patient's needs.[125,179,181] Intracavitary contact irradiation—a technique similar to brachytherapy—delivered in 1 or 2 weekly fractions of 5 Gy each through a source introduced into the oral cavity has been reported as effective, well-tolerated, and associated with only minimal mucosal sensitivity.[141] The potential for oral toxicity with external beam radiotherapy together with the

availability of newer therapeutic alternatives support reserving this modality for limited but symptomatic or obstructive lesions of the aerodigestive tract.[52,179]

The focal, superficial mucocutaneous KS is amenable to surgical excision. Potential drawbacks include functional impairment with repeat procedures in anatomical areas where tissue is sparse,[11,138] as well as local recurrence of KS.[11,126,137] In addition, oral KS is often diffuse or multifocal[33] and not suitable for surgical excision.[32,116] The laser ablation procedure has also proven effective in treating macular KS affecting the face and oral cavity.[142,143] Laser may also be used to treat the surgical bed of exophytic oral KS after excision to achieve postoperative hemostasis.[7] Elastic stockings offer another form of local therapy for KS-associated edema affecting the lower exterimities.[33]

Intralesional injection with vinca alkaloids, such as vincristine and vinblastine, known to disrupt microtubular function, has been efficacious for local treatment of mucocutaneous lesions of classic and epidemic KS.[137,144,145] The procedure is painful, there is potential for necrosis if healthy tissue is injected, and therapeutic effects last about 4 months.[1] Therapeutic efficacy for intralesional bleomycin and interferon-alpha (INF-alpha) in treatment of epidemic and classic KS, respectively, have also been demonstrated.[146,147] Cryotherapy with liquid nitrogen for focal skin lesions of AIDS-KS have been tried, yielding full resolution in 80% of cases, although the procedure may be associated with local blistering and pain.[32,148] Regression of oral KS with local administration of sodium tetradecyl sulfate has also been documented.[149,150]

Retinoid products appear to have an inhibitory effect on IL-6, a cytokine implicated in KS pathogenesis, and an antiproliferative effect on KS lesions.[6] Application of 0.1% alitretinoin gel, the only self-administered FDA-approved topical agent for cutaneous AIDS-KS, has shown efficacy for skin lesions of both classic and HIV-KS.[1,34,151,152] Alitretinoin gel needs to be applied 2 to 5 times daily as tolerated and therapeutic response may be delayed by 3 months.[1,34] It is also expensive and may be associated with skin reactions.[1,34] In a study of cutaneous KS in HIV-seronegative patients, the overall response rate to topical 5% imiquimod cream was 47%, although 53% of subjects experienced local erythema and pruritus.[153] Compared with topical medicaments, such as alitretinoin or imiquimod, intralesional injections are more efficacious because of faster, more precise delivery of therapeutic agents;[137] however, the need for the clinician to perform the injections renders these to be less attractive options.[137]

SYSTEMIC CHEMOTHERAPY

Although early lesions of epidemic KS (T_0S_0) are highly responsive to antiretroviral therapy, systemic chemotherapy is generally indicated for advanced disease with poor prognostic index.[1,34,124,126-128] The current first-line systemic therapy for advanced, progressive AIDS-KS includes liposomal anthracyclines, including PLD and DNX.[1,34,106] PLD has been equally efficacious as a single agent compared with multiple agent systemic chemotherapy in management of AIDS-KS.[154,155] In patients with moderate to severe AIDS-KS, the addition of PLD to HAART led to a significantly better response rate (76%) compared with HAART alone (20%).[127] Liposomal formulations have improved the half-life and toxicity profile relative to anthracyclines alone.[6,35,126] Nevertheless, the response to therapy is delayed by 3 to 6 months,[1] and the main adverse affects include myelosuppression and opportunistic infections.[1,6,34] Although the potential for these adverse effects is reduced by subcutaneous administration of granulocyte colony-stimulating factor,[34,114] development of anemia and neutropenia after multiple cycles of liposmal agents may necessitate reduction of dose or cessation of therapy.[1] Toxicity relevant to DNX includes stomatitis and infusion reactions.[34]

The second-line systemic drug approved by the FDA for AIDS-KS in patients refractory to or intolerant of liposomal anthracycline, is paclitaxel.[1,34,156] Similar to vinca alkaloids, paclitaxel polymerizes microtubules and interferes with cell division.[34,126] The response rate of advanced AIDS-KS to paclitaxel in different studies varies, but is reported as high as 71%.[1,156] Although well tolerated, the intravenous mode of administration and the potential for bone marrow suppression, peripheral neuropathy, renal dysfunction, alopecia, and arthralgia renders paclitaxel a less favorable agent than liposomal anthracyclines in the management of widespread KS.[34,177]

Another second-line drug for progressive AIDS-KS with incomplete response to liposomal anthracyclines is oral etoposide.[1] Oral etoposide has been effective in treatment of both severe classic KS and advanced AIDS-KS.[157-159] Although ideal for self-administration and less myelosuppressive than vinblastine, the risk of alopecia and gastrointestinal toxicity, as well as the potential for myelosuppression in up to 60% of those treated, necessitates close follow-up and limits its application in therapy.[1,6,126]

Cytotoxic regimens with single or multiple chemotherapeutic agents for AIDS-KS may be considered when first- and second-line therapies (liposomal anthracycline and paclitaxel) are unavailable or failed to resolve the

disease.[6,32,42,106] The first- and second-line agents are expensive and often not readily available in developing countries burdened by the HIV epidemic.[6] The combination regimens, including doxorubicin, bleomycin, and either vincristine or vinblastine (ABV or ABVb) have been widely studied in AIDS-KS[6] with response rate varying from 25% to 88%.[154,155,159,160] The response rate and duration of response in AIDS-KS, as well as reported toxicities to single-agent cytotoxic therapy, such as bleomycin or vinca alkaloids, have also been variable.[6,106]

Single-agent vincristine is efficacious for AIDS-KS,[161] has a favorable hematological profile, and is generally safe for anemic and neutropenic patients.[1] The potential risk for neurotoxicity, however, requires exclusion of patients concomitantly treated with specific antiretroviral drugs, as well as those with preexisting neuropathy.[1] In addition, patients should be screened for neuropathy at each visit.[1] Systemic vinblastine alone was found effective in 25% of AIDS-KS cases treated, providing remission for nearly 4 months.[162] Although less neurotoxic than vincristine,[182] the risk of myelosuppression is a concern with systemic administration of vinblastine.[126] In a study by Nasti et al.,[163] efficacy in treatment of AIDS-KS was also achieved with vinorebline, also a vinca alkaloid. Vinorebline has mild and reversible adverse effects and is effective in treating AIDS-KS refractory to regimens containing either vinblastine or vincristine.[126,163] The response rate of AIDS-KS to single-agent chemotherapy with bleomycin is also variable depending on dosing and route of administration.[42,126,164]

INF-alpha, an immunomodulatory agent with antiviral and antiangiogenic properties, has dose-dependent efficacy in treatment of AIDS-KS when administered systemically.[1,165,171] This is particularly evident in patients with relatively preserved immune function, lacking lymphomalike "B" symptoms and those with exclusively skin lesions.[106,165,166,171] Drawbacks, however, include hepatotoxicity, flulike symptoms, myelosuppression, and predisposition to opportunistic infections.[1,34,167,183] Concurrent antiretroviral therapy with a lower dose of INF-alpha appear to provide similar therapeutic outcome for AIDS-KS with less toxicity.[34,106,167] The delayed therapeutic response renders INF-alpha inappropriate for treatment of rapidly progressive or symptomatic visceral KS.[1,34,106]

PATHOGENESIS-BASED THERAPEUTIC APPROACHES

In general, available systemic agents may be used for all forms of KS, although therapeutic efficacy, response duration, and severity of adverse effects may vary for different variants.[126]

To improve efficacy and overcome chemotherapy-associated toxicity, new therapeutic approaches have focused on direct control of KSHV for prevention and treatment of KS.[1] Anti-herpes medications were shown to reduce plasma viral load of KSHV and prevent KS in KSHV-seropositive transplant recepients.[4] Anti-herpes drugs ganciclovir and foscarnet were found to reduce the risk of KS by up to 62% among HIV-positive subjects.[168,169] Moreover, a decrease in mucosal replication of KSHV with valganciclovir has been demonstrated.[170] Although limited efficacy does not support the use of anti-herpes drugs alone,[1] the combination of anti-herpes medications with HAART offers the promise to diminish replication of both viruses, prevent new lesions, and help regress lesions already present.[7] Other efforts have focused on developing novel inhibitors to target angiogenesis,[171,172] VEGF,[173] tyrosine kinase,[60,174] and matrix metalloproteinases,[60,175] all of which appear to play a role in KS pathogenesis.

ROLE OF THE ORAL HEALTH CARE PROVIDER

All forms of KS may manifest in the oral cavity, and KSHV appears essential to development of all clinical variants. Although not clearly understood, oropharyngeal epithelial cells may harbor KSHV, facilitating its replication and transmission through saliva. Oral health care practitioners should be familiar with orofacial manifestations of KS, contribute to prevention of KS by educating patients about risk factors, and question those engaged in risk behaviors about the presence of mucocutaneous lesions. Manifestation of KS in the oral cavity may indicate further deterioration of the immune system or signal development of IRIS following the start of antiretroviral therapy. In an untreated HIV patient, diagnosis of oral KS is also considered a significant prognostic marker of survival. In addition, the onset of oral KS may be the first sign of undiagnosed HIV infection. Therefore, oral lesions clinically suggestive of KS should be biopsied and patients with biopsy-proven KS should be tested for HIV. Development of KS in the oral cavity may cause local tissue damage, pain, bleeding, or interference with oral functions and prosthesis wear, all of which may negatively affect a patient's nutritional status, adherence to medical therapy, and quality of life. Close communication between an oral health care provider and the patient's infectious disease specialist facilitates a mutual understanding of the extent of KS spread, severity of symptoms, available therapeutic strategies, and potential adverse effects of therapy. Oral health care providers may contribute to interdisciplinary management of oral KS by using a variety of local measures, such as surgical excision, laser ablation, and intralesional injections to

help accessible oral lesions regress in size, and to provide palliation.

REFERENCES

1. Lynen L, Zolfo M, Huyst V, Louise F, Barnardt P, Van de Velde A, et al. Management of Kaposi's sarcoma in resource-limited settings in the era of HAART. AIDS Res 2005;7:13-21.
2. Schwartz RA, Micali G, Nasca MR, Scuderi L. Kaposi sarcoma: a continuing conundrum. J Am Acad Dermatol 2008;59: 179-206.
3. Szajerka T, Jablecki J. Kaposi's sarcoma revisited. AIDS Res 2007;9:230-6.
4. Schwartz RA. Kaposi's sarcoma: an update. J Surg Oncol 2004;87:146-51.
5. Mohanna S, Bravo F, Ferrufino JC, Sanchez J, Gotuzzo E. Classic Kaposi's sarcoma presenting in the oral cavity of two HIV-negative Quechua patients. Med Oral Patol Oral Cir Bucal 2007;12:E365-8.
6. Vanni T, Sprinz E, Machado MW, Santana Rde C, Fonseca BA, Schwartsmann G. Systemic treatment of AIDS-related Kaposi sarcoma: current status and perspectives. Cancer Treat Rev 2006;32:445-55.
7. Feller L, Lemmer J, Wood NH, Jadwat Y, Raubenheimer EJ. HIV-associated oral Kaposi sarcoma and HHV-8: a review. J Int Acad Periodontol 2007;9:129-36.
8. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. Arch Dermatol Syph (Prague) 1872;4:265-73.
9. Dreyer WP, de Waal J. Oral medicine case book 21. SADJ 2009;64:362.
10. Iscovich J, Boffetta P, Franceschi S, Azizi E, Sarid R. Classic Kaposi sarcoma: epidemiology and risk factors. Cancer 2000;88:500-17.
11. Bottler T, Kuttenberger J, Hardt N, Oehen HP, Baltensperger M. Non-HIV-associated Kaposi sarcoma of the tongue: Case report and review of the literature. J Oral Maxillofac Surg 2007;36:1218-20.
12. Iscovich J, Boffetta P, Winkelmann R, Brennan P, Azizi E. Classic Kaposi's sarcoma in Jews living in Israel, 1961-1989: a population-based incidence study. AIDS 1998;12:2067-72.
13. Wang J, Stebbing J, Bower M. HIV-associated Kaposi sarcoma and gender. Gend Med 2007;4:266-73.
14. Naschitz JE, Lurie M. Macular palmo-plantar eruption. Eur J Intern Med 2009;20:e118-9.
15. Papagatsia Z, Jones J, Morgan P, Tappuni AR. Oral Kaposi sarcoma: a case of immune reconstitution inflammatory syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:70-5.
16. Cohen CD, Horster S, Sander CA, Bogner JR. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. Ann Rheum Dis 2003;62:684.
17. Lee SY, Jo YM, Chung WT, Kim SH, Kim SY, Roh MS, et al. Disseminated cutaneous and visceral Kaposi sarcoma in a woman with rheumatoid arthritis receiving leflunomide. Rheumatol Int [Epub ahead of press; doi:10.1007/s00296-009-1354-0].
18. Vincent T, Moss K, Coalco B, Venables PJ. Kaposi's sarcoma in two patients following low-dose corticosteroid treatment for rheumatological disease. Rheumatol Oxf Engl 2000;39:1294-6.
19. Loutherenoo W, Kasitanon N, Mahanuphab P, Bhoopat L, Thongprasert S. Kaposi's sarcoma in rheumatic diseases. Semin Arthritis Rheum 2003;32:326-33.
20. Mendez JC, Paya CV. Kaposi's sarcoma in transplantation. Herpes 2000;71:18-23.
21. Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, et al. European Conference on Infections in Leukemia. Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 2008;42:227-40.
22. Penn I. Kaposi's sarcoma in transplant recipients. Transplantation 1997;64:669-73.
23. Luppi M, Barozzi P, Rasini V, Torelli G. HHV-8 infection in the transplantation setting: a concern only for solid organ transplant patients? Leuk Lymphoma 2002;43:517-22.
24. Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med 2000;342:1027-38.
25. Serraino D, Angeletti C, Carrieri MP, Longo B, Piche M, Piselli P, et al. for the Immunosuppression and Cancer Study Group. Kaposi's sarcoma in transplant and HIV-infected patients: an epidemiologic study in Italy and France. Transplantation 2005;80:1699-704.
26. edicoat M, Newton R. Review of the distribution of Kaposi's sarcoma-associated herpesvirus (KSHV) in Africa in relation to the incidence of Kaposi's sarcoma. Br J Cancer 2003;88:1-3.
27. Wamburu G, Masenga EJ, Moshi EZ, Schmid-Grendelmeier P, Kempf W, Orfanos CE. HIV-associated and non–HIV associated types of Kaposi's sarcoma in an African population in Tanzania. Status of immune suppression and HHV-8 seroprevalence. Eur J Dermatol 2006;16:677-82.
28. Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S. Trends in cancer incidence in Kyadondo County, Uganda, 1960-1997. Br J Cancer 2000;82:1585-92.
29. Sinfield RL, Molyneux EM, Banda K, Borgstein E, Broadhead R, Hesseling P, et al. Spectrum and presentation of pediatric malignancies in the HIV era: experience from Blantyre, Malawi, 1998-2003. Pediatr Blood Cancer 2007;48:515-20.
30. Orem J, Otieno MW, Remick SC. AIDS-associated cancer in developing nations. Curr Opin Oncol 2004;16:468-76.
31. Wood NH, Feller L. The malignant potential of HIV-associated Kaposi sarcoma. Cancer Cell Int 2008;31:14.
32. Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy. Lancet Infect Dis 2002;2:281-92.
33. Ramírez-Amador V, Anaya-Saavedra G, Martínez-Mata G. Kaposi's sarcoma of the head and neck: a review. Oral Oncol 2010;46:135-45.
34. Martellotta F, Berretta M, Vaccher E, Schioppa O, Zanet E, Tirelli U. AIDS-related Kaposi's sarcoma: state of the art and therapeutic strategies. Curr HIV Res 2009;7:634-8.
35. Di Lorenzo G, Konstantinopoulos PA, Pantanowitz L, Di Trolio R, De Placido S, Dezube BJ. Management of AIDS-related Kaposi's sarcoma. Lancet Oncol 2007;8:167-76.
36. Lager I, Altini M, Coleman H, Ali H. Oral Kaposi's sarcoma: a clinicopathologic study from South Africa. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;96:701-10.
37. Frisch M, Biggar RJ, Engels EA, Goedert JJ, AIDS-Cancer Match Registry Study Group, for the AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. JAMA 2001;285:1736-45.
38. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma–associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med 1996;2:918-24.
39. Mwanda OW, Fu P, Collea R, Whalen C, Remick SC. Kaposi's sarcoma in patients with and without human immunodeficiency

virus infection, in a tertiary referral centre in Kenya. Ann Trop Med Parasitol 2005;99:81-91.

40. Petit JC, Ripamonti U, Hille J. Progressive changes of Kaposi's sarcoma of the gingiva and palate. Case report in an AIDS patient. J Periodontol 1986;57:159-63.

41. Henderson H. Kaposi sarcoma is the most common cancer diagnosed in HIV-infected persons. HIV Clin 2009;21:1-2.

42. Levine AM, Tulpule A. Clinical aspects and management of AIDS-related Kaposi's sarcoma. Eur J Cancer 2001;37: 1288-95.

43. Danzig JB, Brandt LJ, Reinus JF, Klein RS. Gastrointestinal malignancy in patients with AIDS. Am J Gastroenterol 1991; 86:715-8.

44. Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. Chest 2000;117:1128-45.

45. Turoglu HT, Akisik MF, Naddaf SY, Omar WS, Kempf JS, Abdel-Dayem HM. Tumor and infection localization in AIDS patients: Ga-67 and Tl-201 findings. Clin Nucl Med 1998;23: 446-59.

46. Feller L, Lemmer J. Insights into pathogenic events of HIV-associated Kaposi sarcoma and immune reconstitution syndrome related Kaposi sarcoma. Infect Agent Cancer 2008;3:1.

47. Feller L, Khammissa RA, Wood NH, Jose RJ, Lemmer J. Facial lymphoedema as an indicator of terminal disease in oral HIV-associated Kaposi sarcoma. SADJ 2010;65:16-8.

48. Mwakigonja AR, Pak F, Pyakurel P, Mosha IJ, Urassa WK, Kaaya EE, et al. Oral Kaposi's sarcoma in Tanzania: presentation, immunopathology and human herpesvirus-8 association. Oncol Rep 2007;17:1291-9.

49. Lebbé C, Legendre C, Francès C. Kaposi sarcoma in transplantation. Transplant Rev [Orlando] 2008;22:252-61.

50. Flaitz C, Jin Y, Hicks M, Nicholas M, Wang Y, Su I. Kaposi's sarcoma-associated herpesvirus-like DNA sequences (KSHV/HHV-8) in oral AIDS-Kaposi's sarcoma. A PCR and clinico-pathologic study. Oral Surg Oral Med Oral Pathol Oral Rad Endod 1997;83:259-64.

51. Ficarra G, Berson AM, Silverman S, Quivey JM, Lozada-Nur F, Sooy DD, et al. Kaposi's sarcoma of the oral cavity: a study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects, and treatment. Oral Surg Oral Med Oral Pathol 1988;66:543-50.

52. Nicholas C, Flaitz C, Hicks M. Primary intraosseous Kaposi's sarcoma of the maxilla in HIV infection: Review of the literature and report of a case. J Oral Maxillofac Surg 1995;53:5-9.

53. Reichart PA, Langford-Kuntz A, Pohle HD. Epidemic orofacial Kaposi's sarcoma (eKS)—report of 124 cases. Eur J Cancer B Oral Oncol 1993;29B:187-9.

54. Pantanowitz L, Dezube BJ. Kaposi sarcoma in unusual locations. BMC Cancer 2008;8:190.

55. Lausten LL, Fergusen BL, Barker BF, Cobb CM. Oral Kaposi's sarcoma associated with severe alveolar bone loss: case report and review of the literature. J Periodontol 2003;74:1668-75.

56. Castle JT, Thompson LD. Kaposi sarcoma of major salivary gland origin: a clinicopathologic series of six cases. Cancer 2000;88:15-23.

57. Rohrmus B, Thoma-Greber EM, Bogner JR, Röcken M. Outlook in oral and cutaneous Kaposi's sarcoma. Lancet 2000;356:2160.

58. Epstein JB, Cabay RJ, Glick M. Oral malignancies in HIV disease: changes in disease presentation, increasing understanding of molecular pathogenesis, and current management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:571-8.

59. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994;266:1865-9.

60. Kang T, Ye FC, Gao SJ, Wang LD. Angiogenesis, Kaposi's sarcoma and Kaposi's sarcoma-associated herpesvirus. Virol Sin 2008;123:499–58.

61. Luppi M, Barozzi P, Schulz T, Setti G, Staskus K, Trovato R, et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med 2000;343: 1378-85.

62. Luppi M, Barozzi P, Schulz TF, Trovato R, Donelli A, Nami F, et al. Nonmalignant disease associated with human herpesvirus 8 reactivation in patients who have undergone autologous peripheral blood stem cell transplantation. Blood 2000;96:2355-7.

63. Feller L, Wood NH, Lemmer J. HIV-associated Kaposi sarcoma: pathogenic mechanisms. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:521-9.

64. Casper C. New approaches to the treatment of human herpesvirus 8-associated disease. Rev Med Virol 2008;18:321-9.

65. Feller L, Lemmer J, Wood NH, Raubenheimer EJ. Necrotizing gingivitis of Kaposi sarcoma affected gingivae. SADJ 2006; 61:314-7.

66. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet 1995;346:799-802.

67. Cannon MJ, Dollard SC, Black JB, Edlin BR, Hannah C, Hogan SE, et al. Risk factors for Kaposi's sarcoma in men seropositive for both human herpesvirus 8 and human immunodeficiency virus. AIDS 2003;17:215-22.

68. Jacobson LP, Jenkins FJ, Springer G, Munoz A, Shah KV, Phair J, et al. Interaction of human immunodeficiency virus type 1 and human herpesvirus type 8 infections on the incidence of Kaposi's sarcoma. J Infect Dis 2000;181:1940-9.

69. Krown SE. Therapy of AIDS-associated Kaposi's sarcoma: targeting pathogenetic mechanisms. Hematol/Oncol Clin North Am 2003;17:763-83.

70. Fanales-Belasio E, Moretti S, Nappi F, Barillari G, Micheletti F, Cafaro A, et al. Native HIV-1 Tat protein targets monocyte-derived dendritic cells and enhances their maturation, function and antigen-specific T cell responses. J Immunol 2002;168: 197-206.

71. Pica F, Volpi A. Transmission of human herpesvirus 8: an update. Curr Opin Infect Dis 2007;20:152-6.

72. Parravacini C, Olsen SJ, Capra M, Poli F, Sirchia G, Gao SJ, et al. Risk of Kaposi's sarcoma-associated herpes virus transmission from donor alllografts among Italian posttransplant Kaposi's sarcoma patients. Blood 1997;90:2826-9.

73. Hladik W, Dollard SC, Downing RG, Kataaha P, Pellett PE, Karon JM, et al. Kaposi's' sarcoma in Uganda: risk factors for human herpesvirus 8 infection among blood donors. J Acquir Immune Defic Syndr 2003;33:206-10.

74. Cannon MJ, Dollard SC, Smith DK, Klein RS, Schuman P, Rich JD, et al. HIV Epidemiology Research Study Group. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. N Engl J Med 2001;344:637-43.

75. Bagni R, Whitby D. Kaposi's sarcoma-associated herpesvirus transmission and primary infection. Curr Opin HIV AIDS 2009;4:22-6.

76. de Souza VA, Sumita LM, Nascimento MC, Oliveira J, Mascheretti M, Quiroga M, et al. Human herpesvirus-8 infection and oral shedding in Amerindian and non-Amerindian

populations in the Brazilian Amazon region. J Infect Dis 2007;196:844-52.

77. Davidson A. Kaposi sarcoma: the African HIV epidemic's partner in crime. Pediatr Blood Cancer 2010;54:657-8.

78. Mayama S, Cuevas LE, Sheldon J, Omar OH, Smith DH, Okong P, et al. Prevalence and transmission of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. Int J Cancer 1998;77:817-20.

79. Campbell TB, Borok M, White IE, Guduza I, Ndemera B, Taziwa A, et al. Relationship of kaposi sarcoma (KS)-associated herpesvirus viremia and KS disease in Zimbabwe. Clin Infect Dis 2003;36:1144-51.

80. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and natural history of human herpesvirus 8 infection. N Engl J Med 1998;338:948-54.

81. Smith NA, Sabin CA, Gopal R, Bourboulia D, Labbete W, Boshoff C, et al. Serologic evidence of human herpesvirus 8 transmission by homosexual but not heterosexual sex. J Infect Dis 1999;180:600-6.

82. Zhang X, Fitzpatrick L, Campbell TB, Badaro R, Schechter M, Melo M, et al. Comparison of the prevalence of antibodies to human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) in Brazil and Colorado. J Infect Dis 1998;178:1488-91.

83. Guanira JV, Casper C, Lama JR, Morrow R, Montano SM, Caballero P, et al. for the Peruvian HIV Sentinel Surveillance Working Group. Prevalence and correlates of human herpesvirus 8 infection among Peruvian men who have sex with men. J Acquir Immune Defic Syndr 2008;49:557-62.

84. Pauk J, Huang ML, Brodie SJ, Wald A, Koelle DM, Schacker T, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med 2000;343:1369-77.

85. Casper C, Carrell D, Miller KG, Judson FD, Meier AS, Pauk JS, et al. HIV serodiscordant sex partners and the prevalence of human herpesvirus 8 infection among HIV negative men who have sex with men: baseline data from the EXPLORE study. Sex Transm Infect 2006;82:229-35.

86. Koelle DM, Huang ML, Chandran B, Vieira J, Piepkorn M, Corey L. Frequent detection of Kaposi's sarcoma-associated herpesvirus (human herpesvirus8) DNA in saliva of human immunodeficiency virus-infected men: clinical and immunologic correlates. J Infect Dis 1997;176:94-102.

87. Taylor MM, Chohan B, Lavreys L, Hassan W, Huang ML, Corey L, et al. Shedding of human herpesvirus 8 in oral and genital secretions from HIV-1 seropositive and -seronegative Kenyan women. J Infect Dis 2004;190:484-8.

88. Casper C, Krantz E, Selke S, Kuntz SR, Wang J, Huang ML, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. J Infect Dis 2007;195:30-6.

89. Webster-Cyriaque J, Duus K, Cooper C, Duncan M. Oral EBV and KSHV infection in HIV. Adv Dent Res 2006;19:91-5.

90. Daly CG, Allan BP, Bhagwandeen SB, Sutherland DC. Kaposi's sarcoma of the palate in a patient with AIDS: an unusual presentation. Aust Dent J 1989;34:101-5.

91. Reichart PA, Schiødt M. Non-pigmented oral Kaposi's sarcoma (AIDS). Report of two cases. Int J Oral Maxillofac Surg 1989; 18:197-199.

92. Feller L, Jadwat Y, Raubenheimer EJ. Kaposi sarcoma and calcium channel blocker-induced gingival enlargement occurring simultaneously: review of the literature and report of a case. Oral Biosci Med 2004;4:291-7.

93. Chapple IL, Hamburger J. The significance of oral health in HIV disease. Sex Transm Infect 2000;76:236-43.

94. Schwartz RA. Kaposi's sarcoma: Advances and Perspectives. J Am Acad Dermatol 1996;34:804-14.

95. Reis-Filho JS, Souto-Moura C, Lopes JM. Classic Kaposi's sarcoma of the tongue: case report with emphasis on the differential diagnosis. J Oral Maxillofac Surg 2002;60:951-4.

96. Tappero JW, Conant MA, Wolfe SF, Berger TG. Kaposi's sarcoma. Epidemiology, pathogenesis, histology, clinical spectrum, staging criteria and therapy. J Am Acad Dermatol 1993;28:371-95.

97. Lopez de Blanc S, Sambuelli R, Femopase F, Luna N, Gravotta M, David D, et al. Bacillary angiomatosis affecting the oral cavity. Report of two cases and review. J Oral Pathol Med 2000;29:91-6.

98. Hammock L, Reisenauer A, Wang W, Cohen C, Birdsong G, Folpe AL. Latency-associated nuclear antigen expression and human herpes-8 polymerase chain reaction in the evaluation of Kaposi's sarcoma and other vascular tumors in HIV-positive patients. Mod Pathol 2005;18:463-8.

99. Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. Lancet Infect Dis 2002;2:344-52.

100. Regezi JA, MacPhail LA, Daniels TE, Desouza YG, Greenspan JS, Greenspan D. Human immunodeficiency virus-associated oral Kaposi's sarcoma. A heterogeneous cell population dominated by spindle-shaped endothelial cells. Am J Pathol 1993;143:240-9.

101. Pantanowitz L, Schwartz EJ, Dezube BJ, Kohler S, Dorfman RF, Tahan SR. C-Kit (CD117) expression in AIDS-related, classic, and African endemic Kaposi sarcoma. Appl Immunohistochem Mol Morphol 2005;13:162-6.

102. Wang HW, Trotter MW, Lagos D, Bourboulia D, Henderson S, Mäkinen T, et al. Kaposi sarcoma herpesvirus-induced cellular reprogramming contributes to the lymphatic endothelial gene expression in Kaposi sarcoma. Nat Genet 2004;36:687-93.

103. Hong YK, Foreman K, Shin JW, Hirakawa S, Curry CL, Sage DR, et al. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet 2004;36:683-5.

104. Ramirez-Amador V, Martinez-Mata G, Gonzalez-Ramirez I, Anya-Saavedra G, de Almeida OP. Clinical, histological and immunohistochemical findings in oral Kaposi's sarcoma in a series of Mexican AIDS patients. Comparative study. J Oral Pathol Med 2009;384:328-33.

105. Evangelou E, Kyzas PA, Trikalinos TA. Comparison of the diagnostic accuracy of lymphatic endothelium markers: Bayesian approach. Mod Pathol 2005;18:1490-7.

106. Von Roenn JH. Clinical presentations and standard therapy of AIDS-associated Kaposi's sarcoma. Hematol/Oncol Clin North Am 2003;17:747-62.

107. Douglas JL, Gustin JK, Dezube B, Pantanowitz JL, Moses AV. Kaposi's sarcoma: a model of both malignancy and chronic inflammation. Panminerva Med 2007;49:119-38.

108. Gill PS, Tsai YC, Rao AP, Spruck CH III, Zheng T, Harrington WA Jr, et al. Evidence for multiclonality in multicentric Kaposi's sarcoma. Proc Natl Acad Sci U S A 1998;95:8257-61.

109. Rabkin CS, Janz S, Lash A, Coleman AE, Musaba E, Liotta L, et al. Monoclonal origin of multicentric Kaposi's sarcoma lesions. N Engl J Med 1997;336:988-93.

110. Ablashi DV, Chatlynne LG, Whitman JE Jr, Cesarman E. Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8 diseases. Clin Microbiol Rev 2002;15:439-64.

111. Delabesse E, Oksenhendler E, Lebbe C, Verola O, Varet B, Turhan AG. Molecular analysis of clonality in Kaposi's sarcoma. J Clin Pathol 1997;50:664-8.

112. Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: state of the art and therapeutic challenges. J Clin Oncol 2008;26:4834-42.

113. Tirelli U, Bernardi D. Impact of HAART on the clinical management of AIDS-related cancers. Eur J Cancer 2001;37: 1320-4.

114. Murdaca G, Campelli A, Setti M, Indiveri F, Puppo F. Complete remission of AIDS/Kaposi's sarcoma after treatment with a combination of two nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor. AIDS 2002;16:304-5.

115. Schwarz M, Murphy PM. Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor constitutively activates NF-kappa B and induces proinflammatory cytokine and chemokine production via a C-terminal signaling determinant. J Immunol 2001;167:505-13.

116. Epstein JB. Management of oral Kaposi's sarcoma and a proposal for clinical staging. Oral Dis 1997;3(Suppl 1):S124-8.

117. De Medeiros B, Rezuke W, Ricci A, Tsongalis G, Shen P, Bona R, et al. Kaposi's sarcoma following allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia. Acta Haematol 2000;104:115-8.

118. Diz-Dios P, Ocampo-Hermida A, Miralles-Alvarez C, Vazquez-Garcia E, Martinez-Vazquez C. Regression of AIDS-related Kaposi's sarcoma following ritonavir therapy. Oral Oncol 1998;34:236-8.

119. Nasti G, Martellotta F, Berretta M, Mena M, Fasan M, Di Perri G, et al. Impact of highly active antiretroviral therapy on the presenting features and outcome of patients with acquired immunodeficiency syndrome-related Kaposi sarcoma. Cancer 2003;98:2440-6.

120. Mocroft A, Kirk O, Clumeck N, Gargalianos-Kakolyris P, Trocha H, Chentsova N, et al. The changing pattern of Kaposi sarcoma in patients with HIV, 1994-2003: the EuroSIDA Study. Cancer 2004;100:2644-54.

121. Nasti G, Talamini R, Antinori A, Martellotta F, Jacchetti G, Chiodo F, et al. for GICAT and ICONA Study Groups. AIDS-related Kaposi's sarcoma in 211patients: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group staging system in the HAART era—the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naïve from Antiretrovirals. J Clin Oncol 2003;21: 2876-82.

122. Krown SE, Metroka C, Wrenz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response and staging criteria. J Clin Oncol 1989;7:120-7.

123. Gill J, Bourboulia D, Wilkinson J, Hayes P, Cope A, Marcelin AG, et al. Prospective study of the effects of antiretroviral therapy on Kaposi sarcoma-associated herpesvirus infection in patients with and without Kaposi sarcoma. J Acquir Immune Defic Syndr 2002;3:384-90.

124. Krown S. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol 2004;22:339-402.

125. Aldhoven M, Barrio N, Sanders C. therapeutic strategies for epidemic Kaposi's sarcoma. Int J STD & AIDS 2006;17:571-8.

126. Toschi E, Sgadari C, Monini P, Barillari G, Bacigalupo I, Palladino C, et al. Treatment of Kaposi's sarcoma—an update. Anticancer Drugs 2002;13:977-87.

127. Martin-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS 2004;18:1737-40.

128. Reichart PA. Oral manifestations in HIV infection: fungal and bacterial infections, Kaposi's sarcoma. Med Microbiol Immunol 2003;192:165-9.

129. Bihl F, Mosam A, Henry LN, Chisholm JV 3rd, Dollard S, Gumbi P, et al. Kaposi's sarcoma-associated herpesvirus-specific immune reconstitution and antiviral effect of combined HAART/chemotherapy in HIV clade C-infected individuals with Kaposi's sarcoma. AIDS 2007;21:1245-52.

130. Portsmouth S, Stebbing J, Gill J, Mandalia S, Bower M, Nelson M, et al. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. AIDS 2003;17:F17-22.

131. Patti S, Pelser CB, Dufraine J, Bryant JL, Reitz MS Jr, Weichold FF. Anti-tumorigenic effects of HIV protease inhibitor ritonavir: inhibition of Kaposi's sarcoma. Blood 2002;15: 3771-9.

132. Bower M, Nelson M, Young AM, Thirlwell C, Newsom-Davis T, Mandalia S, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 2005; 23:5224-8.

133. French MA, Lenzo N, John M, Mallal SA, McKinnon EJ, James IR, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med 2000;1:107-15.

134. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis 2006;42:418-27.

135. Soria A, Lazzarin A. Antiretroviral treatment strategies and immune reconstitution in treatment-naive HIV-infected patients with advanced disease. J Acquir Immune Defic Syndr 2007; 46(Suppl 1):S19-30.

136. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002;360:119-29.

137. Brambilla L, Bellinvia M, Tourlaki A, Scoppio B, Gaiani F, Boneschi V. Intralesional vincristine as first-line therapy for nodular lesions in classic Kaposi sarcoma: a prospective study in 151 patients. Br J Dermatol 2010;162:854-9.

138. Caccialanza M, Marca S, Piccinno R, Eulisse G. Radiotherapy of classic and human immunodeficiency virus-related Kaposi's sarcoma: results in 1482 lesions. J Eur Acad Dermatol Venereol 2008;22:297-302.

139. Brenner B, Rakowsky E, Katz A, Gutman H, Sulkes A, Schacter J, et al. Tailoring treatment for classical Kaposi's sarcoma: comprehensive clinical guidelines. Int J Oncol 1999;14:1097-102.

140. Watkins EB, Findlay P, Gelmann E, Lane HC, Zabell A. Enhanced mucosal reactions in AIDS patients receiving oropharyngeal irradiation. Int J Radiat Oncol Biol Phys 1987;13: 1403-8.

141. Caccialanza M, Piccinno R, Gnecchi L, Beretta M, Cusini M. Intracavitary contact x-ray therapy of oral HIV-associated Kaposi's sarcoma. Int J STD AIDS 1997;8:581-4.

142. Marchell N, Alster TS. Successful treatment of cutaneous Kaposi's sarcoma by the 585-nm pulsed dye laser. Dermatol Surg 1997;23:973-5.

143. Convissar RA. Laser palliation of oral manifestations of human immunodeficiency virus infection. J Am Dent Assoc 2002; 133:591-8; quiz 624-5.

144. Boudreaux AA, Smith LL, Cosby CD, Bason MM, Tappero JW, Berger TG. Intralesional vinblastine for cutaneous Kapo-

si's sarcoma associated with acquired immunodeficiency syndrome. A clinical trial to evaluate efficacy and discomfort associated with infection. J Am Acad Dermatol 1993;28:61-5.

145. Epstein JB. Treatment of oral Kaposi sarcoma with intralesional vinblastine. Cancer 1993;71:1722-5.

146. Poignonec S, Lachiver LD, Lamas G, Coutellier A, Caumes E, Soudant J. Intralesional bleomycin for acquired immunodeficiency syndrome-associated cutaneous Kaposi's sarcoma. Arch Dermatol 1995;131:228.

147. Trattner A, Reizis Z, David M, Ingber A, Hagler J, Sandbank M. Therapeutic effect of intralesional interferon in classical Kaposi's sarcoma. Br J Dermatol 1993;129:590-3.

148. Tappero J, Berger T, Kaplan L, Volberding P, Kahn J. Cryotherapy for cutaneous Kaposi's sarcoma (KS) associated with acquired immune deficiency syndrome (AIDS): a phase II trial. J Acquir Immune Defic Syndr 1991;4:839-46.

149. Ramirez-Amador V, Esquivel-Pedraza L, Lozada-Nur F, De la Rosa-Garcia E, Volkow-Fernandez P, Suchil-Bernal L, et al. Intralesional vinblastine vs. 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma. A double blind, randomized clinical trial. Oral Oncol 2002;38:460-7.

150. Muzyka BC, Glick M. Sclerotherapy for the treatment of nodular intraoral Kaposi's sarcoma in patients with AIDS. N Engl J Med 1993;328:210-1.

151. Bodsworth NJ, Bloch M, Bower M, Donnell D, Yocum R, International Panretin Gel KS Study Group. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Am J Clin Dermatol 2001;2:77-87.

152. Morganroth GS. Topical 0.1% alitretinoin gel for classic Kaposi sarcoma. Arch Dermatol 2002;138:542-3.

153. Celestin-Schartz NE, Chevret S, Paz C, Kerob D, Verola O, Morel P, et al. Imiquimod 5% cream for treatment of HIV-negative Kaposi's sarcoma skin lesions: a phase I to II, open-label trial in 17 patients. J Am Acad Dermatol 2008;58:585-91.

154. Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol 1996;14:2353-64.

155. Northfelt DW, Dezube BJ, Thommes JA, Miller BJ, Fischl MA, Friedman-Kien A, et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. Clin Oncol 1998;16:2445-51.

156. Welles L, Saville MW, Lietzau J, Pluda JM, Wyvill KM, Feuerstein I, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. J Clin Oncol 1998;16:1112-21.

157. Brambilla L, Labianca R, Boneschi V, Fossati S, Dallavalle G, Finzi AF, et al. Mediterranean Kaposi's sarcoma in the elderly. A randomized study of oral etoposide versus vinblastine. Cancer 1994;74:2873-8.

158. Evans SR, Krown SE, Testa MA, Cooley TP, Von Roenn JH. Phase II evaluation of low-dose oral etoposide for the treatment of relapsed or progressive AIDS-related Kaposi's sarcoma: an AIDS Clinical Trials Group clinical study. J Clin Oncol 2002;20:3236-41.

159. Laubenstein LJ, Krigel RL, Odajnyk CM, Hymes KB, Friedman-Kien A, Wernz JC, et al. Treatment of epidemic Kaposi's sarcoma with etoposide or a combination of doxorubicin, bleomycin, and vinblastine. Clin Oncol 1984;2:1115-20.

160. Gill PS, Rarick M, McCutchan JA, Slater L, Parker B, Muchmore E, et al. Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. Am J Med 1991; 90:427-33.

161. Mintzer DM, Real FX, Jovino L, Krown SE. Treatment of Kaposi's sarcoma and thrombocytopenia with vincristine in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1985;102:200-2.

162. Volberding PA, Abrams DI, Conant M, Kaslow K, Vranizan K, Ziegler J. Vinblastine therapy for Kaposi's sarcoma in the acquired immunodeficiency syndrome. Ann Intern Med 1985;103:335-8.

163. Nasti G, Errante D, Talamini R, Rizzardini G, Fasan M, Landonio G, et al. Vinorelbine is an effective and safe drug for AIDS-related Kaposi's sarcoma: results of a phase II study. J Clin Oncol 2000;18:1550-7.

164. Lassoued K, Clauvel JP, Katlama C, Janier M, Picard C, Matheron S. Treatment of the acquired immune deficiency syndrome-related Kaposi's sarcoma with bleomycin as a single agent. Cancer 1990;66:1869-72.

165. Volberding PA, Mitsuyasu RT, Golando JP, Spiegel RJ. Treatment of Kaposi's sarcoma with interferon alfa-2b (Intron A). Cancer 1987;59(3 Suppl):620-5.

166. Rios A, Mansell PW, Newell GR, Reuben JM, Hersh EM, Gutterman JU. Treatment of acquired immunodeficiency syndrome—related Kaposi's sarcoma with lymphoblastoid interferon. J Clin Oncol 1985;3:506-12.

167. Krown SE, Li P, Von Roenn JH, Paredes J, Huang J, Testa MA. Efficacy of low-dose interferon with antiretroviral therapy in Kaposi's sarcoma: a randomized phase II AIDS clinical trials group study. J Interferon Cytokine Res 2002;22:295-303.

168. Glesby MJ, Hoover DR, Weng S, Graham NM, Phair JP, Detels R, et al. Use of antiherpes drugs and the risk of Kaposi's sarcoma: data from the multicenter AIDS Cohort Study. J Infect Dis 1996;173:1477-80.

169. Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Antiherpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. AIDS 1996;10:1101-5.

170. Casper C, Krantz EM, Corey L, Kuntz SR, Wang J, Selke S, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. J Infect Dis 2008;198:23-30.

171. Krown SE. Management of Kaposi sarcoma: the role of interferon and thalidomide. Curr Opin Oncol 2001;13:374-81.

172. Little RF, Wyvill KM, Pluda JM, Welles L, Marshall V, Figg WD, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol 2000;18:2593-602.

173. Levine AM, Tulpule A, Quinn DI, Gorospe G 3rd, Smith DL, Hornor L, et al. Phase I study of antisense oligonucleotide against vascular endothelial growth factor: decrease in plasma vascular endothelial growth factor with potential clinical efficacy. J Clin Oncol 2006;24:1712-9.

174. Basciani S, Vona R, Matarrese P, Ascione B, Mariani S, Cauda R, et al. Imatinib interferes with survival of multidrug resistant Kaposi's sarcoma cells. FEBS Lett 2007;581:5897-903.

175. Cianfrocca M, Cooley TP, Lee JY, Rudek MA, Scadden DT, Ratner L, et al. Matrix metalloproteinase inhibitor COL-3 in the treatment of AIDS-related Kaposi's sarcoma: a phase I AIDS malignancy consortium study. J Clin Oncol 2002;20:153-9.

176. Dezube BJ. Management of AIDS-related Kaposi's sarcoma: advances in target discovery and treatment. Expert Rev Anticancer Ther 2002;2:193-200.

177. Dezube BJ, Pantanowitz L, Aboulafia DM. Management of AIDS-related Kaposi sarcoma: advances in target discovery and treatment. AIDS Read 2004;14:236-53.

178. Cooper JS, Fried PR. Toxicity of oral radiotherapy in patients with acquired immunodeficiency syndrome. Arch Otolaryngol Head Neck Surg 1987;113:327-8.

179. Housri N, Yarchoan R, Kaushal A. Radiotherapy for patients with the human immunodeficiency virus: are special precautions necessary? Cancer 2010;116:273-83.

180. Chak LY, Gill PS, Levine AM, Meyer PR, Anselmo JA, Petrovich Z. Radiation therapy for acquired immunodeficiency syndrome-related Kaposi's sarcoma. J Clin Oncol;19886:863-7.

181. Cooper JS, Fried PR. Defining the role of radiation therapy in the management of epidemic Kaposi's sarcoma. Int J Radiat Oncol Biol Phys 1987;13:35-9.

182. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs 2003;63: 1549-63.

183. Aversa SM, Cattelan AM, Salvagno L, Crivellari G, Banna G, Trevenzoli M, et al. Treatments of AIDS-related Kaposi's sarcoma. Crit Rev Oncol/Hematol 2005;53:253-65.

Reprint requests:

Mahnaz Fatahzadeh, DMD, MSD
Division of Oral Medicine, Room D-855
Department of Diagnostic Sciences
New Jersey Dental School-UMDNJ
110 Bergen Street
Newark, NJ 07103
fatahza@umdnj.edu