AIDS-Related Kaposi Sarcoma, Version 2.2019

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ABSTRACT

As treatment of HIV has improved, people living with HIV (PLWH) have experienced a decreased risk of AIDS and AIDS-defining cancers (non-Hodgkin's lymphoma, Kaposi sarcoma, and cervical cancer), but the risk of Kaposi sarcoma in PLWH is still elevated about 500-fold compared with the general population in the United States. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AIDS-Related Kaposi Sarcoma provide diagnosis, treatment, and surveillance recommendations for PLWH who develop limited cutaneous Kaposi sarcoma and for those with advanced cutaneous, oral, visceral, or nodal disease.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Disclosures for the NCCN AIDS-Related Kaposi Sarcoma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN AIDS-Related Kaposi Sarcoma Panel members can be found on page 189. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

Overview

In 2018, it is estimated that more than 1.1 million people in the United States are living with HIV infection.[1] Without treatment, HIV infection causes AIDS and AIDS-defining cancers: non-Hodgkin's lymphoma, Kaposi sarcoma, and cervical cancer.[2,3] Dramatically improved treatment of HIV over the past 2 decades has decreased the risk of AIDS, improved immune function and survival, and reduced AIDS-defining cancers in this population.[4,5] As people living with HIV (PLWH) live longer and healthier lives, however, they experience an increased risk of many non-AIDS–defining cancers.[6–10]

It is estimated that 7,760 PLWH were diagnosed with cancer in the United States in 2010, representing an approximately 50% increase over the expected number in the general population.[11] Other studies have also noted a higher risk for developing cancer in PLWH than in HIV-negative individuals, likely due to underlying immune dysregulation and coinfection with viruses such as human papillomavirus, human herpesvirus 8 (HHV-8), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus.[12–16] In addition, the prevalence of other cancer risk factors in the HIV-positive population (eg, smoking, heavy alcohol consumption) may play a role.[17–21]

The proportion of each major cancer type among total incident cancer cases occurring in PLWH in the United States during 2010 was as follows[11]:

- Non-Hodgkin's lymphoma 21%
- Kaposi sarcoma 12%
- Lung cancer 11%
- Anal cancer 10%
- Prostate cancer 7%
- Liver cancer 5%
- Colorectal cancer 5%
- Hodgkin lymphoma 4%
- Oral/pharyngeal cancer 4%
- Female breast cancer 2%
- Cervical cancer 1%

The NCCN Guidelines for AIDS-Related Kaposi Sarcoma provide treatment recommendations for PLWH who develop Kaposi sarcoma; they are intended to assist health care providers with clinical decision-making. This "Discussion" section provides an overview of the literature supporting the recommendations included in the guidelines. The panel also publishes separate NCCN Guidelines for Cancer in People Living with HIV (available at NCCN.org), which provide recommendations for the management of non-small cell lung cancer, anal cancer, Hodgkin lymphoma, and cervical cancer in PLWH. Those guidelines also offer general advice for this population regarding HIV management during cancer therapy, drug–drug interactions with antiretrovirals and cancer therapies, radiation therapy, and supportive care. Recommendations for the management of non-Hodgkin's lymphoma in PLWH are available in the NCCN Guidelines for B-cell Lymphomas (available at NCCN.org).

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of the NCCN Guidelines for AIDS-Related Kaposi Sarcoma, an electronic search of the PubMed database was performed to obtain key literature in the field published since the previous NCCN Guidelines update, using the following search terms: (cancer or malignancy or carcinoma or adenocarcinoma or lymphoma or leukemia or melanoma or sarcoma or neoplasia) and (HIV or AIDS). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[6]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 101 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the discussion (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

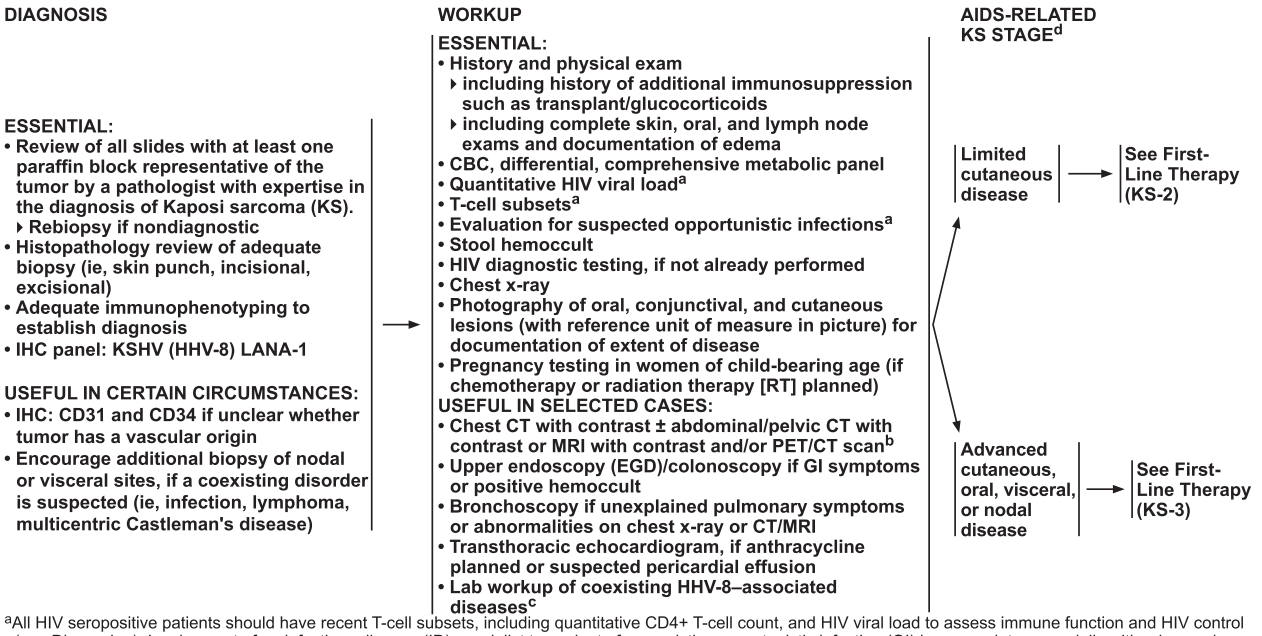
The complete details of the development and update of the NCCN Guidelines are available on the NCCN website (NCCN.org).

HIV Management During Cancer Therapy

Please also see the NCCN Guidelines for Cancer in PLWH (available at NCCN.org) for more information on this topic.

HIV Screening

One of every 7 people in the United States who are infected with HIV (or approximately 157,000 people) are not aware of their infection status.[1] Infected individuals who are unaware of their HIV status do not receive the clinical care they need to reduce HIV-related morbidity and mortality and may unknowingly transmit HIV.[22] The Centers for Disease Control and Prevention therefore recommends HIV screening for all patients in all health care settings unless the patient declines testing (opt-out screening).[23]



[a]All HIV seropositive patients should have recent T-cell subsets, including quantitative CD4+ T-cell count, and HIV viral load to assess immune function and HIV control (see Discussion). Involvement of an infectious disease (ID) specialist to evaluate for coexisting opportunistic infection (OI) is appropriate, especially with advanced immunosuppression.
[b]Imaging should be directed by symptoms or findings concerning for visceral or bone involvement as well as coexisting KSHV-associated inflammatory cytokine syndrome (KICS), multicentric Castleman's disease (MCD), or HHV8+ lymphoma; imaging is standard for staging of transplant-associated KS.
[c]Useful in setting of clinical features (ie, fever, dyspnea, effusions) concerning for KICS or KSHV-associated MCD: C-reactive protein, KSHV serum viral load, SPEP, IL-6, or IL-10.
[d]See Staging Classification for AIDS-Related KS (KS-A).

KS-1

HIV testing may be particularly important in patients with cancer, because identification of HIV infection has the potential to improve clinical outcomes.[24] Results of a retrospective cohort study at MD Anderson Cancer Center revealed, however, that the rate of HIV testing from 2007 to 2009 was only 19.3%.[25] Analysis of data from the 2009 Behavioral Risk Factor Surveillance System showed that 41% of U.S. cancer survivors <65 years of age reported ever being tested for HIV.[26] In both studies, race and other demographic characteristics, as well as tumor type, influenced the likelihood of receiving an HIV test.

The NCCN Panel supports the Centers for Disease Control and Prevention recommendation and believes that all patients diagnosed with cancer who do not opt-out should be tested for HIV if their HIV status is unknown. Testing is particularly important in the context of suspected or confirmed Kaposi sarcoma, given that the risk of Kaposi sarcoma in the United States is approximately 500-fold higher in PLWH compared with the HIV-seronegative population.

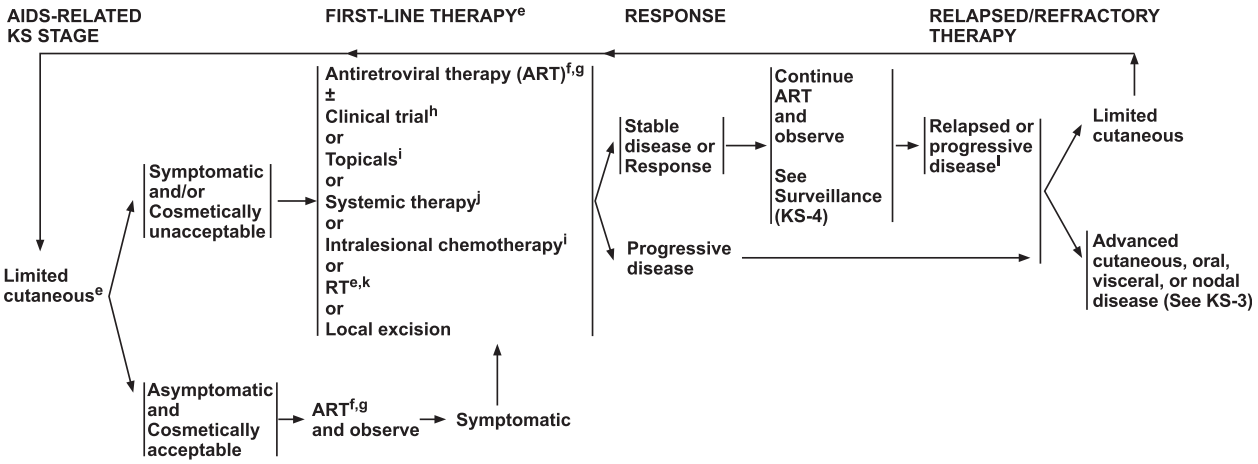
Linkage to HIV Care

The HIV Care Continuum Initiative indicates that all patients diagnosed with HIV should be connected with an HIV specialist.[27] Linkage to care with an HIV specialist has been shown to improve viral suppression and care engagement.[28,29] Patients should initiate and continue antiretroviral therapy (ART) to achieve and maintain viral suppression and immune reconstitution. Early initiation of ART has been shown to improve survival in PLWH.[30] Linkage to HIV care is also essential for PLWH who have cancer, and the oncology team should refer all PLWH who have cancer to an HIV specialist if they are not already linked to one. In all cases, communication between the oncologist and HIV specialist should be established. The HIV.gov website has a map that can be used to locate HIV services (https://locator.hiv.gov/).

HIV Therapy During Cancer Treatment

If the patient has already started ART, it should be continued during cancer treatment. For patients who have not yet started antiviral treatment, ART should optimally be initiated ≥7 days before start of cancer treatment or after the first cycle of cancer therapy to facilitate separate assessment of tolerability of ART and cancer treatment.

ART interruptions during cancer treatment should generally be avoided, because they increase the risk of



[e]See Principles and Goals of Therapy (KS-B).
[f]Initiation of ART may result in immune reconstitution inflammatory syndrome (IRIS) within 3–6 months; IRIS is characterized by marked lesional swelling, increased tenderness, and peripheral edema. However, ART should not be delayed or discontinued unless life-threatening IRIS develops. Reconstitution of immune function is important for obtaining and maintaining control or remission of KS.
[g]Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions including IRIS, their use may be considered.
[h]See clinicaltrials.gov.
[i]See Local Therapy (KS-C).
[j]See Systemic Therapy (KS-D).
[k]See Principles of Radiation Therapy (KS-E).
[l]If after initial response to therapy, KS relapses or progresses, repeat use of previously effective therapy may be considered, particularly if response was durable.

KS-2

immunologic compromise, opportunistic infection, and death.[31] Continuation of ART also may result in better cancer treatment tolerance, higher response rates, and improved survival.[32,33] If drug–drug interactions between cancer treatment and ART are problematic, then alternative ART regimens can be used. The NCCN Guidelines for Cancer in PLWH (available at NCCN.org) contain additional information on the topic of drug–drug interactions, including tables that explain the likelihood of effects on cancer drugs by ART and vice versa, either by ART drug class or by common ART regimens.

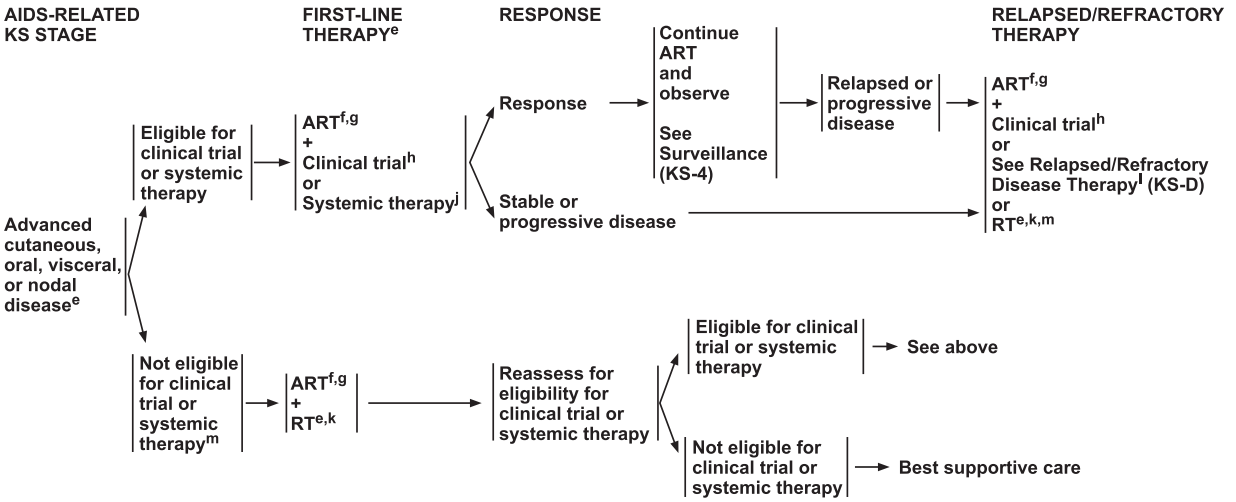
Laboratory testing, including HIV viral load and CD4+ T-cell monitoring, should generally be performed as per normal schedules in conjunction with the patient's HIV specialist.[21] However, more frequent HIV viral load testing (eg, once a month for the first 3 months and then every 3 months) may be needed if systemic cancer therapy is used.[34]

Opportunistic Infection Prophylaxis

The occurrence of opportunistic infections in PLWH has decreased in the ART era, mainly because effective ART reduces infection risk as CD4+ T-cell counts rise.[5,35–37] Furthermore, prophylaxis and treatment of opportunistic infections in PLWH have improved.[37,38] Still, opportunistic infections represent a major cause of morbidity and mortality in PLWH.[37,38]

The risk of bacterial, fungal, and viral infections is also elevated in patients with cancer, who may experience immunosuppression resulting from cancer treatment and sometimes from the disease itself (eg, hypogammaglobulinemia in lymphoid malignancies).[39–43] In particular, chemotherapy can cause neutropenia, which is a major risk factor for the development of infections.[44] Newer targeted agents are also associated with immunosuppression and increased infection risk.[45] The frequency and severity of infection are inversely proportional to the neutrophil count, with the risks of severe infection and bloodstream infection greatest (approximately 10%–20%) at neutrophil counts below 100 cells/mcL.[46]

PLWH may be more susceptible than their uninfected counterparts to infectious complications after chemotherapy, and low CD4+ T-cell counts appear to increase the risk of febrile neutropenia.[47] Furthermore, data show that certain chemotherapy regimens can cause a sustained drop in CD4+ T-cell counts and an increased risk of opportunistic infections.[48] Other



[e]See Principles and Goals of Therapy (KS-B).
[f]Initiation of ART may result in IRIS within 3–6 months; IRIS is characterized by marked lesional swelling, increased tenderness, and peripheral edema. However, ART should not be delayed or discontinued unless life-threatening IRIS develops. Reconstitution of immune function is important for obtaining and maintaining control or remission of KS.
[g]Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions including IRIS, their use may be considered.
[h]See clinical trials.gov.
[j]See Systemic Therapy (KS-D).
[k]See Principles of Radiation Therapy (KS-E).
[m]Systemic therapy is preferred over radiation therapy as first-line therapy and relapsed/refractory therapy for disseminated disease whenever systemic therapy is feasible considering performance status and comorbidities.

KS-3

regimens, however, appear to have similar effects on myelosuppression and infectious complications in PLWH who have cancer and HIV-negative patients with cancer.[49]

Overall, the NCCN Panel believes that PLWH who have cancer should receive the prophylaxis indicated by their HIV status, as recommended in the U.S. Department of Health and Human Services' Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (available at www.aidsinfo.nih.gov/guidelines). Additional prophylaxis may be indicated based on the cancer treatment and will be indicated as such in the guidelines where appropriate. Measurement of the CD4+ T-cell count and viral load can be considered more frequently than otherwise required in patients receiving cancer treatments that are anticipated to cause lymphopenia. If febrile neutropenia occurs during cancer treatment, consultation with an infectious diseases specialist is strongly recommended.

AIDS-Related Kaposi Sarcoma

Kaposi sarcoma is a multifocal malignancy of endothelial cells, which presents with characteristic red or brown papules. The risk for Kaposi sarcoma in the setting of HIV has been reported to be increased as much as 3,640-fold over the general population in the United States,[6–8,14,50] but this risk has declined in the ART era.[6,9,10,15] Still, estimates indicate that the risk of Kaposi sarcoma in PLWH between 2009 and 2012 was elevated approximately 498-fold compared with the general population in the United States,[15] and Kaposi sarcoma accounts for approximately 12% of cancers diagnosed in PLWH, with an estimated 765 to 910 cases diagnosed per year in the United States.[11,51]

Four types of Kaposi sarcoma have been described.[12,52,53] Classic Kaposi sarcoma generally involves indolent cutaneous lesions, often of the lower extremities, that slowly progress over years to decades. It is most common in older people of Mediterranean, Eastern European, Middle Eastern, and/or Jewish origins. It is much more common in men than in women. Endemic Kaposi sarcoma occurs in children and younger adults (<40 years of age) of equatorial Africa. It is usually more aggressive than classic Kaposi sarcoma, sometimes with visceral, bone, and/or lymph node involvement. When Kaposi sarcoma occurs in the context of immunosuppressive therapy (for organ transplant or other reasons),

SURVEILLANCE

- For patients not requiring active therapy and with no signs of progression
  - Follow-up periodically based on the degree of HIV viremia, immune reconstitution, and response to therapy.
    - ◊ History and physical exam
      - – including history of additional immunosuppression such as transplant/glucocorticoids
      - – including complete skin and oral exams, and documentation of edema
    - ◊ CBC, differential, comprehensive metabolic panel, T-cell subsets (CD4+ T-cell count), and HIV viral load
    - ◊ Assess ART compliance
- Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in picture) for documentation of extent of disease if change in disease is noted
- If signs and symptoms concerning for visceral involvement or prior to new therapy if progression/refractory disease
  - Stool hemoccult
  - Chest x-ray or chest CT with contrast
  - EGD/colonoscopy
  - Bronchoscopy
- As KS-associated herpesvirus (KSHV) is not eradicated with treatment of KS, the risk for future KS persists even after complete remission. Optimization and monitoring of HIV control and immune function is important to minimize this risk. This risk depends on immune function and generally decreases with immune reconstitution. However, KS can persist, relapse, or present even in the setting of normal values of T-cell subsets. Less frequent (every 6–12 mo) oncology monitoring may be appropriate for selected patients with undetectable HIV viral loads, normal T-cell subsets, and stable KS for 2 or more years as long as the patient has regular follow-up with an HIV provider.

it is called iatrogenic or transplant-associated Kaposi sarcoma. Although this form of Kaposi sarcoma can be aggressive and involve lymph nodes, mucosa, and/or visceral organs, it frequently responds to a reduction or cessation of immunosuppression. Finally, when Kaposi sarcoma occurs in the setting of HIV seropositivity, it is considered an AIDS-defining illness and is referred to as AIDS-related or epidemic Kaposi sarcoma. When immunosuppression is advanced, AIDS-related Kaposi sarcoma is more common, more aggressive, and more likely to involve viscera and/or lymph nodes than when immunosuppression is minimal. However, AIDS-related Kaposi sarcoma can occur in PLWH with normal CD4+ T-cell counts and viral load. Overall, AIDS-related Kaposi sarcoma tends to be more aggressive than other types.

Kaposi sarcoma is universally associated with HHV-8 infection (also known as Kaposi sarcoma-associated herpesvirus, KSHV).[52] Serologic confirmation of HHV-8 infection is present in 95%–98% of patients with Kaposi sarcoma.[52,53] In a study of 5,022 ART-naïve PLWH enrolled in 6 U.S. randomized clinical trials, 38% were infected with HHV-8.[54] HHV-8 infections are usually asymptomatic, and immunosuppression is likely an important factor in the pathogenesis of Kaposi sarcoma in HHV-8–infected individuals. In fact, CD4+ T-cell counts and HIV viral load correlate with the risk of Kaposi sarcoma in PLWH.[55] Thus, effective ART likely lowers the risk of Kaposi sarcoma development. Evidence also suggests that ART improves prognosis for Kaposi sarcoma. The 5-year survival of patients with AIDS-related Kaposi sarcoma has improved in the post-ART era, from 12.1% in 1980 to 1995 to as high as 88% in the post-ART era.[56–58]

Diagnosis and Workup of AIDS-Related Kaposi Sarcoma

As described in the algorithm, AIDS-related Kaposi sarcoma is diagnosed using pathology and immunophenotyping. Workup should include a history and physical exam that includes any history of additional immunosuppression such as transplant or glucocorticoids and HIV testing (if HIV status is unknown). In addition, complete skin, oral, and lymph node exams, with documentation of edema and photography of oral, conjunctival, and cutaneous lesions for documentation of extent of disease, are recommended. It is important to note that certain opportunistic infections can result in cutaneous lesions that can mimic Kaposi sarcoma lesions (eg, bacillary angiomatosis, blastomycosis, cryptococcosis).[59–62] Therefore, in addition to

STAGING CLASSIFICATION FOR AIDS-RELATED KS[a]

	Good risk (all of the following)	Poor risk (any of the following)
Tumor, T	**T0: Confined to skin and/or lymph nodes and/or minimal oral disease (non-nodular KS confined to palate)**	**T1: Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in organs other than lymph nodes**
Immune system, I[1]	**I0: CD4+ T-cell count ≥150/μL**	**I1: CD4+ T-cell count <150/μL**
Systemic disease, S	**S0: No history of opportunistic infection or thrush No "B" symptoms[2] Karnofsky performance status ≥70**	**S1: History of opportunistic infection and/or thrush "B" symptoms present Karnofsky performance status <70 Other HIV-related illness (eg, neurologic disease, lymphoma)**

[1]I stage has less prognostic value than T or S stages in the presence of ART therapy
[2]"B" symptoms are unexplained fever, night sweats, >10 percent involuntary weight loss, or diarrhea persisting more than two weeks

[a]Adapted from Krown SE, Metroka C, Wernz JC. Kaposi's sacoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging critera. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1989;7:1201-1207.

KS-A

biopsy of suspected lesions, involvement of an infectious diseases specialist may be appropriate to determine the correct diagnosis or diagnoses, especially in the setting of advanced immunosuppression.

Referral to an HIV specialist is also recommended, as is care coordination between the HIV specialist and the oncology team (see "HIV Management During Cancer Therapy," page 172). All PLWH should have recent T-cell subsets including quantitative CD4+ T-cell counts and HIV viral load to assess immune function and HIV control. This testing may be done in conjunction with the HIV specialist. Other essential workup items are fecal occult blood testing and chest X-ray to assess for gastrointestinal and pulmonary involvement.

Depending on symptoms and findings that may be concerning for visceral or bone involvement, and coexisting HHV-8–associated lymphoma, multicentric Castleman's disease (MCD), or KSHV-associated inflammatory cytokine syndrome (KICS), additional workup may be necessary. This may include upper and lower endoscopy and additional imaging to evaluate lymphadenopathy, visceral masses, splenomegaly, effusions, or bone lesions such as contrast CTs of chest, abdomen, and pelvis; MRI with contrast; and/or a PET/CT scan. Unexplained fevers occurring in the context of Kaposi sarcoma should prompt workup of MCD and KICS with C-reactive protein, HHV-8 serum viral load, serum protein electrophoresis, interleukin-6, and interleukin-10. The diagnosis of KICS requires excisional biopsy of lymphadenopathy to exclude MCD.[63]

It is important to note that imaging in PLWH who have cancer is complicated by the increased incidence of nonmalignant lesions that may be mistaken for cancer spread or recurrence. Opportunistic infections in the lung include *Mycobacterium tuberculosis*, cytomegalovirus, and *Pneumocystis jirovecii* pneumonia.[64] Furthermore, noninfectious, nonmalignant pulmonary manifestations of HIV can be difficult to interpret on imaging studies, including interstitial pneumonia and granulomatous disease.[64,65] Furthermore, brain lesions seen in PLWH may result from opportunistic infections such as viral encephalitis, aspergillosis, toxoplasmosis, cryptococcosis, bacterial meningitis, tuberculosis, progressive multifocal leukoencephalopathy, and *Mycobacterium avium* complex.[66,67] Benign noninfectious brain lesions can also occur in PLWH (eg, vascular complications, hydrocephalus).[66,67] Similarly, immune response to HIV and opportunistic infections commonly cause lymphadenopathy in PLWH,

PRINCIPLES AND GOALS OF THERAPY

Principles of Therapy:

- **Individual KS lesions may be distinct clones that arise due to the common risk factors of immunosuppression and persistent HHV-8 infection as opposed to metastases. Treatment of existing disease therefore may not prevent occurrence of future lesions.**
- **Reconstitution of immune function, maintenance of viral suppression, and avoidance of additional immunosuppression are critical to prevention of additional KS lesions and maintenance of response to therapy. For AIDS-related KS, it is important to work with an HIV specialist to optimize suppression of HIV and reconstitution of immune function with ART. Important examples of iatrogenic immunosuppression, which may promote KS, include not only systemic but local glucocorticoids (ie, inhaled, topical, intra-articular). Note that KS may flare in a remote location from the site of local glucocorticoids. Patients requiring rituximab for treatment of NHL with coexisting KS or multicentric Castleman's disease may develop flares of KS or incident KS. This may be mitigated by use of concurrent chemotherapy active against both KS and disease for which rituximab is prescribed (ie, doxorubicin).**
- **Persons with AIDS-related KS, especially those with advanced immunosuppression, are at increased risk of opportunistic infections (OIs), marrow suppression with neutropenic fever, or thrombocytopenic bleeding and should be monitored closely. It is important to collaborate with an HIV specialist to ensure adequate OI prophylaxis appropriate to CD4+ T-cell count (which may temporarily decrease with cytotoxic chemotherapy). Growth factor support may be needed to facilitate systemic therapy.**
- **Lymphedema and soft tissue infections: KS is often complicated by lymphedema with increased risk of cellulitis and deep tissue infections in affected limbs. Risk of severe lymphedema and delayed wound healing may be increased after radiation. Refer to a lymphedema specialist. In the setting of advanced cutaneous disease, radiation should be reserved for circumstances when systemic therapy is not feasible with the goal of palliation or short-term disease management until systemic therapy may be delivered. Note that treatment responses may be delayed in the context of significant lymphedema.**

Goals of Therapy:

- **Patients with limited cutaneous disease that is asymptomatic and cosmetically acceptable may be observed while continuing ART with optimization of immune function and HIV viral suppression as above. Remissions or stable disease may occur with ART and optimization of immune function and HIV viral suppression alone.**
- **Patients with symptomatic or cosmetically unacceptable disease should use minimally invasive and the least toxic therapy to control disease. A limited number of cycles of systemic therapy (eg, 3–6) may be sufficient for those initiating or re-initiating ART.**
- **Patients with advanced symptomatic cutaneous, visceral, nodal, or oral disease should be treated with systemic therapy with the goal of reducing or reversing symptoms, lymphedema, or threat to organ function. Complete remissions are rare.**
  - **Treatment is typically continued until unacceptable toxicity or plateau in response; maintenance therapy beyond 2 cycles of systemic therapy after determination of plateau is not recommended. If response is then clinically acceptable, patients may be observed on ART alone. Otherwise, alternative therapy should be initiated.**

KS-B

which can be seen on F-18 fluorodeoxyglucose PET/CT.[68,69] Nonmalignant causes of lymphadenopathy are more common in patients with higher viral loads and lower CD4+ T-cell counts.[70] Therefore, patients with cancer and HIV infection should have an infectious disease workup for imaging findings, as clinically indicated.

Staging of AIDS-Related Kaposi Sarcoma

As delineated in the algorithm, AIDS-related Kaposi sarcoma is staged using a TIS system in which aspects of the tumor (T), immune system (I), and systemic disease (S) are assessed with a 0 for good risk and 1 for poor risk.[71] However, more recent data have shown that the I stage has less prognostic value than the T or S stages in the presence of ART.[57] Patients staged as T1S1 appear to have the worst prognosis. In a study of 211 patients with AIDS-related Kaposi sarcoma, those staged as T1S1 had a 3-year survival rate of 53%, whereas for those staged as T0S0, T1S0, or T0S1, the 3-year survival rates were 88%, 80%, and 81%, respectively (P=.0001).[57]

Initial Management of AIDS-Related Kaposi Sarcoma

Patients with limited cutaneous disease that is asymptomatic and cosmetically acceptable to the patient may be treated with ART alone (see "Antiretroviral Therapy," opposite page). Those with symptomatic and/or cosmetically unacceptable limited cutaneous disease should be treated with ART and with the most minimally invasive and least toxic therapy possible. A limited number of cycles of systemic therapy (eg, 3–6; options discussed subsequently) may be sufficient for those initiating or reinitiating ART. Other options include topical treatment, intralesional chemotherapy, radiation, and local excision (all discussed subsequently). Intralesional chemotherapy and radiation to plantar and palmar surfaces may be useful in selected cases, but should be approached with caution.

If disease progresses on initial therapy, a different treatment option should be tried based on the extent of disease. If disease is stable or a response is seen on initial therapy, ART should be continued while the patient is observed. If the disease progresses or relapses after an initial response to therapy, repeat use of the previously effective therapy may be considered, particularly if the response was durable.

Preferred initial treatment for patients with advanced cutaneous, oral, visceral, or nodal AIDS-related Kaposi sarcoma is ART with clinical trial or systemic

LOCAL THERAPY

Topical
- **Alitretinoin 0.1% gel[1]**
  - **Apply 3–4 times daily to affected skin sites**
- **Imiquimod, 5% cream[2]**
  - **Apply 20 cm^2 of skin sachet under occlusion 3 times weekly; titrate dose to effect, tolerability**

Intralesional chemotherapy
- **Vinblastine[3]**
  - **0.2 mg/mL solution with a volume of 0.1 mL per 0.5 cm^2 of lesion**
    - ◊ **Other treatment schemas have been studied, with a variety of vinblastine concentrations, doses, administration volumes, frequency of administration, and total doses/volumes administered. See Discussion for additional references and information.**
  - **Pain from injection is common and may persist for several days. NSAIDs may be useful to relieve pain from injection.**
  - **Intralesional chemotherapy to plantar and palmar surfaces might be useful in selected cases, but should be approached with caution.**

Radiotherapy
- **See Principles of Radiation Therapy (KS-E)**

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KS-C

therapy. For those not eligible for clinical trial or systemic therapy, radiation can be used with ART. The data supporting these treatment options are described subsequently.

It is important to note that individual Kaposi sarcoma lesions may be distinct clones that arise because of the common risk factors of immunosuppression and persistent HHV-8 infection as opposed to metastases. Furthermore, persistence of HHV-8 infection results in ongoing risk of recurrence/disease progression. Currently, eradication of HHV-8 is not possible. Therefore, treatment of existing disease may not prevent occurrence of future lesions, and the goals of therapy are based on disease control.

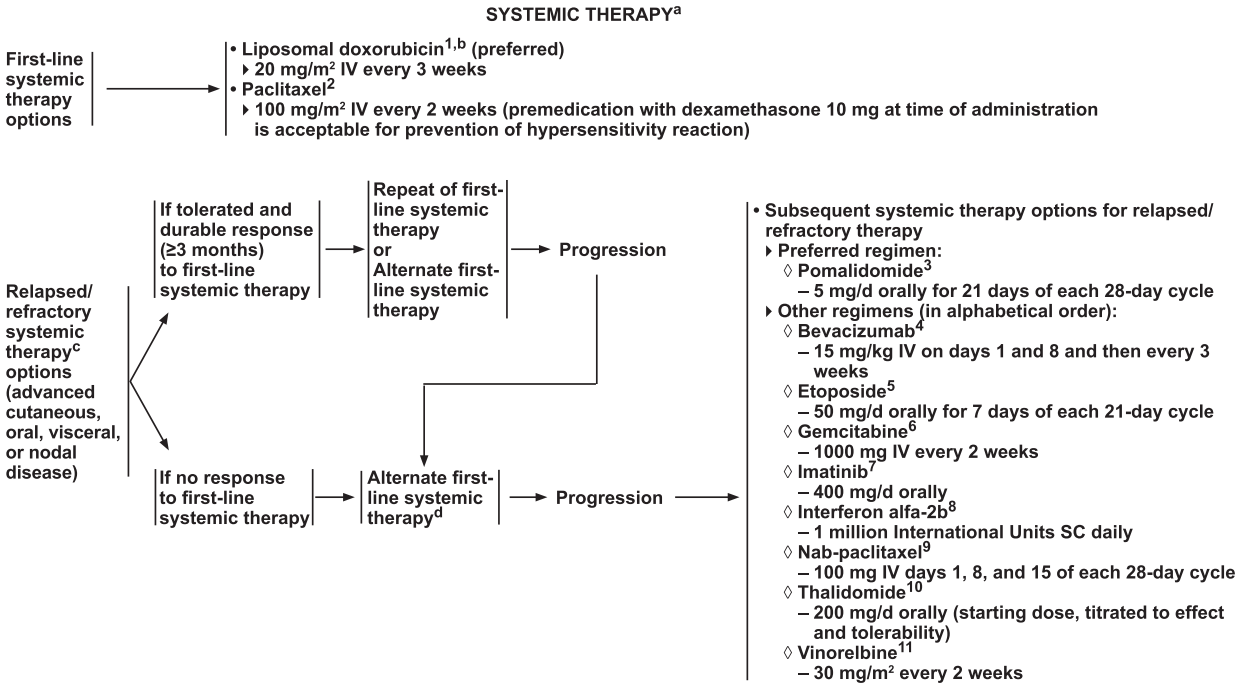
Antiretroviral Therapy

Reconstitution of immune function, maintenance of viral suppression, and avoidance of additional immunosuppression are critical to prevent additional Kaposi sarcoma lesions and maintain response to therapy. In fact, in the setting of limited cutaneous disease, remissions or stable disease may occur with optimization of immune function and HIV viral suppression alone.[72–78] Therefore, comanagement with an HIV specialist to optimize suppression of HIV and reconstitution of immune function with ART is important for patients with AIDS-related Kaposi sarcoma (see "HIV Management During Cancer Therapy," page 172).

Initiation of ART may result in immune reconstitution inflammatory syndrome (IRIS) within 3 to 6 months in a reported 6%–39% of patients with AIDS-related Kaposi sarcoma.[79–82] IRIS is characterized by marked lesional swelling, increased tenderness, and peripheral edema. Individuals with pulmonary involvement, concurrent or recent use of glucocorticoids, and/or advanced immunosuppression may be at increased risk.[79,80,82] In contrast with management of IRIS for some opportunistic infections, glucocorticoids are generally contraindicated in Kaposi sarcoma, as well as in Kaposi sarcoma-associated IRIS, because of the potential for life-threatening Kaposi sarcoma exacerbation resulting from stimulatory effects of glucocorticoids on Kaposi sarcoma spindle cells.[83,84] Management of Kaposi sarcoma-associated IRIS should involve coordination with an HIV specialist. ART should not be delayed or discontinued unless life-threatening IRIS develops.

Topical Therapies

Topical therapies are an option for patients with limited cutaneous disease that is symptomatic and/or



[a]See references for regimens on KS-D 2 of 2.
[b]Due to risk of cardiotoxicity, perform echocardiogram prior to initial and repeat course of liposomal doxorubicin and limit lifetime dose to 400–450 mg/m².
[c]Consider repeating any prior systemic therapy that was tolerated and resulted in a durable response.
[d]If both first-line options have already been given, the patient should proceed to the subsequent systemic therapy options.

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cosmetically unacceptable. Alitretinoin gel, a retinoid, was studied in a phase III vehicle-controlled, double-blind, multicentered study in which 134 patients with AIDS-related Kaposi sarcoma received either 0.1% alitretinoin gel or vehicle gel twice daily for 12 weeks.[85] The cutaneous tumor response rates were 37% in the alitretinoin group compared with 7% in the control group. Another very similar randomized, multicenter, double-blind, vehicle-controlled study also compared tumor response rates in patients with AIDS-related Kaposi sarcoma between an alitretinoin group and a control group.[86] Response rates in the 268 patients were 35% for those receiving 0.1% alitretinoin gel compared with 18% for those who received the vehicle gel. In both of these studies, alitretinoin gel was well tolerated, with mostly mild to moderate adverse events that were limited to the application site and that were relieved when treatment was stopped.

Imiquimod is a topical immune response modulator with antiviral and antitumor activity.[87] It is used in a variety of skin conditions including malignancies and warts.[87,88] Case reports have shown that imiquimod cream can be safe and effective in some patients with classic or transplant-associated Kaposi sarcoma.[89–94] In a single-center, open-label, phase I/II trial, 17 HIV-negative patients with Kaposi sarcoma received imiquimod 5% cream 3 times per week for 24 weeks.[95] The response rate was 47%. More than half of the patients reported local itching and erythema, but treatment was generally well tolerated. Imiquimod is not well studied as a treatment for patients with cutaneous AIDS-related Kaposi sarcoma.[96,97] The panel includes imiquimod as an option for patients with cutaneous AIDS-related Kaposi sarcoma based on extrapolation from the data presented previously in other settings, expert opinion, and nonpublished anecdotal data.

Intralesional Chemotherapy

Intralesional vinblastine is another option for patients with limited mucocutaneous disease that is symptomatic and/or cosmetically unacceptable. Intralesional injection of vinblastine has been studied in case reports, case series, and one small randomized trial of patients with oral AIDS-related Kaposi sarcoma.[98–104] In a large series of 144 oral Kaposi sarcoma lesions in 50 HIV-positive men, complete response was seen in 74% of lesions and partial response in 26%.[101] The recurrence rate was 26%, with a mean disease-free period of 12.9 weeks. Consistent

SYSTEMIC THERAPY
REFERENCES

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with the safety profile seen in other studies, pain was reported by 72% of participants, ulceration occurred in 22%, and temporary numbness was seen in 12%. Pain is generally mild to moderate and relieved with pain medication, and ulceration is generally self-limiting.

Studies on the use of intralesional vinblastine injection for cutaneous lesions are more limited.[105,106] In a trial of 11 men with AIDS-related Kaposi sarcoma, 88% of cutaneous lesions showed a complete or partial clinical response.[105] Treatment resulted in inflammation and blistering of the lesion before healing, and the final results were not cosmetically optimal because of post-inflammation hyperpigmentation. Most patients reported aching pain 6 to 48 hours after treatment that was relieved with pain medication.

Intralesional vinblastine has also been used in cutaneous lesions in patients with classic Kaposi sarcoma.[107]

Local Excision

Local excision is an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically unacceptable. However, data regarding outcomes of the excision of cutaneous Kaposi sarcoma lesions are limited and appear to be restricted to HIV-negative individuals.[108–112]

Radiation Therapy

AIDS-related Kaposi sarcoma is radioresponsive, with complete responses rates of treated lesions reported in the range of 68%–92%.[113–117] Radiation therapy for AIDS-related Kaposi sarcoma is used in patients with limited cutaneous disease that is symptomatic and/or cosmetically unacceptable. For patients with advanced disease, systemic therapy is preferred over radiation therapy in first-line and for relapsed/refractory disease as long as systemic therapy is feasible based on performance status and comorbidities. Radiation in this setting should be reserved for circumstances when systemic therapy is not feasible or when palliative therapy is needed to mitigate pain or other symptoms.[118]

When radiation is used, hypofractionated regimens (eg, 20 Gy in 5 fractions) appear to be equally effective as the standard regimen of 24 Gy in 12 fractions.[119,120] Dose fractionation should be based on the site of treatment with consideration for surrounding normal tissue tolerance.

PRINCIPLES OF RADIATION THERAPY[1,2,3]

- **General Principles**
  - **For most skin lesions, electrons or superficial x-rays can be used to deliver optimal dosimetry and minimize dose to underlying structures. To ensure sufficient dose is delivered for deeper or larger lesions, conformal photon therapy or mixed photon-electron treatment plans may be utilized. IMRT with or without image guidance may be useful for larger or deeper lesions.**
  - **The use of bolus may be necessary to achieve adequate skin dose.**
  - **Radiation therapy to plantar and palmar surfaces might be useful in selected cases, but should be approached with caution.**

- **General Treatment Information**
  - **Dosing Prescription Regimen**
    - ◊ **24 Gy in 12 fractions in 2.0 Gy per fraction**
    - ◊ **Other dosing schemas ranging from 6–8 Gy in 1 fraction to 30 Gy in 10–15 fractions may be used.**

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KS-E

The side effects of radiation for AIDS-related Kaposi sarcoma are site-dependent, but typically manageable given the low doses needed to achieve a response.[113–116] Early recognition and treatment of dermatitis, oral mucositis, and lymphedema are especially important.[113,115,121] The risk of lymphedema is already elevated in patients with Kaposi sarcoma and may increase after radiation.[122] Early referral to and comanagement with a lymphedema specialist is recommended.

Systemic Therapy

The preferred first-line systemic therapy for both limited cutaneous disease and advanced disease is liposomal doxorubicin. In a randomized phase III trial, 258 patients with advanced AIDS-related Kaposi sarcoma were randomized to receive pegylated-liposomal doxorubicin or doxorubicin/bleomycin/vincristine (ABV).[123] The overall response rate was 46% (95% CI, 37%–54%) in the liposomal doxorubicin arm and 25% (95% CI, 17%–32%) in the ABV arm. The median time to treatment failure was approximately 4 months in both groups. Most patients in both arms experienced ≥1 grade 3/4 adverse event, with leukopenia, nausea/vomiting, anemia, and peripheral neuropathy as the most common adverse events in the liposomal doxorubicin group. Pegylated-liposomal doxorubicin was also compared with bleomycin/vincristine (BV) in another randomized trial of patients with AIDS-related Kaposi sarcoma (N=241).[124] As in the other trial, response rates were superior in the liposomal doxorubicin group compared with the BV group (59% vs 23%; $P<.001$). Pegylated-liposomal doxorubicin resulted in an increased risk of neutropenia but was less likely to result in early treatment cessation.

Liposomal doxorubicin is associated with risk of cardiotoxicity.[125–127] Therefore, a baseline echocardiogram should be performed before initial and repeat courses of liposomal doxorubicin, and the lifetime dose should be limited to 400 to 450 mg/m^2.[128]

An alternative option for first-line systemic therapy for limited cutaneous and advanced disease is paclitaxel. Early studies showed that it has significant activity in the advanced disease setting, with neutropenia as the most frequent dose-limiting toxicity.[129,130]

One trial randomized 73 patients with advanced AIDS-related Kaposi sarcoma to paclitaxel or pegylated-liposomal doxorubicin.[131] The 2 arms were statistically equivalent with regard to response rates, median progression-free survival, and 2-year survival. A trend

toward increase in grade 3 to grade 5 toxicity was seen in the paclitaxel arm (84% vs 66%; P=.077), with 1 lethal, grade 5 pulmonary embolism in a patient treated with paclitaxel. A systematic review of randomized trials and observational studies in patients with advanced AIDS-related Kaposi sarcoma found no evident differences between liposomal doxorubicin, liposomal daunorubicin, and paclitaxel, although the number of studies identified was low.[132]

Surveillance of Patients With AIDS-Related Kaposi Sarcoma

Patients treated for AIDS-related Kaposi sarcoma who do not require active treatment and who are without signs of progression should be followed periodically based on the degree of HIV viremia, immune reconstitution, and response to therapy. Surveillance should include history and physical (including complete skin and oral exams and documentation of edema and history of additional immunosuppression such as transplant/glucocorticoids), complete blood count, differential, comprehensive metabolic panel, T-cell subsets (CD4+ T-cell count), and HIV viral load. ART compliance should also be assessed. If a change in disease is noted, lesions should be photographed for documentation. Stool testing, chest X-ray or chest CT with contrast, esophagogastroduodenoscopy/colonoscopy, and bronchoscopy should be performed only for signs and symptoms concerning for visceral involvement or, in the case of progression/refractory disease, before a new therapy is initiated.

It is important to note that HHV-8 is not eradicated with treatment of Kaposi sarcoma, and the risk of future Kaposi sarcoma persists even after complete remission. Optimization and monitoring of HIV control and immune function is important to minimize this risk, because disease risk generally decreases with immune reconstitution. However, Kaposi sarcoma can persist, relapse, or present even in the setting of normal values of T-cell subsets. Less frequent (every 6–12 months) oncologic monitoring may be appropriate for select patients with undetectable HIV viral loads, normal T-cell subsets, and Kaposi sarcoma that is stable for ≥2 years, provided the patient has regular follow-up with an HIV specialist.

Systemic Therapy of Relapsed/Refractory Disease

At first progression, the same systemic therapy options as in first line (liposomal doxorubicin and paclitaxel, discussed previously) may be considered as follows:

- If first-line therapy was tolerated and a durable response (>3 months) was seen, then a repeat of the therapy used in first line should be considered.
- If there was no response to first-line systemic therapy, then an alternative first-line therapy option should be given.

After subsequent progressions, liposomal doxorubicin or paclitaxel, whichever has not yet been administered, is recommended.[133,134] In third line, the panel recommends pomalidomide as the preferred regimen. Pomalidomide was studied in a phase I/II trial of 7 HIV-negative individuals and 15 PLWH with Kaposi sarcoma.[135] PLWH were required to have viremia controlled and either progressive or stable Kaposi sarcoma on ART. Most of the participants (17 of 22; 77%) had previous therapy for Kaposi sarcoma, exclusive of ART.[136] The response rate was 60% in the HIV-infected group (95% CI, 32%–84%). Grade 3/4 adverse events that might have occurred due to pomalidomide were neutropenia, infection, and edema.

Other treatment options for subsequent lines of therapy for relapsed/refractory disease, listed in alphabetical order, include bevacizumab, etoposide, gemcitabine, imatinib, interferon, nab-paclitaxel, thalidomide, and vinorelbine, but data for these agents are generally limited, as described subsequently.

Bevacizumab was assessed in a phase II study of 17 PLWH with Kaposi sarcoma who had progressive or stable disease on ART.[137] Thirteen of the patients had received prior chemotherapy for Kaposi sarcoma. The complete response rate was 19% and the partial response rate was 12%, for an overall response rate of 31% (95% CI, 11%–59%). Adverse events included hypertension (N=7), neutropenia (N=5), cellulitis (N=3), and headache (N=2).

Etoposide has been studied in multiple phase II trials of patients with AIDS-related Kaposi sarcoma.[138–140] In one of these trials, 36 patients with previously treated AIDS-related Kaposi sarcoma received a course of oral etoposide, and the overall response rate was 36%, with stable disease occurring in 33% of the participants.[140] The median duration of response was about 6 months. Grade 3/4 neutropenia occurred in 28%, and opportunistic infections occurred in 22%. The other trials also showed oral etoposide to have clinical activity and be fairly well tolerated.

Evidence for the use of gemcitabine in patients with refractory AIDS-related Kaposi sarcoma comes only from a retrospective analysis of 23 patients who had been treated with first-line ABV.[141] Complete response was seen in 3 patients (13%), partial response in 8 (35%), and stable disease in 11 (48%). Only 1 patient had progressive disease. Grade 3/4 adverse events include leukopenia, pain, fatigue, and neutropenia. Gemcitabine has also been studied as first-line systemic therapy in a phase IIA trial in West Kenya, with a complete response rate of 33% and a partial response rate of 53%.[142]

Imatinib appears to have activity in AIDS-related Kaposi sarcoma.[143,144] The strongest evidence comes from a multicenter phase II trial, in which 30 patients were treated with imatinib.[145] Eighteen patients (60%) had received prior therapy. Although no complete responses were seen, 33% achieved partial response and 20% had stable disease. The median duration of response was approximately 8 months, with disease progression in 7 patients (23%). Grade 3/4 adverse events attributed to imatinib included allergic reaction/hypersensitivity, nausea, dehydration, and cellulitis, but only 5 patients (17%) discontinued therapy because of adverse events.

Early studies suggested that various forms of interferon had clinical activity in AIDS-related Kaposi sarcoma.[146–149] Several studies in the post-ART era have focused specifically on interferon alpha-2b in this population.[150,151] In one randomized phase II trial, the safety and efficacy of low-dose interferon alpha-2b was assessed in 35 patients with AIDS-related cutaneous Kaposi sarcoma.[150] The response rate was 40%, and the median duration of response was approximately 25 months. Grade 3/4 neutropenia occurred in 3% of patients.

Evidence for the use of nab-paclitaxel in Kaposi sarcoma appears to be limited to 1 abstract of a phase II trial of 6 patients with classic Kaposi sarcoma.[152] Partial (n=2) or complete responses (n=4) were seen in all patients. Grade 3 adverse events were neutropenia in half of the patients and thrombocytopenia in 1 of 6 patients.

Thalidomide has been studied in AIDS-related Kaposi sarcoma in 2 phase II trials.[153,154] One of these trials included 17 assessable patients with progressive disease.[153] Partial responses were seen in 47%, and stable disease was seen in 12%. Time to progression was a median 7.3 months. The most frequently reported side effects were drowsiness in 45% of participants and depression in 35%.

Evidence for the activity of vinorelbine in AIDS-related Kaposi sarcoma comes from a phase II trial of 35 assessable patients with progressive disease.[155] Complete clinical responses were seen in 9%, and partial responses were seen in 34%. The median duration of response was about 6 months. Neutropenia was the most frequent dose-limiting toxicity, but other side effects were mild and reversible and the treatment was generally well tolerated.

Summary

Management of AIDS-related Kaposi sarcoma depends on location and extent of disease. Patients with limited cutaneous disease that is asymptomatic and cosmetically acceptable to the patient may be treated with ART alone. Remissions or stable disease may occur with optimization of immune function and HIV viral suppression alone.

Those with symptomatic and/or cosmetically unacceptable limited cutaneous disease should be treated with ART and with therapy that is minimally invasive with the least toxicity possible. Options include a limited number of cycles of systemic therapy, topical treatment, intralesional chemotherapy, radiation, and local excision.

Preferred initial treatment of patients with advanced cutaneous, oral, visceral, or nodal AIDS-related Kaposi sarcoma is ART with clinical trial or systemic therapy. For those not eligible for clinical trial or systemic therapy, radiation can be used with ART. As lymphedema often complicates Kaposi sarcoma, early involvement of a lymphedema specialist is recommended.

Surveillance of patients treated for AIDS-related Kaposi sarcoma is important, because disease can recur after an initial complete response and in the setting of normal values of T-cell subsets. Persistence of HHV-8 and emergence of distinct tumor clones can lead to disease progression and relapse. Furthermore, because individual Kaposi sarcoma lesions are often distinct clones as opposed to metastases, treatment of existing disease does not prevent occurrence of new lesions.

For relapsed/refractory disease, a typical systemic therapy sequence would be first-line liposomal doxorubicin, followed by second-line paclitaxel, followed by pomalidomide in the third line of treatment. Additional lines of other therapies can be given, and any systemic therapy that was tolerated with a durable response can be repeated.

Glucocorticoids should be avoided in patients with active or prior Kaposi sarcoma given the potential to cause significant flares or relapses. The use of glucocorticoids should be limited to use for life-threatening conditions for which glucocorticoids are otherwise indicated (ie, anaphylaxis). Other therapies associated with flares of Kaposi sarcoma include those suppressing B- and T-cell numbers and/or function, such as rituximab and cyclosporine, respectively.[156,157]

Overall, the survival of patients with AIDS-related Kaposi sarcoma has greatly improved, and long-term survival can be the goal for many patients. However, the goals of therapy for patients with advanced disease are namely reducing or reversing symptoms and mitigating end organ damage. Complete remissions in this setting are rare, but effective therapy can lead to long-term disease control.

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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Michelle Rudek, PhD, PharmD: Novavax, Inc.