National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kaposi Sarcoma

Version 1.2023 — December 20, 2022

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Kaposi Sarcoma

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.
See NCCN Categories of Preference.

Updates in Version 1.2023 of the NCCN Guidelines for Kaposi Sarcoma from Version 1.2022 include:

KS-1
- Workup: Essential
  - Evaluation for suspected opportunistic infections (OIs) moved to Useful in Selected Cases.
  - Stool hemoccult moved to Useful in Selected Cases and revised to: *Stool hemoccult in the setting of advanced cutaneous, oral, visceral, or nodal involvement*
  - Chest x-ray moved to Useful in Selected Cases and revised to: *Chest x-ray in the setting of advanced cutaneous, oral, visceral, or nodal disease*
  - Bullet added: HIV screening and/or diagnostic testing
  - Bullet removed: HIV diagnostic testing
    - ◊ Sub-bullet removed: Quantitative HIV viral load
    - ◊ Sub-bullet removed: T-cell subsets
- Workup: Useful in Selected Cases
  - Bullet 4 revised: *Chest CT with contrast and* bronchoscopy if unexplained pulmonary symptoms or abnormalities on chest x-ray ~~or CT/MRI~~
  - Bullet 5 revised: *Abdomen/pelvis CT with contrast or MRI with contrast and* ~~upper endoscopy~~ *esophagogastroduodenoscopy* (EGD)/colonoscopy if gastrointestinal (GI) symptoms or positive hemoccult
  - Bullet 6 revised: ~~Chest CT with contrast ± Abdomen/pelvis CT with contrast or MRI with contrast and/or~~ *FDG*-PET/CT scan *if concerns for coexisting KSHV-associated inflammatory cytokine syndrome (KICS), MCD, or KSHV+ lymphoma*
  - Footnote b revised: Imaging should be directed by symptoms or findings concerning for visceral or bone involvement as well as coexisting KICS, MCD, or KSHV+ lymphoma~~; imaging is standard for staging of transplant-associated KS~~. See NCCN Guidelines for B-Cell Lymphomas *(CD-1)* (Also for KS-4)

KS-4
- Surveillance
  - Bullet 3 revised: If signs and symptoms concerning for visceral involvement or prior to new therapy if progression/refractory disease or if change in disease is noted, *the following are indicated depending on the clinical circumstances*:
  - Sub-bullet 1 added: Evaluation for suspected OIs
  - Sub-bullet 2 revised: Stool hemoccult *in the setting of advanced cutaneous, oral, visceral, or nodal involvement*
  - Sub-bullet 3 revised: Chest x-ray *in the setting of advanced cutaneous, oral, visceral, or nodal disease*
  - Sub-bullet 4 revised: Chest CT *with contrast and bronchoscopy if unexplained pulmonary symptoms or abnormalities on chest x-ray*
  - Sub-bullet 5 revised: Abdomen/pelvis CT with contrast ~~depending on clinical concerns~~ *or MRI with contrast and EGD/colonoscopy if GI symptoms or positive hemoccult*
  - Sub-bullet 6 revised: *FDG*-PET/CT *if concerns for coexisting KICS, MCD, or KSHV+ lymphoma*
  - Sub-bullet removed: EGD/colonoscopy
  - Sub-bullet removed: Bronchoscopy
  - Sub-bullet added: The diagnosis of KICS ideally requires excisional biopsy of lymphadenopathy to exclude MCD, if feasible

KS-C
- Principles of Immune Reconstitution Inflammatory Syndrome (IRIS)
  - Clinical Presentation/Definition
    - ◊ Bullet 3 added: The risk of IRIS is higher in patients with baseline low CD4 T-cell counts and high HIV viral loads.
  - Reference 2 added: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed 9/6/2022.

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Updates in Version 1.2023 of the NCCN Guidelines for Kaposi Sarcoma from Version 1.2022 include:

KS-D
- Local Therapy
  - Topical
    - Imiquimod, 5% cream, sub-bullet revised: Apply one sachet to up to 20 cm^2 of affected skin and cover with occlusive dressing for 8 hours three times per week; titrate *frequency of application* ~~dose~~ to effect and tolerability *(up to once daily), with treatment breaks if tolerability issues occur.*

KS-E
- Principles of Radiation Therapy
  - General Principles
    - Bullet 3 revised: Radiation therapy to plantar and palmar surfaces might be useful in selected cases. *However,* ~~but~~ *high doses* should be approached with caution because of *theoretical* toxicity *concerns like long-term wound healing, particularly* ~~or functional adverse events. Increased risk of long-term wound healing, particularly~~ in the setting of coexisting lymphedema~~, is a concern~~.
    - Bullet 4 revised: Risk of secondary cancer, severe or worsening lymphedema, and long-term wound healing complications may be increased after radiation*; however, toxicity can be mitigated by utilizing lower-dose radiotherapy regimens*.
  - General Treatment Information
    - Dosing Prescription Regimen
      - Sub-bullet 1 revised: Various dosing schemas may be used. *Lower doses are preferred for smaller and more superficial lesions. Higher doses may be preferred for more extensive, deeply invasive lesions. More fractionated regimens may be preferred for sites with adjacent radiosensitive structures, such as the oral cavity.* Examples:
    - Biologically Equivalent Doses added

KS-F (1 of 3)
- Systemic Therapy
  - Subsequent systemic therapy options for relapsed/refractory therapy
    - Other recommended regimens
      - Nab-paclitaxel moved from Other Recommended Regimens to Useful in Certain Circumstances and revised to: Nab-paclitaxel *(if paclitaxel intolerant)*
    - Useful in certain circumstances
      - Ipilimumab + nivolumab (for classic KS) added as a category 2A recommendation.
      - Pembrolizumab (for endemic and classic KS) added as a category 2A recommendation.
      - Last sub-bullet revised: Thalidomide (for patients with ~~corticosteroid-refractory~~ IRIS)
    - Footnote c revised: Due to *potential* risk of cardiotoxicity, perform echocardiogram prior to initial ~~and repeat~~ course of liposomal doxorubicin *and repeat periodically.* ~~and~~ *Consider* limit*ing* lifetime dose *per prescribing guidelines; however, other data suggest that the patients who need continued treatment may be safely treated beyond 1000* ~~to 400–450~~ mg/m^2. (Also for KS-F 2 of 3)

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Updates in Version 1.2023 of the NCCN Guidelines for Kaposi Sarcoma from Version 1.2022 include:

KS-F (2 of 3)
- Systemic Therapy Dosing
  - First-Line Systemic Therapy Dosing
    - ◊ Preferred regimens
      - – 2nd bullet, sub-bullet revised: Loading dose 0.15 mg/kg PO followed by 0.04–0.06 mg/kg/day to maintain trough blood levels of 6–10 ng/mL *or 2 mg PO daily (adjust to maintain trough levels of 6–10 ng/mL)*
      - – 3rd sub-bullet added: For PWH on ART, providers should consult with an ID pharmacist prior to dosing sirolimus
  - Subsequent Systemic Therapy Options for Relapsed/Refractory Therapy Dosing
    - ◊ Other recommended regimens
      - – Gemcitabine
        - ▪ Sub-bullet 2 added: 1000 mg/m^2 IV every 2 weeks
        - ▪ Sub-bullet 3 added: Or 1000 mg/m^2 IV on days 1 and 8 every 21 days
        - ▪ Sub-bullet removed: 1000 mg IV every 2 weeks
      - – Nab-paclitaxel dosing moved to useful in certain circumstances and revised to: Nab-paclitaxel *(if paclitaxel intolerant)* 100 mg IV on days 1, 8, and 15 of each 28-day cycle
    - ◊ Useful in certain circumstances
      - – Etoposide revised: 50 mg/day orally for 7 days of each 14-day cycle. After 2 cycles, escalate dose to 100 mg/day orally for 7 days of each 14-day cycle in patients without PR or CR and no toxicity >Grade 2. Dose can be further escalated to 150 mg/day ~~and then to a maximum dose of 200 mg/day~~ based on tolerance and response
      - – Ipilimumab + nivolumab (for classic KS) added as a category 2A recommendation.
        - ▪ Ipilimumab 1 mg/kg IV every 6 weeks and nivolumab 240 mg IV every 2 weeks
      - – Pembrolizumab (for endemic and classic KS) added as a category 2A recommendation.
        - ▪ 200 mg IV every 3 weeks for up to 6 months
      - – Bullet 6 revised: Sirolimus *(for transplant KS)*
        - ▪ Bullet 6, sub-bullet 1 revised: Loading dose 0.15 mg/kg PO followed by 0.04–0.06 mg/kg/day to maintain trough blood levels of 6–10 ng/mL *or 2 mg PO daily (adjust to maintain trough levels of 6–10 ng/mL).*
        - ▪ Bullet 6, sub-bullet 2 added: *For PWH on ART, providers should consult with an ID pharmacist prior to dosing sirolimus*
      - – Bullet 7 revised: Thalidomide *(for patients with IRIS)*

KS-F (3 of 3)
- Systemic Therapy References
  - Ipilimumab + nivolumab
    - ◊ Added: Zer A, Icht O, Avram D, et al. Phase II single-arm study of nivolumab and ipilimumab (Nivo/Ipi) in previously treated classical Kaposi sarcoma (cKS). Ann Oncol 2022;33:720-727.
  - Lenalidomide
    - ◊ Added: Reid E, Shimabukuro K, Moore P,et al. AMC-070: Lenalidomide is safe and effective in HIV-associated Kaposi sarcoma. Clin Cancer Res 2022;28:2646-2656.
  - Liposomal doxorubicin
    - ◊ Added: Jones RL, Berry GJ, Rubens RD, et al. Clinical and pathological absence of cardiotoxicity after liposomal doxorubicin. Lancet Oncol 2004;5:575-577.
  - Pembrolizumab
    - ◊ Added: Delyon J, Biard L, Renaud M, et al. PD-1 blockade with pembrolizumab in classic or endemic Kaposi's sarcoma: a multicentre, single-arm, phase 2 study. Lancet Oncol 2022;23:491-500.
  - Sirolimus
    - ◊ Added: Krown SE, Roy D, Lee JY, et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: An AIDS Malignancy Consortium study. J Acquir Immune Defic Syndr 2012;59:447-454.

ABBR-1
- New section added: Abbreviations.

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DIAGNOSIS

ESSENTIAL:
- Review of all slides with at least one paraffin block representative of the tumor by a pathologist with expertise in the diagnosis of Kaposi sarcoma (KS)
  - Rebiopsy if non-diagnostic
- Histopathology review of adequate biopsy (ie, skin punch, incisional, excisional)
- Adequate immunophenotyping to establish diagnosis
- Immunohistochemistry (IHC) panel: Kaposi sarcoma-associated herpesvirus (KSHV; human herpesvirus 8 [HHV-8]), LANA-1

USEFUL IN CERTAIN CIRCUMSTANCES:
- IHC: CD31 and CD34 if unclear whether the tumor has a vascular origin
- Encourage additional biopsy of nodal or visceral sites if a coexisting disorder is suspected (ie, infection, lymphoma, multicentric Castleman disease [MCD])

→

WORKUP

ESSENTIAL:
- History and physical examination
  - including history of additional immunosuppression such as transplant/glucocorticoids
  - including complete skin, oral, and lymph node examinations, and documentation of edema
- Complete blood count (CBC), differential, and comprehensive metabolic panel
- HIV screening and/or diagnostic testing[a]
- Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in the picture) for documentation of extent of disease
- Pregnancy testing in patients of childbearing potential (if chemotherapy or radiation therapy [RT] planned)

USEFUL IN SELECTED CASES:
- Evaluation for suspected opportunistic infections (OIs)[a]
- Stool hemoccult in the setting of advanced cutaneous, oral, visceral, or nodal involvement
- Chest x-ray[b] in the setting of advanced cutaneous, oral, visceral, or nodal disease
- Chest CT with contrast[b] and bronchoscopy if unexplained pulmonary symptoms or abnormalities on chest x-ray
- Abdomen/pelvis CT with contrast[b] or MRI with contrast[b] and esophagogastroduodenoscopy (EGD)/colonoscopy if gastrointestinal (GI) symptoms or positive hemoccult
- FDG-PET/CT scan[b] if concerns for coexisting KSHV-associated inflammatory cytokine syndrome (KICS), MCD, or KSHV+ lymphoma
- Transthoracic echocardiogram, if anthracycline planned or suspected pericardial effusion
- Lab workup of coexisting KSHV-associated diseases[c]

KS STAGE[d]

Limited cutaneous disease → See First-Line Therapy (KS-2)

Advanced cutaneous, oral, visceral, or nodal disease → See First-Line Therapy (KS-3)

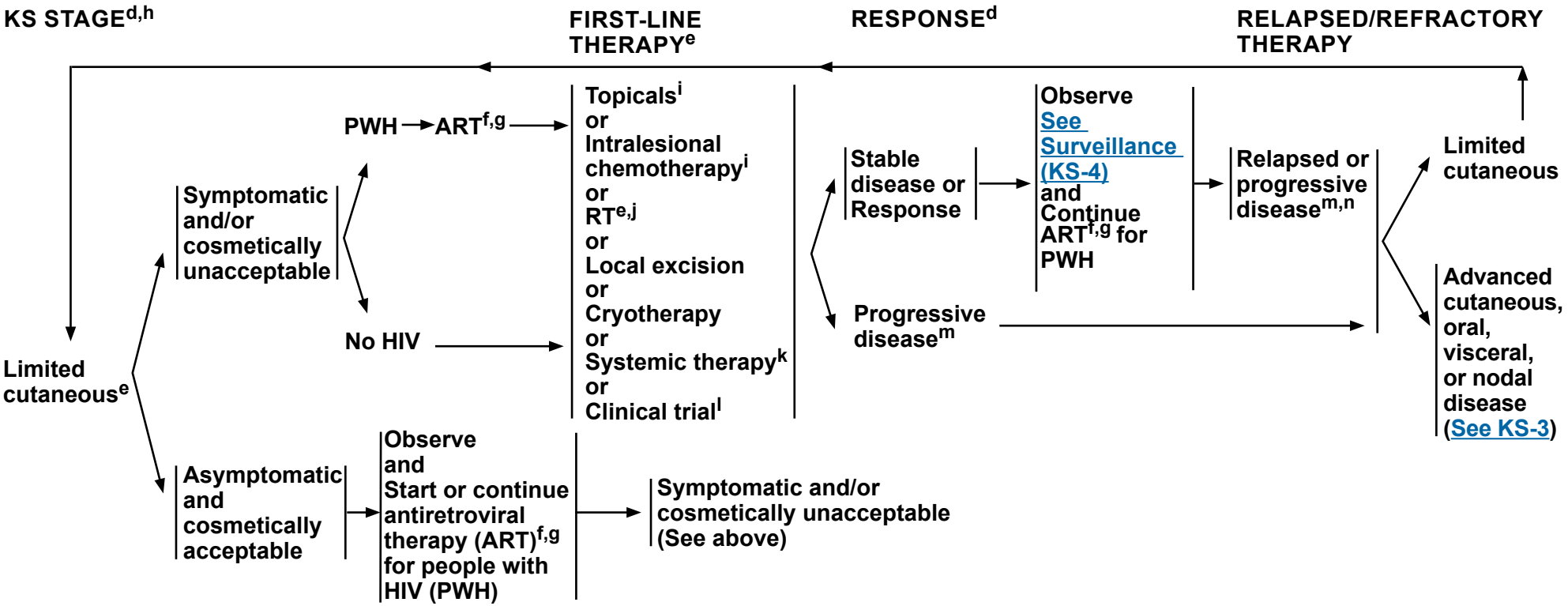
[a] All patients who are HIV seropositive should have recent T-cell subsets, including quantitative CD4+ T-cell count and HIV viral load to assess immune function and HIV control (see Discussion). Involvement of an infectious disease (ID) specialist to evaluate for coexisting OI is appropriate, especially with advanced immunosuppression.

[b] Imaging should be directed by symptoms or findings concerning for visceral or bone involvement as well as coexisting KICS, MCD, or KSHV+ lymphoma. See NCCN Guidelines for B-Cell Lymphomas (CD-1).

[c] Useful in patients with clinical features (ie, fever, dyspnea, effusions) concerning for KICS or KSHV-associated MCD: C-reactive protein, KSHV serum viral load, serum protein electrophoresis (SPEP), IL-6, or IL-10.

[d] See Staging Classification for KS (KS-A, 1 of 2) and Response Definitions for KS (KS-A, 2 of 2).

Note: All recommendations are category 2A unless otherwise indicated.
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.



[d] See Staging Classification for KS (KS-A 1 of 2) and Response Definitions for KS (KS-A, 2 of 2).
[e] See Principles and Goals of Therapy (KS-B).
[f] All PWH who have limited cutaneous disease that is symptomatic and/or cosmetically unacceptable should receive ART with or without another first-line therapy. 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. See Principles of Immune Reconstitution Inflammatory Syndrome (IRIS) (KS-C).
[g] Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions, their use may be considered.
[h] Oncology and HIV clinicians, along with both an oncology pharmacist and HIV pharmacist, if available, should review proposed cancer therapy, supportive care medications, and ART for possible drug-drug interactions (DDIs) and overlapping toxicities prior to initiation. Co-management by an oncologist and an HIV clinician is recommended for the duration of therapy. See NCCN Guidelines for Cancer in People with HIV.
[i] See Local Therapy (KS-D).
[j] See Principles of Radiation Therapy (KS-E).
[k] See Systemic Therapy (KS-F).
[l] See clinicaltrials.gov.
[m] If progressive or relapsed disease, evaluate for inadequate HIV control/ART failure as a contributing factor to inadequate KS control and address possible change in ART in conjunction with an HIV specialist. See NCCN Guidelines for Cancer in People with HIV.
[n] If after initial response to therapy, KS relapses or progresses, repeat use of previously effective therapy may be considered, particularly if response was durable.

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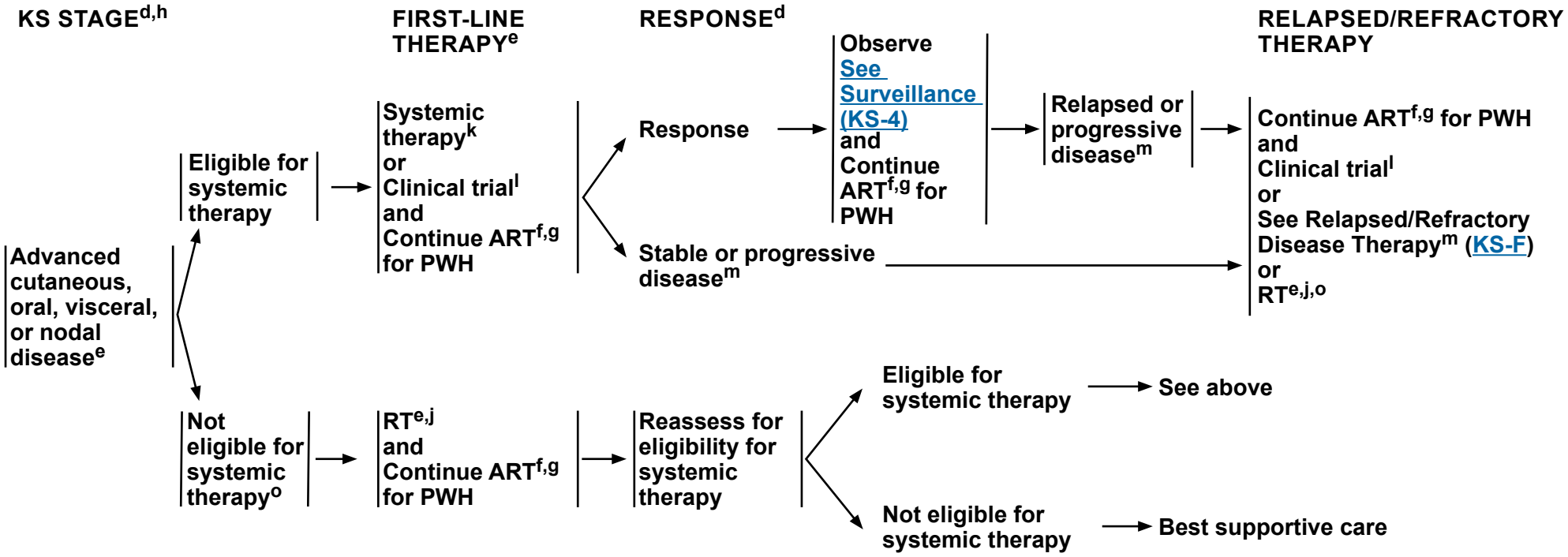

[d] See Staging Classification for KS (KS-A 1 of 2) and Response Definitions for KS (KS-A, 2 of 2).
[e] See Principles and Goals of Therapy (KS-B).
[f] All PWH who have limited cutaneous disease that is symptomatic and/or cosmetically unacceptable should receive ART with or without another first-line therapy. 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. See Principles of Immune Reconstitution Inflammatory Syndrome (IRIS) (KS-C).
[g] Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions, their use may be considered.
[h] Oncology and HIV clinicians, along with both an oncology pharmacist and HIV pharmacist, if available, should review proposed cancer therapy, supportive care medications, and ART for possible DDIs and overlapping toxicities prior to initiation. Co-management by oncologist and HIV clinician is recommended for the duration of therapy. See NCCN Guidelines for Cancer in People with HIV.
[j] See Principles of Radiation Therapy (KS-E).
[k] See Systemic Therapy (KS-F).
[l] See clinical trials.gov.
[m] If progressive or relapsed disease, evaluate for inadequate HIV control/ART failure as a contributing factor to inadequate KS control and address possible change in ART in conjunction with an HIV specialist. See NCCN Guidelines for Cancer in People with HIV.
[o] Systemic therapy is preferred over RT as first-line therapy and relapsed/refractory therapy for disseminated disease whenever systemic therapy is feasible considering performance status and comorbidities.

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SURVEILLANCE

- **For patients not requiring active therapy and with no signs of progression**
  - **Follow-up periodically based on response to therapy and, if applicable, degree of HIV viremia and immune reconstitution**
    - ◊ **History and physical examination**
      - **– including history of additional immunosuppression such as transplant/glucocorticoids**
      - **– including complete skin and oral examinations, and documentation of edema**
    - ◊ **CBC, differential, comprehensive metabolic panel**
    - ◊ **PWH**
      - **– 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 the 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 or if change in disease is noted, the following are indicated depending on the clinical circumstances[b]:**
  - **Evaluation for suspected OIs**
  - **Stool hemoccult in the setting of advanced cutaneous, oral, visceral, or nodal involvement**
  - **Chest x-ray[b] in the setting of advanced cutaneous, oral, visceral, or nodal disease**
  - **Chest CT with contrast[b] and bronchoscopy if unexplained pulmonary symptoms or abnormalities on chest x-ray**
  - **Abdomen/pelvis CT[b] with contrast or MRI with contrast[b] and EGD/colonoscopy if GI symptoms or positive hemoccult**
  - **FDG-PET/CT[b] if concerns for coexisting KICS, MCD, or KSHV+ lymphoma**
  - **The diagnosis of KICS ideally requires excisional biopsy of lymphadenopathy to exclude MCD, if feasible**

- **As KSHV is not eradicated with treatment of KS, the risk for future KS persists even after complete remission.**
- **For PWH, 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.**

[b] Imaging should be directed by symptoms or findings concerning for visceral or bone involvement as well as coexisting KICS, MCD, or KSHV+ lymphoma. See NCCN Guidelines for B-Cell Lymphomas (CD-1).

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STAGING CLASSIFICATION FOR 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 patients on ART therapy.
[2] "B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting >2 weeks.

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

Note: All recommendations are category 2A unless otherwise indicated.
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.

RESPONSE DEFINITIONS FOR KS[a]

Complete response (CR)	**The absence of any detectable residual disease, including tumor-associated (local) edema, persisting for at least 4 weeks. Patients known to have had visceral disease should have restaging with appropriate endoscopic or radiographic procedures relevant to sites involved at baseline.**
Partial response (PR)	**No new mucocutaneous lesions, visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions; AND** **▸ A 50% or greater decrease in the number of all previous existing lesions lasting for at least 4 weeks; OR** **▸ Complete flattening of at least 50% of all previously raised lesions (ie, 50% of all previously nodular or plaque-like lesions become macules); OR** **▸ A 50% decrease in the sum of the products of the largest perpendicular diameters of at least 5 measurable lesions.** **NOTE: When there is residual tumor-associated edema or effusion, but disease otherwise meets criteria for complete response, response should be classified as "partial."**
Stable disease (SD)	**Any response that does not meet the criteria for progressive disease or PR.**
Progressive disease (PD)	**An increase of ≥25% in the size of pre-existing lesions and/or the appearance of new lesions or sites of disease and/or a change in the character of the skin or oral lesions from macular to plaque-like or nodular of ≥25%. If new or increasing tumor-associated edema or effusion develop, disease is considered to be progressive.**

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

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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 KSHV infection as opposed to metastases. Treatment of existing disease therefore may not prevent occurrence of future lesions.
- Optimization of immune function and avoidance of additional immunosuppression are critical to prevention of additional KS lesions and maintenance of response to therapy. For AIDS-related KS, reconstitution of immune function and maintenance of viral suppression are important. Also, 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.
    - ◊ Glucocorticoids in any formulation should be avoided due to their association with KS progression. However, in cases of life-threatening conditions, their use may be considered.
  - Patients requiring rituximab for treatment of non-Hodgkin lymphoma (NHL) with coexisting KS or MCD 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 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:

- PWH with limited cutaneous disease that is asymptomatic and cosmetically acceptable may be observed while starting or 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. When necessary, 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 (while continuing ART, in PWH). Otherwise, alternative therapy should be initiated.

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

CLINICAL PRESENTATION/DEFINITION[1]

- **IRIS is characterized by first presentation or paradoxical worsening of pre-existing KS infection following ART initiation.**
- **Typically occurs within 3 months of ART initiation, but possible to occur any time after starting ART.**
- **The risk of IRIS is higher in patients with baseline low CD4 T-cell counts and high HIV viral loads.[2]**
- **Clinical manifestations may include development of new lesions or enlargement of existing lesions, worsening lymphadenopathy, or worsening edema. The clinical presentation of IRIS may be challenging to distinguish from the natural history of progressive disease.**
- **If IRIS is suspected, consult with an HIV specialist.**

MANAGEMENT

- **Treatment for KS-IRIS includes systemic chemotherapy and supportive measures; ART should not be discontinued.**
- **If the patient is on ART only: Symptomatic management; consider addition of systemic chemotherapy (see list of first-line options).**
  - **Consider thalidomide as an active agent against both KS and corticosteroid-refractory IRIS.**
- **If the patient is on ART and chemotherapy: Symptomatic management; consider modification of chemotherapy regimen if progressive.**
- **Avoid corticosteroids, which may exacerbate KS.**
- **Use of systemic chemotherapy for extensive disease prior to ART initiation may help prevent KS-IRIS, but this has not been systematically studied.**

PROPOSED CRITERIA FOR DIAGNOSIS OF KS-IRIS[3]

KS-IRIS requires at least one major and one minor criterion:

Major Criteria

- **New onset or enlargement of KS lesion and subsequent regression**
- **Painful lesions**

Minor Criteria

- **Decrease in plasma HIV RNA by >1 $\log^{10}$ copies/mL**
- **Increased blood CD4 T-cell count after ART**

[1] Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS 2013;27:1603-1613.
[2] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed 9/6/2022.
[3] French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18:1615-1627.

Note: All recommendations are category 2A unless otherwise indicated.
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.

LOCAL THERAPY

Topical

- **Alitretinoin 0.1% gel[1]**
  - **Apply 3–4 times daily to affected skin sites**
- **Imiquimod, 5% cream[2]**
  - **Apply one sachet to up to 20 cm^2 of affected skin and cover with occlusive dressing for 8 hours three times per week; titrate frequency of application to effect and tolerability (up to once daily), with treatment breaks if tolerability issues occur.**

Radiotherapy

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

For small lesions (ie, ≤1 cm), the following may be considered for local control of symptomatic lesions

- **Excision**
- **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, frequencies 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. Nonsteroidal anti-inflammatory drugs (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.**
- **Cryotherapy**

[1] Bodsworth NJ, Bloch M, Bower M, et al. 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.
[2] Schatz NEC, Chevret S, Paz C, 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;58:585-591.
[3] Epstein JB. Treatment of oral Kaposi sarcoma with intralesional vinblastine. Cancer 1993;71:1722-1725.

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PRINCIPLES OF RADIATION THERAPY

- **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 used. Intensity-modulated RT (IMRT) with or without image guidance may be useful for larger, deeper disease, or disease located anatomically adjacent to critical structures.**
  - **The use of bolus may be necessary to achieve adequate skin dose.**
  - **RT to plantar and palmar surfaces might be useful in selected cases. However, high doses should be approached with caution because of theoretical toxicity concerns like long-term wound healing, particularly in the setting of coexisting lymphedema.**
  - **Risk of secondary cancer, severe or worsening lymphedema, and long-term wound healing complications may be increased after radiation; however, toxicity can be mitigated by utilizing lower-dose radiotherapy regimens.**
    Caution should be exercised with the use of RT to sites of pre-existing lymphedema. 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.

- **General Treatment Information**
  - **Dosing Prescription Regimen[1,2,3]**
    - ◊ **Various dosing schemas may be used. Lower doses are preferred for smaller and more superficial lesions. Higher doses may be preferred for more extensive, deeply invasive lesions. More fractionated regimens may be preferred for sites with adjacent radiosensitive structures, such as the oral cavity. Examples:**

Fractionated Dose	Biologically Equivalent Dose [BED]10	BED3
6–8 Gy in 1 fraction[4]	10.8 –14.4 Gy	18–29 Gy
20 Gy in 5 fractions[1,3]	28 Gy	47 Gy
24 Gy in 12 fractions[1]	28.8 Gy	40 Gy
30 Gy in 10–15 fractions[2,3]	36–39 Gy	50–60 Gy
40 Gy in 20 fractions[5]	48 Gy	67 Gy

[1] Singh NB, Lakier RH, Donde B. Hypofractionated radiation therapy in the treatment of epidemic Kaposi sarcoma – a prospective randomized trial. Radiother Oncol 2008;88:211-216.
[2] Hauerstock D, Gerstein W, Vuong T. Results of radiation therapy for treatment of classic Kaposi sarcoma. J Cutan Med Surg 2009;13:18-21.
[3] Kirova YM, Belembaogo E, Frikha H, et al. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. Radiother Oncol 1998;46:19-22.
[4] Tsao MN, Sinclair E, Assaad D, et al. Radiation therapy for the treatment of skin Kaposi sarcoma. Ann Palliat Med 2016;5:298-302.
[5] Stelzer KJ, Griffin TW. A randomized prospective trial of radiation therapy for AIDS-associated Kaposi's sarcoma. Int J Radiat Oncol Biol Phys 1993;27:1057-1061.

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SYSTEMIC THERAPY[a]

First-line systemic therapy options

- **Preferred regimens**
  - **Liposomal doxorubicin[c]**
  - **For transplant KS, sirolimus[d]**
- **Other recommended regimen**
  - **Paclitaxel**

Relapsed/ refractory systemic therapy[b] options (advanced cutaneous, oral, visceral, or nodal disease)

If tolerated and durable response (≥3 months) to first-line systemic therapy → **Repeat of first-line systemic therapy or Alternate first-line systemic therapy** → **Progression**

If no response to first-line systemic therapy → **Alternate first-line systemic therapy[e]** → **Progression**

See Systemic Therapy Dosing (KS-F 2 of 3)

- **Subsequent systemic therapy options for relapsed/ refractory therapy[f]**
  - **Preferred regimen**
    - ◊ **Pomalidomide[g]**
  - **Other recommended regimens (in alphabetical order)**
    - ◊ **Bortezomib**
    - ◊ **Gemcitabine**
    - ◊ **Lenalidomide**
    - ◊ **Vinorelbine**
  - **Useful in certain circumstances (in alphabetical order)**
    - ◊ **Etoposide**
    - ◊ **Imatinib**
    - ◊ **Ipilimumab + nivolumab (for classic KS)**
    - ◊ **Nab-paclitaxel (if paclitaxel intolerant)**
    - ◊ **Pembrolizumab (for endemic and classic KS)**
    - ◊ **Sirolimus[d] (for transplant KS)**
    - ◊ **Thalidomide (for patients with IRIS)**

[a] See references for regimens on KS-F (3 of 3).

[b] Consider repeating any prior systemic therapy that was tolerated and resulted in a durable response.

[c] Due to potential risk of cardiotoxicity, perform echocardiogram prior to initial course of liposomal doxorubicin and repeat periodically. Consider limiting lifetime dose per prescribing guidelines; however, other data suggest that the patients who need continued treatment may be safely treated beyond 1000 mg/m^2.

[d] For KS associated with immunosuppression from solid organ transplant switching to sirolimus for immunosuppression may be sufficient for KS control and treatment.

[e] If both first-line options have already been given, the patient should proceed to the subsequent systemic therapy options.

[f] Patients can continue through all treatment options listed, and treatments can be repeated if tolerated and response was durable (≥3 months). In select cases, best supportive care may be an appropriate option.

[g] Pomalidomide has been U.S. Food and Drug Administration (FDA) approved for the treatment of adult patients with AIDS-related KS after failure of highly active ART or in patients with KS with no HIV.

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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.

SYSTEMIC THERAPY DOSING[a,i]

FIRST-LINE SYSTEMIC THERAPY DOSING

Preferred regimens

- Liposomal doxorubicin[c]
  - 20 mg/m² IV every 2 to 3 weeks
- Sirolimus (for transplant KS)
  - Loading dose 0.15 mg/kg PO followed by 0.04–0.06 mg/kg/day to maintain trough blood levels of 6–10 ng/mL or 2 mg PO daily (adjust to maintain trough levels of 6–10 ng/mL)
  - For PWH on ART, providers should consult with an ID pharmacist prior to dosing sirolimus

Other recommended regimen

- Paclitaxel
  - 100 mg/m² IV every 2 weeks or 135 mg/m² IV every 3 weeks or 60 mg/m² IV weekly
    - ◊ Premedication with dexamethasone may not be needed; if used, the dose should be minimized and tailored to patient needs.

SUBSEQUENT SYSTEMIC THERAPY OPTIONS FOR RELAPSED/REFRACTORY THERAPY DOSING

Preferred regimen

- Pomalidomide
  - 4 or 5 mg/day PO for 21 days of each 28-day cycle[h]

Other recommended regimens (in alphabetical order)

- Bortezomib
  - 1.6 mg/m² IV/SC on days 1, 8, and 15 of each 28-day cycle
- Gemcitabine
  - 1000 mg/m² IV every 2 weeks
  - Or 1000 mg/m² IV on days 1 and 8 every 21 days
- Lenalidomide
  - 25 mg/day PO for 21 days of each 28-day cycle
- Vinorelbine
  - 30 mg/m² IV every 2 weeks

Useful in certain circumstances (in alphabetical order)

- Etoposide
  - 50 mg/day PO for 7 days of each 14-day cycle. After 2 cycles, escalate dose to 100 mg/day PO for 7 days of each 14-day cycle in patients without PR or CR and no toxicity >Grade 2. Dose can be further escalated to 150 mg/day based on tolerance and response
- Imatinib
  - 400 mg/day PO
- Ipilimumab + nivolumab (for classic KS)
  - Ipilimumab 1 mg/kg IV every 6 weeks and nivolumab 240 mg IV every 2 weeks
- Nab-paclitaxel (if paclitaxel intolerant)
  - 100 mg IV on days 1, 8, and 15 of each 28-day cycle
- Pembrolizumab (for endemic and classic KS)
  - 200 mg IV every 3 weeks for up to 6 months
- Sirolimus (for transplant KS)
  - Loading dose 0.15 mg/kg PO followed by 0.04–0.06 mg/kg/day to maintain trough blood levels of 6–10 ng/mL or 2 mg PO daily (adjust to maintain trough levels of 6–10 ng/mL).
  - For PWH on ART, providers should consult with an ID pharmacist prior to dosing sirolimus
- Thalidomide (for patients with IRIS)
  - 200 mg/day orally (starting dose, titrated to effect and tolerability)

[a] See references for regimens on KS-F (3 of 3).
[c] Due to potential risk of cardiotoxicity, perform echocardiogram prior to initial course of liposomal doxorubicin and repeat periodically. Consider limiting lifetime dose per prescribing guidelines; however, other data suggest that the patients who need continued treatment may be safely treated beyond 1000 mg/m².
[h] The clinical trial for pomalidomide used a dose of 5 mg/day. However, pomalidomide is provided in a 4-mg dose and the NCCN Panel believes that this is a sufficient dose.
[i] For PWH, See NCCN Guidelines for Cancer in People with HIV, Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).

Note: All recommendations are category 2A unless otherwise indicated.
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.

SYSTEMIC THERAPY
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Reid E, Shimabukuro K, Moore P,et al. AMC-070: Lenalidomide is safe and effective in HIV-associated Kaposi sarcoma. Clin Cancer Res 2022;28:2646-2656.

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Paclitaxel
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Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005;352:137-1323.

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Note: All recommendations are category 2A unless otherwise indicated.
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ABBREVIATIONS

AIDS	**acquired immunodeficiency syndrome**
ART	**antiretroviral therapy**
CR	**complete response**
DDIs	**drug-drug interactions**
EGD	**esophagogastroduodenoscopy**
ID	**infectious disease**
IHC	**immunohistochemistry**
IRIS	**immune reconstitution inflammatory syndrome**
KICS	**KSHV–associated inflammatory cytokine syndrome**
KS	**Kaposi sarcoma**
KSHV	**Kaposi sarcoma-associated herpesvirus**
MCD	**multicentric Castleman disease**
NHL	**non-Hodgkin lymphoma**
OI	**opportunistic infection**
PR	**partial response**
PWH	**people with HIV**

NCCN Categories of Evidence and Consensus	
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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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Discussion

This discussion corresponds to the NCCN Guidelines for Kaposi Sarcoma. Last updated: June 7, 2021.

Table of Contents

Overview

Kaposi sarcoma is a multifocal malignancy of endothelial cells, which presents with characteristic red or brown papules. Four types of Kaposi sarcoma have been described: AIDS-related, classic, iatrogenic or transplant-associated, and endemic.[1-3] Kaposi sarcoma is universally associated with Kaposi sarcoma-associated herpesvirus (KSHV) infection (also known as human herpesvirus-8, or HHV-8).[2] Serologic confirmation of KSHV infection is present in 95% to 98% of patients with Kaposi sarcoma.[2,3] KSHV infections are usually asymptomatic, and immunosuppression is likely an important factor in the pathogenesis of Kaposi sarcoma.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kaposi Sarcoma provide treatment recommendations for patients with AIDS-related, classic, and iatrogenic Kaposi sarcoma and 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 with HIV (available at www.NCCN.org), which give recommendations regarding HIV management during cancer therapy, drug-drug interactions (DDIs) with antiretrovirals and cancer therapies, radiation therapy, and supportive care for people with HIV (PWH). Recommendations for the management of Kaposi sarcoma for patients in sub-Saharan Africa can be found in the NCCN Harmonized Guidelines for Sub-Saharan Africa for Kaposi Sarcoma (available at www.NCCN.org/harmonized).

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of the NCCN Guidelines for Kaposi Sarcoma, an electronic search of the PubMed database was performed to obtain key literature in the field published since the previous 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). An additional literature search was performed using (classic or transplant) and Kaposi sarcoma as the search terms to identify key literature published in the preceding decade. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[4]

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 data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. 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 at www.NCCN.org.

AIDS-Related Kaposi Sarcoma

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. The risk for Kaposi sarcoma in the setting of HIV has been reported to be increased as much as 3640-fold over the general U.S. population,[5-9] but this risk has declined in the antiretroviral therapy (ART) era.[5,10-13] Still, estimates indicate that the risk of Kaposi

sarcoma in PWH between the years of 2009 and 2012 was elevated approximately 498-fold compared with the general U.S. population,[10] and Kaposi sarcoma accounts for approximately 12% of cancers diagnosed in PWH, with an estimated 765 to 910 cases diagnosed per year in the United States.[14,15] 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.[16-18]

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. In fact, CD4+ T-cell counts and HIV viral load correlate with the risk of Kaposi sarcoma in PWH, and effective ART lowers the risk of Kaposi sarcoma development.[19] Evidence also suggests that ART improves prognosis of Kaposi sarcoma in PWH. However, AIDS-related Kaposi sarcoma can occur in PWH with normal CD4+ T-cell counts and undetectable HIV viral load.

HIV management during treatment of Kaposi sarcoma in PWH is critical. Co-management by oncologist and HIV clinician is recommended for the duration of therapy. Oncology and HIV clinicians, along with both an oncology pharmacist and HIV pharmacist if available, should review proposed cancer therapy, supportive care medications, and ART for possible DDIs and overlapping toxicities prior to initiation of therapy for PWH. The NCCN Guidelines for Cancer in People with HIV (available at www.NCCN.org) provide additional recommendations on HIV screening, linkage to HIV care, prevention of opportunistic infections, DDIs between antiretrovirals and cancer therapies, radiation therapy, and supportive care for PWH.

Classic Kaposi Sarcoma

Classic Kaposi sarcoma generally involves indolent cutaneous lesions, often of the lower extremities, that may wax and wane or slowly progress over years to decades. It is most common in people of Mediterranean, Eastern European, Middle Eastern, and/or Jewish origins, with a mean age of 74 years at diagnosis.[1,3] It is reported to be 7 to 15 times more common in males than females.[1,3] Separate malignancies may be fairly common in patients with classic Kaposi sarcoma, and are more likely to be the cause of death in these patients.[3]

Iatrogenic Kaposi Sarcoma

When Kaposi sarcoma occurs in the context of immunosuppressive therapy (for organ transplant or other reasons), it is called iatrogenic or transplant-associated Kaposi sarcoma.[1] Lesions often appear 2 to 8 months after initiation of immunosuppression, and occur 2 to 3 times more often in males.[1] 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.

Endemic Kaposi Sarcoma

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, although it often begins as skin lesions that remain indolent for several years.[1] As with classic Kaposi sarcoma, endemic disease is 10 to 17 times more common in males than females.[1]

Please see the NCCN Harmonized Guidelines for Sub-Saharan Africa for Kaposi Sarcoma (available at www.NCCN.org/harmonized) for recommendations for the management of Kaposi sarcoma in patients in sub-Saharan Africa.

Management of Kaposi Sarcoma

Diagnosis and Workup of Kaposi Sarcoma

Multiple clinical and histologic presentations of Kaposi sarcoma have been described. Mucosal and cutaneous lesions may be characterized clinically as papules, plaques, nodules (sometime pedunculated), and bullae. Large plaques may form from coalescence of smaller plaques or nodules and may ulcerate or develop bullae. Hyperpigmented macules (lacking change in palpable skin thickness) rarely represent active disease; rather, they are very common after lesion regression due to residual hyperpigmentation. Histologic subtypes include anaplastic, telangiectatic, lymphedematous, hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, and intravascular variants of Kaposi sarcoma.

Lymphedema is a common complication of Kaposi sarcoma and may also be a predisposing factor to the development of Kaposi sarcoma. Lymphedema can be caused by not only nodal involvement but involvement of lymphatic vessels. Hyperkeratotic variants with verrucous and hyperkeratotic changes are notably associated with chronic and severe Kaposi sarcoma-associated lymphedema, and may require deeper biopsy to confirm presence of Kaposi sarcoma.

As described in the guidelines above, Kaposi sarcoma is diagnosed by 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).[20-23] Therefore, in addition to biopsy of suspected lesions, involvement of an infectious disease specialist may be appropriate to determine the correct diagnosis/diagnoses, especially in the setting of advanced immunosuppression. Other essential workup items are fecal occult blood testing (FOBT) and chest x-ray to assess for gastrointestinal and pulmonary involvement.

For PWH, 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*, above). All PWH 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.

Depending on symptoms and findings that may be concerning for visceral or bone involvement, as well as coexisting KSHV–associated lymphoma, multicentric Castleman 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, KSHV serum viral load, serum protein electrophoresis (SPEP), IL-6, and IL-10. The diagnosis of KICS requires excisional biopsy of lymphadenopathy to exclude MCD.[24]

It is important to note that imaging in PWH who have cancer is complicated by the increased incidence of non-malignant lesions that may be mistaken for cancer spread or recurrence. Opportunistic infections in the lung include mycobacterium tuberculosis (Mtb), cytomegalovirus (CMV), and Pneumocystis jirovecii pneumonia (PCP).[25] Furthermore, non-infectious, non-malignant pulmonary manifestations of HIV can be difficult to interpret on imaging studies, including interstitial pneumonia and

granulomatous disease.[25,26] Furthermore, brain lesions seen in PWH may result from opportunistic infections, such as viral encephalitis, aspergillosis, toxoplasmosis, cryptococcosis, bacterial meningitis, tuberculosis, progressive multifocal leukoencephalopathy, and mycobacterium avium complex (MAC).[27,28] Benign non-infectious brain lesions can also occur in PWH (eg, vascular complications, hydrocephalus).[27,28] Similarly, immune response to HIV and opportunistic infections commonly cause lymphadenopathy in PWH, which can be seen on F-18 FDG PET/CT.[29,30] Non-malignant causes of lymphadenopathy are more common in patients with higher viral loads and lower CD4+ T-cell counts.[31] Therefore, PWH who have cancer should have an infectious disease workup for imaging findings, as clinically indicated.

Staging of Kaposi Sarcoma

As delineated in the guidelines above, 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.[32] However, more recent data have shown that the I stage has less prognostic value than the T or S stages for PWH in the presence of ART.[17] Kaposi sarcoma staged as T1S1 appears 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).[17]

Assessing Response of Kaposi Sarcoma

Response of Kaposi sarcoma to therapy has been formally defined by the AIDS Clinical Trials Group (ACTG) Oncology Committee as follows[32]:

- Complete response (CR) is defined as the absence of any detectable residual disease, including tumor-associated (local) edema, persisting for at least 4 weeks. Patients known to have had visceral disease should have restaging with appropriate endoscopic or radiographic procedures relevant to sites involved at baseline.
- Partial response (PR) is defined as no new mucocutaneous lesions, visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions; AND
  - A 50% or greater decrease in the number of all previously existing lesions lasting for at least 4 weeks; OR
  - Complete flattening of at least 50% of all previously raised lesions (ie, 50% of all previously nodular or plaque-like lesion become macules); OR
  - A 50% decrease in the sum of the products of the largest perpendicular diameters of at least 5 measurable lesions.
  - Note that when there is residual tumor-associated edema or effusion but disease otherwise meets criteria for complete response, response should be classified as partial.
- Stable disease (SD) is defined as any response that does not meet the criteria for progressive disease (PD) or PR.
  PD is defined as an increase of greater than or equal to 25% in the size of pre-existing lesions and/or the appearance of new lesions or sites of disease and/or a change in the character of the skin or oral lesions from macular to plaque-like or nodular of greater than or equal to 25%. If new or increasing tumor-associated edema or effusion develop, disease is considered to be progressive.

Many Kaposi sarcoma lesions that are responsive to therapy will flatten and change color but remain pigmented (ranging from very dark brown to tan) as non-palpable macular skin lesions. Biopsy of these will often confirm lack of residual tumor cells with residual siderophages and or free hemosiderin pigment in the tissue. This is attributed to long-term iron deposition resulting from red blood cell extravasation into the tissue (dermal layer characteristically in cutaneous lesions). Care should be

taken to distinguish this “tattoo” effect from active disease, as additional therapy is not indicated for the former. Over time, many lesions will gradually fade, depending on many factors, including chronicity and size of the lesion as well as degree to which extravasation occurred.

Initial Management of Kaposi Sarcoma

PWH with limited cutaneous disease that is asymptomatic and cosmetically acceptable to the patient may be treated with ART alone (see below). Patients without HIV can be observed until the disease becomes symptomatic and/or cosmetically unacceptable.

PWH 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. When necessary, a limited number of cycles of systemic therapy (eg, 3–6; options discussed below) may be sufficient for those initiating or re-initiating ART. Other options include radiation, and for small lesions (ie, ≤1 cm), topical treatment, intralesional chemotherapy, cryotherapy, and local excision (all discussed below). Intralesional chemotherapy and radiation to plantar and palmar surfaces may be useful in selected cases, but should be approached with caution because of toxicity or functional adverse events. Increased risk of long-term wound healing, particularly in the setting of coexisting lymphedema, is a concern.

The same treatment options, without ART, are recommended for patients without HIV who have limited cutaneous disease that is symptomatic and/or cosmetically unacceptable.

If disease progresses on therapy in PWH, inadequate HIV control/ART failure should be considered as a contributing factor to inadequate Kaposi sarcoma control. Possible change in ART in conjunction with an HIV specialist may control the disease (see the NCCN Guidelines for Cancer in People with HIV, available at www.NCCN.org).

For PWH with adequate HIV control and those without HIV, a different Kaposi sarcoma treatment option should be tried based on the extent of disease. If disease is stable or a response is seen on initial therapy, the patient should be observed (while ART is continued in PWH). If the disease progresses or relapses after an initial response to therapy, repeat use of the previously effective therapy may be considered, particularly if response was durable.

Preferred initial treatment for patients with advanced cutaneous, oral, visceral, or nodal Kaposi sarcoma is systemic therapy, with ART for PWH. For those not eligible for systemic therapy, radiation can be used, with ART for PWH. The data supporting these treatment options are described below. Well-designed clinical trials with agents previously demonstrated to have significant activity in relapsed/refractory Kaposi sarcoma may also be considered for frontline therapy.

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 KSHV infection as opposed to metastases. Furthermore, persistence of KSHV infection results in ongoing risk of recurrence/disease progression. Currently, eradication of KSHV is not possible. Therefore, treatment of existing disease may not prevent occurrence of future lesions. Given this and the fact that many presentations of Kaposi sarcoma are not life-threatening, the goals of therapy are focused on disease control.

Antiretroviral Therapy for PWH

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 PWH. 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.[33-39] Therefore, co-management 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 the NCCN Guidelines for People with HIV, available at www.NCCN.org).

Immune Reconstitution Inflammatory Syndrome (IRIS)

Initiation of ART may result in immune reconstitution inflammatory syndrome (IRIS) within 3 to 6 months in a reported 6% to 39% of patients with AIDS-related Kaposi sarcoma.[40-44] Kaposi sarcoma-associated 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.[40,41,43] 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 and association of glucocorticoid use with increased mortality.[41,45,46] Management of Kaposi sarcoma-associated IRIS will often require systemic Kaposi sarcoma therapy and should involve coordination with an HIV specialist. ART should not be delayed or discontinued unless life-threatening IRIS develops. Whereas there are no prospective trials using thalidomide for Kaposi sarcoma-associated IRIS, successful control of steroid-refractory IRIS with thalidomide has been reported, and thalidomide is an active agent in Kaposi sarcoma.[47]

Topical Therapies

Topical therapies are an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically unacceptable. Alitretinoin gel, a retinoid, was studied in a phase III vehicle-controlled, double-blind, multi-centered study, in which 134 patients with AIDS-related Kaposi sarcoma received either 0.1% alitretinoin gel or vehicle gel twice daily for 12 weeks.[48] 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.[49] 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. Data on the use of alitretinoin in classic Kaposi sarcoma is limited to 2 case reports, in which one patient showed significant improvement and the other did not.[50,51]

Imiquimod is a topical immune response modulator with antiviral and antitumor activity.[52] It is used in a variety of skin conditions including malignancies and warts.[52,53] Case reports have shown that imiquimod cream can be safe and effective in some patients with classic or transplant-associated Kaposi sarcoma.[54-61] In a single-center, open-label, phase I/II trial, 17 patients without HIV who had Kaposi sarcoma received imiquimod 5% cream 3 times per week for 24 weeks.[62] The response rate was 47%. Over 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.[63,64] The panel includes imiquimod as an option for patients with limited cutaneous AIDS-related Kaposi sarcoma based on extrapolation from the data presented above in other settings, expert opinion, and non-published 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.[65-71] In a large series of 144 oral Kaposi sarcoma lesions in 50 PWH, complete response was seen in 74% of lesions and partial response in 26%.[68] The recurrence rate was 26%, with a mean disease-free period of 12.9 weeks. Consistent 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.[72,73] In a trial of 11 patients with AIDS-related Kaposi sarcoma, 88% of cutaneous lesions showed a complete or partial clinical response.[72] Treatment resulted in inflammation and blistering of the lesion prior to healing, and the final results were not cosmetically optimal because of post-inflammation hyperpigmentation. Most patients reported aching pain 6 to 48 hours post-treatment that was relieved with pain medication.

Intralesional vinblastine has also been used in cutaneous lesions in patients with classic Kaposi sarcoma.[74]

Local Excision

Local excision is an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically unacceptable. Data regarding outcomes of the excision of cutaneous Kaposi sarcoma lesions are limited and appear to be restricted to individuals without HIV.[75-79]

Radiation Therapy

Kaposi sarcoma is radioresponsive, with complete responses rates of treated lesions reported in the range of 60% to 93%.[60,80-84] Radiation therapy for 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.[85]

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.[86,87] Dose fractionation should be based on the site of treatment with consideration for surrounding normal tissue tolerance.

The side effects of radiation for Kaposi sarcoma are site-dependent, but typically manageable given the low doses needed to achieve a response.[80-83] Still, the risk of secondary cancer, severe or worsening lymphedema, and long-term wound healing complications may be increased after radiation. Early recognition and treatment of dermatitis, oral mucositis, and lymphedema are especially important.[80,82,88] The risk of lymphedema is already elevated in patients with Kaposi sarcoma and may increase after radiation.[89] Therefore, caution should be exercised with the use of radiation to sites of pre-existing lymphedema. Early referral to and co-management with a lymphedema specialist is recommended. In the setting of advanced cutaneous disease, radiation therapy should be reserved for cases where systemic therapy is not feasible, with the goal of palliation or short-term disease management until systemic therapy may be delivered. Radiation therapy may also be used for disease refractory to multiple types of systemic therapy.

Cryotherapy

Cryotherapy is also an option for patients with limited cutaneous disease that is symptomatic and/or cosmetically unacceptable. In a small study of 30 patients, 125 lesions were treated with cryotherapy.[90] Nineteen (63%) patients experienced a complete response without recurrence. Blistering

was frequent, local pain was limited, and the treatment was well-tolerated overall. Other studies also suggest that cryotherapy can be effective in patients with classic Kaposi sarcoma.[61]

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).[91] 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 greater than or equal to 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).[92] 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 has also been shown to have activity in classic and transplant-associated Kaposi sarcoma.[60,93]

Liposomal doxorubicin is associated with risk of cardiotoxicity.[94-96] Therefore, a baseline multigated acquisition (MUGA) or echocardiogram should be performed prior to initial and repeat courses of liposomal doxorubicin,[97] and the lifetime dose should be limited to 400 to 450 mg/m^2.

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.[60,98,99]

One trial randomized 73 patients with advanced AIDS-related Kaposi sarcoma to paclitaxel or pegylated-liposomal doxorubicin.[100] The two 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.[101] Data on the use of paclitaxel in non–AIDS-related Kaposi sarcoma are more limited.[102,103]

Surveillance of Patients with Kaposi Sarcoma

Patients treated for Kaposi sarcoma who do not require active treatment and who are without signs of progression should be followed periodically based on response to therapy and, if applicable, degree of HIV viremia and immune reconstitution. 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 (CBC), differential, and comprehensive metabolic panel. For PWH, surveillance should also include T-cell subsets (CD4+ T-cell count) and HIV viral load, and ART compliance should be assessed.

If a change in disease is noted, lesions should be photographed for documentation. Stool testing, chest x-ray or chest CT and/or abdominal/pelvic CT with contrast depending on clinical concerns, esophagogastroduodenoscopy (EGD)/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 KSHV is not eradicated with treatment of Kaposi sarcoma, and the risk of future Kaposi sarcoma persists even after complete remission. Avoidance of iatrogenic immunosuppression as well as optimization and monitoring of immune function and HIV control are 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" CD-4 counts. Less frequent (every 6–12 months) oncologic monitoring may be appropriate for select patients with Kaposi sarcoma that is stable for greater than or equal to 2 years and, for PWH, undetectable HIV viral loads, normal T-cell subsets, and 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 above) 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.

Following subsequent progressions, liposomal doxorubicin or paclitaxel, whichever has not yet been administered, is recommended.[104,105] Following treatment with liposomal doxorubicin and paclitaxel, the panel recommends pomalidomide as the preferred regimen. Pomalidomide was studied in a phase I/II trial of 7 people without HIV and 15 PWH who had Kaposi sarcoma.[106] PWH 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.[107] The response rate was 60% in the PWH group (95% CI, 32%–84%). Grade 3/4 adverse events that might have occurred due to pomalidomide were neutropenia, infection, and edema. Pomalidomide has received accelerated FDA approval for the treatment of adult patients with AIDS-related Kaposi sarcoma after failure of highly active ART and for patients without HIV who have Kaposi sarcoma.

Other treatment options for subsequent lines of therapy for relapsed/refractory disease include bortezomib, gemcitabine, lenalidomide, nab-paclitaxel, and vinorelbine. Etoposide, imatinib, and thalidomide may also be useful under certain circumstances. Patients can continue through all treatment options listed, and treatments can be repeated if they were tolerated and the response was durable (≥3 months). In select cases, best supportive care may be an appropriate option.

Bortezomib was studied in the dose-escalation, pilot AMC-063 trial, which included 17 patients with relapsed/refractory AIDS-related Kaposi sarcoma on ART.[108] The maximum tolerated dose was not reached. The partial response rate was 60% in 15 evaluable patients and 83% in the 1.6 mg/m^2 cohort. The rest of the participants experienced stable disease. The most common adverse events were diarrhea, fatigue, and nausea.

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.[109] 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%.[110] Gemcitabine also has activity in classic Kaposi sarcoma.[60]

The phase II ANRS 154 Lenakap trial evaluated the rate of partial response or complete response at week 24 after treatment with lenalidomide in 12 patients with relapsed/refractory AIDS-related Kaposi sarcoma.[111] The primary endpoint was the rate of partial response or complete response by Physical Global Assessment (PGA) criteria. Although none of the 10 patients who were evaluable at 24 weeks met PGA at 24 or 48 weeks, 4 met ACTG criteria for partial response at 48 weeks.

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.[112] 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.

Evidence for the activity of vinorelbine in AIDS-related Kaposi sarcoma comes from a phase II trial of 35 assessable patients with progressive disease.[113] 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. Data on the use of vinorelbine in classic and post-transplant Kaposi sarcoma are limited.[114,115]

Etoposide has been studied in multiple phase II trials and in the A5264/AMC-067 trial of patients with AIDS-related Kaposi sarcoma.[116-119] In one of the phase II 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.[118] The median duration of response was about 6 months. Grade 3/4 neutropenia occurred in 28%, and opportunistic infections occurred in 22%. The other phase II trials also showed oral etoposide to have clinical activity and be fairly well tolerated. In the A5264/AMC-067 trial, 190 patients with mild-to-moderate AIDS-related Kaposi sarcoma in Africa and South America were randomized to ART alone with etoposide given for progression or ART plus immediate etoposide.[119] No difference in response between the groups was seen at 48 months. If oral etoposide is used, the panel recommends the dose escalation used in this trial, as indicated in the guidelines. Etoposide also has activity in classic Kaposi sarcoma.[60,120]

For Kaposi sarcoma associated with immunosuppression from solid organ transplant, switching to sirolimus for immunosuppression may be sufficient for Kaposi sarcoma control and treatment. In a study of 15 patients who underwent kidney transplants and developed Kaposi sarcoma, cyclosporine therapy was stopped and sirolimus was initiated.[121] At 3 months after the start of sirolimus therapy, all cutaneous lesions had disappeared in all patients, all with confirmed histologic remission at 6 months. No acute episodes of rejection or changes in kidney-graft function were seen.

Imatinib has activity in AIDS-related Kaposi sarcoma.[122,123] The strongest evidence comes from a multicenter phase II trial in which 30 patients were treated with imatinib.[124] Eighteen patients (60%) had received prior therapy. Partial response occurred in 33% 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.

Thalidomide has been studied in AIDS-related Kaposi sarcoma in 2 phase II trials.[125,126] One of these trials included 17 assessable patients with

progressive disease.[125] 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%. Although no prospective trials have used thalidomide for Kaposi sarcoma-associated IRIS, successful control of steroid-refractory IRIS with thalidomide has been reported, and thalidomide is an active agent in Kaposi sarcoma.[47] The panel thus believes that thalidomide may be a useful option for patients with Kaposi sarcoma and corticosteroid-refractory IRIS.

Summary

Management of Kaposi sarcoma depends on location and extent of disease. PWH 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 therapy that is minimally invasive with the least toxicity possible, and with ART, if HIV-positive. Options include a limited number of cycles of systemic therapy, topical treatment, intralesional chemotherapy, radiation, cryotherapy, and local excision.

Preferred initial treatment for patients with significant lymphedema and advanced cutaneous, oral, visceral, or nodal AIDS-related Kaposi sarcoma is ART with systemic therapy or systemic therapy for those without HIV. Alternatively, a well-designed clinical trial of an agent previously demonstrated to have activity is an appropriate option. For those not eligible for systemic therapy, radiation can be used (with ART for PWH). As lymphedema often complicates Kaposi sarcoma, early involvement of a lymphedema specialist is recommended.

Surveillance of patients treated for Kaposi sarcoma is important, as disease can recur after an initial complete response and in the setting of normal values of T-cell subsets. Persistence of KSHV 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 in any formulation should be avoided in patients with active or prior Kaposi sarcoma, or other KSHV-associated conditions, given the potential to cause significant flares or relapses of Kaposi sarcoma. The use of glucocorticoids should be limited to 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.[127,128] Of note, patients with AIDS-related lymphomas who have concurrent Kaposi sarcoma are often able to receive multiagent chemotherapy regimens including glucocorticoids and rituximab without flare of Kaposi sarcoma if the regimen also includes agents active against Kaposi sarcoma such as anthracyclines.

Overall, the survival of patients with Kaposi sarcoma has greatly improved, and long-term survival can be the goal for many patients. 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 result in long-term disease control.

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