KAPOSI’S SARCOMA

Executive Summary

Kaposi’s sarcoma (KS) is the most common tumor in HIV-infected individuals in Africa (1). However, it was relatively common in South Africa before the HIV/AIDS epidemic with an incidence of 5 per 100,000 individuals being at risk of developing it (2). After the advent of HIV/AIDS, the incidence increased dramatically (3). In Kenya, a study by Onyango et al (2004) at Kenyatta National Hospital showed that mucocutaneous KS had a relative frequency of 2 to 5% of all malignancies with a male to female ratio of 2:1.

KS is a vascular tumor which arises in multifocal sites. The skin is most commonly involved, though virtually any organ, except perhaps the brain can be involved. It exists in four forms – classic, equatorial Africa endemic, secondary to iatrogenic immunosuppression, and HIV/AIDS-related forms.

The classic form occurs in older men of Mediterranean or Jewish background. It presents with a few cutaneous lesions on the lower limbs and has an indolent nature. The equatorial Africa form occurs in all age groups (endemic KS). It is usually aggressive in nature, affecting both adults and children. The form associated with immune suppression post organ transplantation was first noted in renal transplant recipients and has been described in other transplant recipient patients. HIV-1 associated KS (epidemic form) is an aggressive form which presents with cutaneous and/or visceral lesions. It has been noted that highly active antiretroviral therapy (HAART) alone improves the outcome of HIV associated KS (4,5). In South Africa, addition of chemotherapy to HAART achieve higher KS response over 12 months as compared to HAART alone (6).

Patients with aggressive forms of KS are commonly treated with paclitaxel or doxorubicin (or liposomal doxorubicin), bleomycin and vinblastine or vincristine (ABV). The ABV regimen has been shown to give better response rates than BV (Bleomycin, vinblastine / vincristine) alone (6,8). This regimen was however not very popular because of toxicity (8). Gemcitabine monotherapy has been suggested as an alternative option in patients previously treated with ABV (9).

Paclitaxel, with response rates ranging from 59%-71% when given without HAART (12,13), is considered the most attractive agent since it is effective and tolerable over long-term administration especially when combined with growth factors (13,14). Paclitaxel for this reason should be added to the essential medicines list.

Liposomal daunorubicin (Dauno Xsome) and pegylated liposomal doxorubicin (Doxil) are popular in high-income countries because of a better toxicity profile, and have similar efficacy as ABV though no studies support its superiority when compared to ABV or doxorubicin (8,10).
These agents are more costly, and without clear proved incremental benefit over other regimens, are not being recommended for including in the EML.

Alpha interferon and radiotherapy have also been used in the management of AIDS-associated KS. Their use has been limited by the toxicity profile. Rapamycin was noted to be safe in HIV infected individuals with KS and can in some cases induce tumor regression (11).

Public Health Relevance
Kaposi’s sarcoma is a relatively rare cancer worldwide. GLOBOCAN estimated 44,247 new cases and 26,974 deaths worldwide in 2012 (22). 2012 data shows 40,874 of new cases in less developed regions and 3,373 new cases in more developed regions. The African continent is disproportionately affected, where 37,509 (85%) of all cases occur. Men are approximately 2 times more at risk for developing Kaposi’s sarcoma than women worldwide.

Kaposi’s sarcoma has four classifications, based on varying clinical characteristics and risk factors (23). Classic Kaposi’s sarcoma affects elderly, immunocompetent individuals of Mediterranean or Eastern European descent. It is a slow-progressing and relatively benign form of the cancer. Endemic or African Kaposi’s sarcoma is most common in Central and Eastern Africa and primarily affects adults. Iatrogenic Kaposi’s sarcoma is found in populations with compromised immune systems, primarily in patients who have received organ transplants. AIDS-Kaposi’s sarcoma develops in populations infected with HIV-AIDS. In Western countries, AIDS-KS is most commonly found in HIV-infected men who have sex with men. In certain African countries with high rates of HIV, AIDS-KS affects men and women proportionately, and there is also a high incidence in children (23).

Requirements for diagnosis, treatment, and monitoring

Diagnostics:
First and foremost is the clinical picture of erythematous violaceous cutaneous lesions that can be macular, patch, plaque, nodular or exophytic. The lesions can be solitary, localized or disseminated. This in the background of HIV/AIDS should alert the physician to the diagnosis of KS. The presence of local/regional lymphoedema almost gives away the diagnosis. However tissue confirmation is mandatory before instituting any form of therapy.

Local punch biopsy or rarely, excision biopsy are all that are required for a skin biopsy. Lymph node excision can also be done in predominantly nodal lesions. Endoscopic biopsies may be required for lesions presenting solely in visceral lumens. Tissues should be subjected to pathologic examination by an experienced histopathologist.

Testing:
Any patient with a diagnosis of Kaposi’s sarcoma must have HIV test done. Positive cases must have differential lymphocyte counts and where possible HIV viral load. Quite often the patients
are anemic, or thrombocytopenic, or neutropenic. Complete blood counts must be assayed. Various forms of kidney injury also occur; therefore renal function studies must be carried out. Liver function tests and coagulation assays should also be carried out. Cardiac function assessment should be carried out because the anthracycline doxorubicin, whether pegylated or not, is a key agent in the management of this disease, with the attendant risk of cardiotoxicity.

Patients with HIV/AIDS commonly have concurrent opportunistic infections including tuberculosis, and opportunistic tumors including aggressive subtypes of B cell lymphomas. Their coexistence greatly alter the treatment approaches, therefore appropriate imaging should be carried out as indicated.

Solitary asymptomatic, nonulcerated patch lesions can just be managed with appropriate combination antiretroviral therapy. Surgical excision may have a role if lesions are raised and/or symptomatic, though this is controversial, since there is a tendency for new lesions to spring up from the excision wound edges. Locoregional lesions can be managed appropriately with radiation.

**Administration and Care of Patients:**

Clinical needs include the ability to manage patients with HIV who are on antiretroviral therapy, and the issues surrounding that treatment. Facilities need to be adept at managing additional services for HIV-positive patients, including following of CD4 counts, organ function, and management of HIV related infectious complications. Management of cytopenias related to HIV and cytotoxic agents is paramount.

In regard to management of KS, clinical assessment skills are required.

For the administration of the regimens described, there is the need for safe and effective ordering, preparation and administration of parenteral chemotherapy as listed. Care and skill in the administration of vesicants such as vincristine and doxorubicin is needed. Specifically clinical and laboratory assessment are required, as well as the infrastructure to deliver parenteral chemotherapy. Management of potential allergic reactions to taxanes, bleomycin and other drugs are required. Skills in management of potential lung toxicity from bleomycin is also required. Skills in management of potential neuro-toxicity from vincristine and taxanes is needed.
Overview of Regimens

The following tables include basic information on administration and dosing for a Basic Regimen and an Advanced Regimen, and exclude ancillary medications pertaining to the management of side effects. For the therapeutic regimens considered, treatment duration is based on clinical judgment.

### Standard Regimen

| Paclitaxel | Intravenous infusion | 100 mg/m² q 2 wks |
| Paclitaxel | Intravenous infusion | 135 mg/m² q 3 wks |

### Alternative Regimens (if paclitaxel is not available or not tolerated)

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Note: The liposomal doxorubicin preparations are acceptable for treatment of Kaposi’s sarcoma, and in some patients have a favorable toxicity profile, but are no more efficacious than the regimens described above, and considerably more costly, therefore we are not recommending that it be added to the EML.
Review of Benefits and Harms

Benefits

In high-income countries where patients with HIV/KS are likely to present with disease that is not widespread, response rates ranging between 22% - 80% have been reported with combined antiretroviral therapy alone (4,5,15,16). This situation is highly unlikely to hold for low-income countries where patients present with bulky, advanced disease (6). In a South African study patients on combined antiretroviral therapy and chemotherapy fared better than patients on combined antiretroviral therapy alone(6). Krown and colleagues in New York also noted that it was extremely rare for patients with extensive, poor risk KS to respond to HAART alone (17).

The treatment of HIV KS is basically palliative and complete remission is not a realistic goal. Various treatment regimens are available with differing response rates and toxicity profiles. Paclitaxel, with response rates ranging from 59%-71% when given without HAART (12,13), is considered the most attractive agent since it is effective and tolerable over long term administration especially when hematopoietic growth factor support is incorporated (13,14,

Harms and Toxicity Considerations

Common

Patients with KS treated with paclitaxel commonly experience alopecia, myelosuppression including neutropenia, anemia and thrombocytopenia, and mild peripheral neuropathy.(13) Paclitaxel administration requires premedication with glucocorticoids and antihistamines to reduce the risk of infusion reactions.

Vinca alkaloids including vincristine and vinblastine are associated with a high incidence of neurotoxicity, typically manifesting as sensory neuropathy, which is usually reversible.(18) This neuropathy also reduces GI transit time leading to constipation specifically with vincristine and vinblastine, which may warrant prophylaxis.(19)

Serious

Myelosuppression with paclitaxel, PLD and/or vinblastine can be severe and may lead to an increased risk of opportunistic infection or other serious infection in this patient population. (10,13)

Bleomycin is associated with rare but potentially serious cases of pulmonary fibrosis. (10,21) The risk of toxicity is dose-dependent (increasing with cumulative doses above 400 units) and therefore bleomycin dosed in the regimens above has very little risk of this adverse effect.

Doxorubicin/PLD can lead to long term cardiomyopathy when cumulative doses exceed 450mg/m². This risk is dose-dependent and at the doses delivered with regimens here (<300 mg/m2), the risk is small.(10,20) This information has been kept in for comprehensiveness, however PLD is not recommended for addition to the List of Essential Medicines.
Systematic Reviews


Background: Kaposi's sarcoma remains the most common cancer in Sub-Saharan Africa and the second most common cancer in HIV-infected patients worldwide. Since the introduction of highly active antiretroviral therapy (HAART), there has been a decline in its incidence. However, Kaposi's sarcoma continues to be diagnosed in HIV-infected patients. Objectives: To assess the added advantage of chemotherapy plus HAART compared to HAART alone; and the advantages of different chemotherapy regimens in HAART and HAART naive HIV infected adults with severe or progressive Kaposi's sarcoma. Selection Criteria: Randomised trials and observational studies evaluating the effects of any chemotherapeutic regimen in combination with HAART compared to HAART alone, chemotherapy versus HAART, and comparisons between different chemotherapy regimens. Data Collection and Analysis: Two review authors assessed the studies independently and extracted outcome data. We used the risk ratio (RR) with a 95% confidence interval (CI) as the measure of effect. We did not conduct meta-analysis as none of the included trials assessed identical chemotherapy regimens. Main Results: We included six randomised trials and three observational studies involving 792 HIV-infected adults with severe Kaposi's sarcoma. Seven studies included patients with a mix of mild to moderate (T0) and severe (T1) Kaposi’s sarcoma. However, this review was restricted to the subset of participants with severe Kaposi's sarcoma disease. Studies comparing HAART plus chemotherapy to HAART alone showed the following: one trial comparing HAART plus doxorubicin, bleomycin and vincristine (ABV) to HAART alone showed a significant reduction in disease progression in the HAART plus ABV group (RR 0.10; 95% CI 0.01 to 0.75, 100 participants); there was no statistically significant reduction in mortality and no difference in adverse events. A cohort study comparing liposomal anthracyclines plus HAART to HAART alone showed a non-statistically significant reduction in Kaposi's sarcoma immune reconstitution inflammatory syndrome in patients that received HAART plus liposomal anthracyclines (RR 0.49; 95% CI 0.16 to 1.55, 129 participants). Studies comparing HAART plus chemotherapy to HAART plus a different chemotherapy regimen showed the following: one trial involving 49 participants and comparing paclitaxel versus pegylated liposomal doxorubicin in patients on HAART showed no difference in disease progression. Another trial involving 46 patients and comparing pegylated liposomal doxorubicin versus liposomal daunorubicin showed no participants with progressive Kaposi's sarcoma disease in either group. Studies comparing different chemotherapy regimens in patients from the pre-HAART era showed the following: in the single RCT comparing liposomal daunorubicin to ABV, there was no significant difference with the use of liposomal daunorubicin compared to ABV in disease progression (RR 0.78; 95% CI 0.34 to 1.82, 227 participants) and overall response rate. Another trial involving 178 participants and comparing oral etoposide versus ABV demonstrated no difference in mortality in either group. A non-randomised trial comparing bleomycin alone to ABV demonstrated a higher median survival time in the ABV group; there was also a non-statistically significant reduction in adverse events and disease progression in the ABV group (RR 11; 95% CI 0.67 to 179.29, 24 participants). An additional non-randomised study showed a non-statistically significant overall mortality benefit from liposomal doxorubicin as compared to conservative
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management consisting of either bleomycin plus vinblastine, vincristine or single-agent antiretroviral therapy alone (RR 0.93; 95% CI 0.75 to 1.15, 29 participants). The overall quality of evidence can be described as moderate quality. The quality of evidence was downgraded due to the small size of many of the included studies and small number of events. **Authors’ Conclusions:** The findings from this review suggest that HAART plus chemotherapy may be beneficial in reducing disease progression compared to HAART alone in patients with severe or progressive Kaposi's sarcoma. For patients on HAART, when choosing from different chemotherapy regimens, there was no observed difference between liposomal doxorubicin, liposomal daunorubicin and paclitaxel.

Additional reviews supporting the use of paclitaxel in HIV KS can be found in:


**Recommendations**

The reviewers recommend the incorporation of Kaposi’s sarcoma treatment options into the WHO Model List of Essential Medicines. All medicines are already listed in the WHO’s 2013 List of Essential Medicines.

**Additions proposed for Section 8.2 of the EML**

None
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References


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