Kaposi sarcoma – EML

The application sought the inclusion on the WHO Model List of Essential Medicines of bleomycin, doxorubicin, paclitaxel, vinblastine and vincristine for the treatment of Kaposi sarcoma.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Kaposi sarcoma is a vascular tumour that arises in multifocal sites. The skin is most commonly involved, although almost any organ, except perhaps the brain, can be involved. It exists in four forms, based on varying clinical characteristics and risk factors – classic; endemic African; secondary to iatrogenic immunosuppression; and HIV/AIDS-related *(1)*.

Classic Kaposi 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 sarcoma is most common in central and eastern Africa and affects adults primarily. Iatrogenic Kaposi sarcoma is found in populations with compromised immune systems, primarily patients who have received organ transplants. HIV/AIDS-related Kaposi sarcoma (AIDS-KS) develops in populations infected with HIV-AIDS; in developed countries, it is most commonly found in HIV-infected men who have sex with men.

Kaposi sarcoma (KS) is the most common tumour in HIV-infected individuals in Africa *(2)*. It was relatively common in central Africa before the HIV/AIDS epidemic, with an estimated incidence of more than 6 per 1000 individuals in Uganda, United Republic of Tanzania and Zaire (now the Democratic Republic of the Congo) *(3)*. After the advent of HIV/AIDS, the incidence increased dramatically *(4)*. A study by Onyango et al. showed that mucocutaneous KS diagnosed from 1968 to 1997 at Kenyatta National Hospital, Nairobi, represented 2–5% of all malignancies *(5)*. In certain African countries with high rates of HIV, AIDS-KS affects men and women equally, and there is also a high incidence in children *(1)*.

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, 7)*; however, this regimen was unpopular because of toxicity *(6)*.

Paclitaxel, with response rates ranging from 59% to 71% when given without HAART (highly active antiretroviral therapy) *(8, 9)*, is considered the most attractive agent since it is both effective and tolerable over long-term administration, especially when combined with growth factors *(8, 10)*. For this reason, the application requested that paclitaxel be added to the EML.

Liposomal daunorubicin and pegylated liposomal doxorubicin are popular in high-income countries because of their better toxicity profile and their efficacy, which is similar to

that of ABV. However, no studies support the superiority of these agents when compared with ABV or doxorubicin *(6, 11)*. Moreover, they are more costly and, without clear, proved incremental benefit over other regimens, they are not proposed for inclusion in the EML.

It has been noted that HAART alone improves the outcome of HIV-KS *(12, 13)*. In South Africa, addition of chemotherapy to HAART has achieved better KS response over 12 months compared with HAART alone *(7)*.

Public health relevance

KS is a relatively rare cancer worldwide. GLOBOCAN estimated 44 247 new cases and 26 974 deaths worldwide in 2012 *(14)*. Data for 2012 data show 40 874 new cases in less developed regions and 3373 new cases in more developed regions. The African continent is disproportionately affected: 85% of all cases occur here. The risk for men of developing KS is approximately twice that for women worldwide. In classic KS, however, the male:female ratio is about 10:1.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The principal diagnostic feature of KS is erythematous, violaceous cutaneous lesions, which can be macular, patch, plaque, nodular or exophytic. The lesions can be solitary, localized or disseminated. Against a background of HIV/AIDS, this should alert the physician to the diagnosis of KS. The presence of local/regional lymphoedema supports the diagnosis. However, tissue confirmation is mandatory before any form of therapy is instituted.

Skin biopsy by local punch biopsy or, rarely, excision biopsy is recommended. Lymph node excision can also be done in predominantly nodal lesions. Endoscopic biopsies may be required for lesions presenting solely in visceral lumens. Pathological examination of tissues should be carried out by an experienced histopathologist.

Testing

Any patient with a diagnosis of KS must be tested for HIV. Positive cases must have differential lymphocyte counts and where possible HIV viral load assessment performed. Patients are often anaemic, thrombocytopenic or neutropenic, and complete blood counts must be performed. Renal function studies must be carried out, because there may be various forms of kidney injury. Liver function tests and coagulation assays are also essential. Cardiac function should be assessed because the anthracycline doxorubicin, pegylated or not, which is a key agent in the management of KS, carries an attendant risk of cardiotoxicity.

Patients with HIV/AIDS commonly have concurrent opportunistic infections including tuberculosis and opportunistic tumours including aggressive subtypes of B-cell

lymphomas. Concurrent diseases have significant implications for the treatment approaches, and appropriate imaging should therefore be carried out.

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

Administration and care of patients

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

Treatment with the regimens described requires safe and effective ordering, preparation and administration of parenteral chemotherapy. Care and skill in the administration of vesicants such as vincristine and doxorubicin is needed. Specifically, the capacity for clinical and laboratory assessment is required, as well as the infrastructure to deliver parenteral chemotherapy and to manage potential allergic reactions to taxanes, bleomycin and other drugs. Skills in management of potential lung toxicity from bleomycin and of potential neurotoxicity from vincristine and taxanes are needed.

Overview of regimens

The following provides basic information on administration and dosing of standard and alternative chemotherapy regimens for KS; no details are given of ancillary medications pertaining to the management of adverse events. Treatment duration is based on clinical judgement.

The addition of liposomal doxorubicin preparations is acceptable for treatment of KS, and in some patients the toxicity profile is favourable; however, efficacy is no greater than that of the other regimens described *(15)*, and the cost is considerably higher. These preparations were therefore not proposed as standard of care at the time of the application, nor were they recommended for inclusion in the EML.

Standard regimen

- **Paclitaxel**
  - paclitaxel 100 mg/m^2 IV infusion every 2 weeks
  - paclitaxel 135 mg/m^2 IV infusion every 3 weeks

Alternative regimens (if paclitaxel is unavailable or not tolerated)

- **Vincristine: 6 cycles**
  - vincristine 1.4 mg/m^2 IV bolus every 2 weeks
- **Vincristine/bleomycin: 6 cycles**
  - vincristine 1.4 mg/m^2 IV bolus every 2 weeks
  - bleomycin 10 IU/m^2 IV bolus every 2 weeks
- **ABV for HIV-positive patients: 6 cycles**
  - vinblastine 6 mg/m^2 IV bolus every 2 weeks
  - bleomycin 10 IU/m^2 IV bolus every 2 weeks
  - doxorubicin 25 mg/m^2 IV infusion every 2 weeks
- **ABV for HIV-negative patients: 6 cycles**
  - vinblastine 6 mg/m^2 IV bolus every 3 weeks
  - bleomycin 10 IU/m^2 IV bolus every 3 weeks
  - doxorubicin 50 mg/m^2 IV infusion every 3 weeks

Review of benefits and harms

Benefits

The treatment of HIV-KS is basically palliative – complete remission is not a realistic goal. Various treatment regimens are available, with differing response rates and toxicity profiles.

In high-income countries, where patients with HIV-KS are likely to present with disease that is not widespread, response rates ranging between 22% and 80% have been reported with combined antiretroviral therapy alone *(12, 16, 17)*. The same is highly unlikely to be true of low-income countries, where patients present with bulky, advanced disease *(7)*. Krown and colleagues noted that it was extremely rare for patients with extensive KS and poor prognosis to respond to HAART alone *(18)*.

HAART plus chemotherapy may be beneficial in reducing disease progression compared with HAART alone in patients with severe or progressive KS. A Cochrane systematic review of six randomized controlled trials and three observational studies compared HAART plus chemotherapy with HAART alone in patients with severe KS *(15)*. The review found that HAART plus chemotherapy was associated with reduced disease progression compared with HAART alone. Chemotherapy regimens used included

medicines proposed for inclusion on the EML. For example, the comparison by Mosam et al. demonstrated a significant reduction in progressive disease in patients treated with HAART plus ABV compared with those given HAART alone (risk ratio (RR) 0.10; 95% CI: 0.01–0.75) *(7)*. However, no statistically significant reduction in mortality or difference in adverse events was observed. With regard to different chemotherapy regimens for patients on HAART with severe KS, there was no large observed difference between liposomal doxorubicin, liposomal daunorubicin and paclitaxel *(15)*.

Paclitaxel, with complete or partial response rates ranging from 59% to 71% when given without HAART in patients with previously treated severe KS *(8, 9)*, could be considered an attractive option. It is effective and tolerable over prolonged administration, especially when haematopoietic growth factor support is incorporated *(8, 10)*.

Harms and toxicity considerations

Common

Vinca alkaloids, including vincristine and vinblastine, are associated with a high incidence of neurotoxicity, typically manifesting as sensory neuropathy, which is usually reversible *(19)*. This neuropathy also reduces gastrointestinal transit time and, specifically with vincristine and vinblastine, leads to constipation, which may warrant prophylaxis *(20)*.

Patients with KS treated with paclitaxel commonly experience alopecia, myelosuppression including neutropenia, anaemia and thrombocytopenia, and mild peripheral neuropathy *(8)*. Paclitaxel administration requires premedication with glucocorticoids and antihistamines to reduce the risk of infusion reactions.

Serious

Myelosuppression with paclitaxel, pegylated liposomal doxorubicin and/or vinblastine can be severe and may lead to an increased risk of opportunistic or other serious infections *(8, 11)*.

Bleomycin is associated with rare but potentially serious cases of pulmonary fibrosis *(11, 21)*. The risk of toxicity is dose-dependent, increasing with cumulative doses above 400 IU; at the doses used in the regimens detailed above, therefore, bleomycin carries very little risk of this adverse event.

Doxorubicin can lead to long-term cardiomyopathy when cumulative doses exceed 450 mg/m^2. This risk is dose-dependent, however, and at the doses delivered in the regimens detailed above (<300 mg/m^2), the risk is small *(11, 22)*.

Recommendations

The Expert Committee noted that all medicines proposed in the application for treatment of Kaposi sarcoma are currently listed on the complementary list of the Model List of Essential Medicines. On the basis of the evidence presented, the Committee recommended that

paclitaxel, vincristine, vinblastine, bleomycin and doxorubicin be specifically endorsed on the Model List for the treatment of Kaposi sarcoma.

The Committee also noted that chemotherapy in combination with HAART is associated with improved outcomes for patients with Kaposi sarcoma, and considered that combination therapy should be used whenever clinically appropriate and possible.

1. Sarid R, Calabro M. Kaposi's sarcoma-associated herpesvirus: epidemiology, biological characteristics and pathogenesis. In: Kaslow RA, Stanberry LR, Le Duc JW, editors. Viral infections of humans. New York: Springer; 2014. p. 879-931.
2. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet. 1995;346(8978):799-802.
3. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. Br J Cancer. 1998;78(11):1521-8.
4. Dal Maso L, Serraino D, Franceschi S. Epidemiology of AIDS-related tumours in developed and developing countries. Eur J Cancer. 2001;37(10):1188-201.
5. Onyango JF, Njiru A. Kaposis sarcoma in a Nairobi hospital. East Afr Med J. 2004;81(3):120-3.
6. Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol. 1996;14(8):2353-64.
7. Mosam A, Shaik F, Uldrick TS, Esterhuizen T, Friedland GH, Scadden DT, et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa. J Acquir Immune Defic Syndr. 2012;60(2):150-7.
8. Gill PS, Tulpule A, Espina BM, Cabriales S, Bresnahan J, Ilaw M, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. J Clin Oncol. 1999;17(6):1876-83.
9. Saville MW, Lietzau J, Pluda JM, Feuerstein I, Odom J, Wilson WH, et al. Treatment of HIV-associated Kaposi's sarcoma with paclitaxel. Lancet. 1995;346(8966):26-8.
10. Saville MW, Lietzau J, Pluda JM. A phase II trial of paclitaxel (Taxol) in patients with HIV-associated Kaposi's sarcoma. AIDS Res Hum Retrovirol. 1994;10(suppl):S103.
11. Stewart S, Jablonowski H, Goebel FD, Arasteh K, Spittle M, Rios A, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol. 1998;16(2):683-91.
12. Dupin N, Rubin De Cervens V, Gorin I, Calvez V, Pessis E, Grandadam M, et al. The influence of highly active antiretroviral therapy on AIDS-associated Kaposi's sarcoma. Br J Dermatol. 1999;140(5):875-81.
13. Mosam A, Uldrick TS, Shaik F, Carrara H, Aboobaker J, Coovadia H. An evaluation of the early effects of a combination antiretroviral therapy programme on the management of AIDS-associated Kaposi's sarcoma in KwaZulu-Natal, South Africa. Int J STD AIDS. 2011;22(11):671-3.

14. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [Available from: http://globocan.iarc.fr.
15. Gbabe OF, Okwundu CI, Dedicoat M, Freeman EE. Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults. Cochrane Database Syst Rev. 2014;9:CD003256.
16. Aversa SM, Cattelan AM, Salvagno L, Crivellari G, Banna G, Trevenzoli M, et al. Treatments of AIDS-related Kaposi's sarcoma. Crit Rev Oncol Hematol. 2005;53(3):253-65.
17. Cattelan AM, Calabro ML, De Rossi A, Aversa SM, Barbierato M, Trevenzoli M, et al. Long-term clinical outcome of AIDS-related Kaposi's sarcoma during highly active antiretroviral therapy. Int J Oncol. 2005;27(3):779-85.
18. Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol. 2004;22(3):399-402.
19. Lee EQ, Wen PY. Overview of neurologic complications of non-platinum cancer chemotherapy. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.
20. Krishnamurthi SS. Enterotoxicity of chemotherapeutic agents. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.
21. Gilligan T. Bleomycin-induced lung injury. In: UpToDate [website]. Waltham, MA: UpToDate; 2014 [
22. Floyd J, Morgan JP. Cardiotoxicity of anthracycline-like chemotherapy agents. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.