Management of HIV associated Kaposi's Sarcoma in Malawi

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Abstract

Kaposi's sarcoma is a common malignancy in Malawi and is often managed with single agent vincristine. This article outlines feasible combination chemotherapy for Kaposi's sarcoma in Malawi which should be made more widely available.

Importance of Kaposi's Sarcoma

Kaposi's sarcoma is an AIDS related malignancy. Infection with Human herpesvirus-8 (HHV-8), also known as the Kaposi's sarcoma-associated herpesvirus (KSHV) leads to its development.

In Europe and North America, the standardised incidence ratio for Kaposi's sarcoma among people with AIDS has remained much higher in the post-Highly Active Antiretroviral Therapy (HAART) period (from 1996) than in the general population [1] so that KS has remained a significant cause of morbidity among HIV-infected individuals. In Africa, rates of HIV-HHV8 coinfection and the incidence of KS are believed to be much higher than in Europe and North America. In 2002, of 66,200 estimated KS cases worldwide, 58,800 are estimated to have occurred in Africa[2]. Many of these cases are not on HAART.

Current cancer data suggests that Kaposi's sarcoma (KS) is the most common cancer in Malawi among male and female patients. Most of the cases have HIV associated Kaposi's sarcoma although non-HIV associated cases also do occur. It has been suggested that the frequency of KS in Malawi is due to underdiagnosis of other cancers, nevertheless, KS is common in Malawi. Granulomatous conditions, prominent lymph node vascularity, bacillary angiomatosis and melanoma can be confused with KS and so tissue confirmation of the diagnosis is advised.

Treatment options for HIV-associated Kaposi's Sarcoma

The options available in the management of HIV-associated KS (table 1) include HAART alone, local therapy, immunotherapy, cytotoxic chemotherapy, molecular targeted therapy and treatments that directly target KSHV/HHV8. A 2003 Cochrane review on how best to treat HIV-associated KS in resource limited settings found no suitable evidence[3]. However, relevant practical guidelines on the management of KS in resource limited settings are available [4,5]. Only treatment options accessible in Malawi will be discussed in this article.

All HIV-associated KS patients should receive HAART. HAART reduces the outcome of KS. Histological regression of existing KS lesions has been shown in response to HAART[6] . With HAART, HIV-associated KS can be cured[7] but HAART alone can not effectively control all cases of KS, as there may be initial tumour progression as part of the immunoreconstitution syndrome[8] ; response of KS to HAART alone is unpredictable, patients on effective HAART may still develop KS[9] and response to HAART can be very slow[10]. HIV-associated KS is a stage IV HIV-disease but Kaposi's Sarcoma itself, as is true of all cancers, should also be staged before treatment decisions are made. The AIDS Clinical Trials Group staging system can be used to classify patients into good and poor risk categories on the basis of tumour extent (T), severity of immunosuppression (I), and the presence of any other systemic HIV-associated illness (S) [4,5,11,12]. Good-risk patients are likely to show tumor regression with HAART alone [13]. Details of how to start treatment, how to assess response to treatment and how to change HAART in the management of KS are available in the guidelines by Lynen [4,5].

Local therapeutic options are mainly indicated for local disease and they include excision surgery, cryotherapy, radiation, alitretinoin gel, intralesional chemotherapy (usually vinblastine but vincristine or interferon alpha can also be used), laser therapy and photodynamic treatment. Surgery is perhaps the most readily available of these options in Malawi for excision of localized KS; but heroic surgery is unjustified. Intralesional vinblastine (at 0.1 ml per 0.5 cm^2 of lesion every three to four weeks) can be used as therapy for lesions in the mouth preferably with concurrent use of a local anaesthetic to reduce injection pain. Healthy tissue must not be injected to avoid severe tissue necrosis. A 10 mg vial of vinblastine costs MK1600 - MK5600 (USD 12-40) in Malawi.

In Malawi many HIV-associated KS patients present with advanced and/or extensive disease (with oedema, extensive mucocutaneous lesions, pulmonary involvement with symptoms or gastrointestinal involvement with symptoms) and such poor-risk patients usually require a combination of HAART and chemotherapy with discontinuation of the chemotherapy after regression of the KS [13], Chemotherapy can be restarted for recurrent KS.

Single agent chemotherapy

The majority of KS patients in Malawi are treated with single agent vincristine at dosages of 2 mg weekly, fortnightly or three-weekly in addition to HAART. The dose of vincristine should not exceed 2 mg per administration. The main attraction for vincristine seems to be its affordability. However, single agent vincristine is rarely used elsewhere [4]. Its benefit is thought to be small as a single agent even at its optimal dose of 2 mg per week. When the administration intervals are increased to 2 mg every two or 2 mg every three weeks, its efficacy gets worse. A contributing factor to this loss of efficacy is the fact that vinca alkaloids are S-phase specific which means that cells that are in other phases of the cell cycle are not affected by these drugs and a prolonged interval between drug administrations allows these cells to transit through S-phase unaffected and contribute to tumour re-growth. At its optimal dose of 2 mg per week, vincristine has problems of severe neurotoxicity which include peripheral neuropathy, constipation and ileus. Patients need to be assessed for neuropathy before administration of all doses of vincristine. A possible solution to the neurotoxicity

Table 1: Treatment options for HIV-associated Kaposi's Sarcoma

Treatment option		Reference
HAART alone		Krown SE. J Clin Oncol 2004;22:399-402.
Local Therapy	Excision surgery	No convincing evidence [Simonart T. J Eur Acad Dermatol Venereol. 2007; 21(4):573]
	Cryotherapy (surgery)	Tappero JW et al. J Acquir Immune Defic Syndr 1991;4:839–846.
	Radiation	Kigula-Mugambe JB et al. Radiother Oncol. 2005;76:59–62.
	Alitretinoin gel	Walmsley S et al. J Acquir Immune Defic Syndr 1999;22:235–246
	Intralesional chemotherapy	Ramirez-Amador V et al. Oral Oncol. 2002;38:460–467
	Laser therapy (surgery)	Abels C et al. Br J Cancer. 1998;77(6):1021-4
	Photodynamic treatment (experimental)	Bernstein ZP et al. Aids 1999;13:1697–1704
Immunotherapy	Interferon-alpha	Lane HC et al. Lancet 1988;2:1218-1222
Cytotoxic chemotherapy	Liposomal doxorubicin	Osoba D et al. Cancer Invest 2001;19:573–580
	Liposomal daunorubicin	Gill PS et al. J Clin Oncol 1996;14:2353–2364
	Paclitaxel	Welles L et al. J Clin Oncol 1998;16:1112-1121
	Etoposide	Paredes J et al. J Acquir Immune Defic Syndr Hum Retrovirol 1995;9:138-144
	Vincristine alone	Mintzer DM et al. Annals of Internal Medicine 1985;102(2):200-202. [poor results, however HAART was not used]
	Vinblastine alone	Volberding PA et al. Ann Intern Med 1985;103:335-338
	Bleomycin alone	Lassoued K et al. Cancer 1990;66:1869-72.
	Vincristine/Vinblastine	Kaplan L et al. Cancer Treat Rep 1986;70(9):1121-2.
	Vincristine/Bleomycin (BV)	Gill P et al. Am J Clin Oncol. 1990;13(4):315-9.
	Vincristine/Bleomycin/ Doxorubicin (ABV)	Gill PS et al. Am J Med 1991;90:427-433
	Gemcitabine	Brambilla L et al. Dermatology 2001;202(2):119-22.
	Vinorelbine	Nasti G et al. J Clin Oncol. 2000;18(7):1550-7.
Molecularly targeted therapy examples (mainly experimental)	Angiogenesis inhibitors : imatinib or sunitinib (tyrosine kinase inhibitors)	Koon HB et al. J Clin Oncol 2005;23:982–989
	Angiogenesis inhibitors: thalidomide, fumagillin (TNP-470) or bevacizumab	Soler RA et al. Clin Infect Dis 1996;23:501-505
	Angiogenesis inhibitors : COL-3 (matrix metalloproteinase inhibitor)	Dezube BJ et al. J Clin Oncol 2006;24:1389–1394
	Inhibitors of the PI3K/AKT/ mTOR pathway (rapamycin or sirolimus)	Stallone G et al. N Engl J Med 2005;352:1317–1323
	Nuclear factor κB inhibitors (bortezomib)	Keller SA et al. Blood 2000; 96:2537–2542
KSHV/HHV8 therapy	Ganciclovir or Foscarnet (theoretical benefit)	Robles R et al. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:34-38

problem is to alternate vincristine with vinblastine. This reduces vincristine neurotoxicity but introduces vinblastine myelosuppression. Ideally, vincristine should be avoided in a patient with existing neuropathy or in a patient on neuropathic drugs such as isoniazid (INH), didanosine (ddl) and stavudine (d4T). In such patients vinblastine or other agents should be used.

Another drug being used as a single agent on a much smaller scale than vincristine in the management of KS in Malawi and which can be used in case of vincristine or other neurotoxicity considerations is bleomycin [14].

The current recommended mainstay of treating HIV-associated KS is single agent liposomal doxorubicin, liposomal daunorubicin or paclitaxel in combination with HAART. These three drugs are not available in Malawi and are generally expensive. Liposomal anthracyclines cost about MK1,540,000 (USD 11,000) per full course in a responding patient. For those who can afford it the drugs could be imported and given locally.

The other chemotherapeutic single agents which have been studied in the management of KS are etoposide, gemcitabine and vinorelbine. Etoposide comes in oral and injectable form. The oral form, which might be available in some hospitals in Malawi, was studied mainly in pretreated KS patients and it is often used as second line. Oral administration makes

the drug attractive for use in resource limited settings but it is myelosuppressive which means that it requires frequent monitoring. A study from Zimbabwe[15] showed a better quality of life and less toxicity after using oral etoposide than with either a three drug combination consisting of actinomycin-D, vincristine and bleomycin; or radiotherapy or supportive care. The three drug combination was given every four weeks (and not every three weeks), actinomycin-D was used (and not doxorubicin), and the patients did not receive HAART. Although etoposide showed the best quality of life, the three drug combination showed the highest response rates among the four modalities compared. Oral etoposide is not a cheap drug at MK42,000 (USD 300) per 28 tablets but its potential needs further exploration in Malawi. The intravenous form is more effective than the oral form but has more severe side effects.

Combination chemotherapy

In the 1950's, cancer chemotherapy was mainly given as single agents. Complete responses were few and of short duration[16]. The "cell kill hypothesis"[17] prompted wide usage of combination chemotherapy beginning in the 1960s. The use of single agent liposomal doxorubicin, liposomal daunorubicin or paclitaxel in the treatment of KS is an example of a renewed interest in some single-agent therapy in recent years. However, combination chemotherapy remains the main practice in cancer therapy. The recommended combination chemotherapy in KS, which was the standard of care in the West prior to the development of the newer expensive single-agent KS regimens, is possible and affordable in Malawi; all the drugs required for the combination are locally available at a cost that ranges from MK4,000 (USD 28.5) per cycle to MK30,000 (USD 214.2) per cycle depending on whether a two or three drug combination is used. This compares with vincristine 2 mg (USD 2 – USD 14.4) per cycle . The combination chemotherapy includes two or three drugs:- bleomycin and vincristine (BV) as a two drug combination and doxorubicin, bleomycin and vincristine (ABV) as the three drug combination (table 2). The usual number of cycles for effective therapy is three to six cycles. However, the actual length of chemotherapy treatment depends upon the response of the KS to therapy. Chemotherapy may continue for 1-2 cycles beyond complete remission to maximize the chance of having attacked all microscopic KS. If the KS lesions shrink but do not disappear, chemotherapy could continue as long as it is tolerated and the KS does not grow. Care should be taken not to exceed maximum cumulative doses of bleomycin and doxorubicin (table 2). If KS grows, chemotherapy should be stopped and the effectiveness of HAART should be assessed. If HAART failure is ruled out, alternative treatment modalities for the KS should be considered where possible; or else palliative KS management should be started. Palliative care for KS may include adequate pain control, reduction of the size of tumours with radiotherapy (for those patients who can and are willing to travel to countries like Zambia and Tanzania for treatment as Malawi does not have radiotherapy facilities), and reduction of the offensive smell of ulcerated KS lesions with metronidazole powder.

In private practice , it is important to ensure that the patient has potential to pay for at least six cycles of therapy otherwise treatment interruptions and/or default may occur resulting in less than satisfactory outcome for the patient.

The two drug combination may be preferred in HIV positive patients because such patients are already prone to bone marrow dysfunction and doxorubicin causes significant bone marrow suppression which is at its nadir on day 14 after administration of drugs. This bone marrow suppression recovers slowly over 7-10 days but in an HIV positive patient the magnitude and duration of the bone marrow suppression may be longer. The three drug combination can still be given to HIV positive patients with caution.

Improving the management of HIV-associated KS in Malawi

Except for HAART, the two other current mainstays of HIV-associated KS management in Malawi, single agent intravenous vincristine and surgery, have weak evidence to support their use [18-20] . Their low-cost advantage should be assessed in terms of cost-effectiveness to take into account cost as well as response rates. A cost-effectiveness analysis comparing chemotherapy regimens in the treatment of HIV-related KS in a developing country did not include single agent vincristine [21]. This study favoured ABV combination chemotherapy. Combination chemotherapy for KS in Malawi is feasible and should be made available more widely.

The World Health Organisation (WHO) included bleomycin and doxorubicin on its model list of essential medicines. However, cancer is not part of the essential health package in Malawi and the essential drug list which is based on the essential health package excludes drugs like bleomycin and doxorubicin. The essential drug list is aimed at drugs which the government should provide to patients for free in Malawi. Many patients would benefit from the availability of combination chemotherapy for KS in public hospitals in Malawi, bearing in mind the extent of the HIV-associated KS in Malawi.

The aim of this article is not to encourage irresponsible and indiscriminate use of combination chemotherapy in KS in Malawi; but rather to recognise that KS patients go to great lengths to look for treatment. Vincristine, bleomycin and doxorubicin are available in pharmacies in Malawi which suggests that these drugs are being used in the country. Cytotoxic chemotherapy can kill. Lack of trained oncology practitioners is important when addressing the common question of who should administer chemotherapy. Most professional bodies such as the Intravenous Nursing Society and the Oncology Nursing Society in the United States of America, base their guidelines on the basic principle that because chemotherapy drugs are toxic (to the patient as well as to the practitioner), only oncology practitioners (physicians and registered nurses) trained specifically in chemotherapy administration should perform treatment. Guidelines from developing countries are more flexible in allowing for all cytotoxic therapy to be administered by specially trained nurses under the direct supervision of a senior doctor in case of immediate adverse reactions. The College of Medicine, which is the leading academic institution in Malawi in terms of improving medical services, should be able to provide practical training to eligible and interested practitioners in the country in administration of combination chemotherapy for KS.

Table 2 KS chemotherapy regimens feasible in Malawi

Agent	Dosage	*RR	Major side effects
Single agent vincristine	1.4 mg/m^2 (max. 2 mg) 1x /week intravenous bolus (IV) over 1-2 minutes or as short intra venous infusion (IVI) over 10-15 minutes.	10-85%	• Cumulative neurotoxicity • May produce severe constipation • Necrosis in case of extravasation
Single agent vinblastine	4-6 mg/m^2 1x /week IV over 2-3 minutes or as IVI over 10-15 minutes	25-85%	Vinblastine-induced myelosuppression
Single agent bleomycin	15 mg single doses or 5 mg/day for 3 days every 2-3 weeks IM	10-75%	• Give test dose of 1-2 units • Must adjust dose for renal insufficiency •Total lifetime dose should not exceed 400 units
Vincristine/ Vinblastine	Vincristine 1.4 mg/m^2 (max. 2 mg) and vinblastine 0.1 mg/kg IV alternating weekly. Modality of administration as described for single agents	Up to 43%	As described for single agents
BV bleomycin/vincristine	Vincristine 1.4 mg/m^2 (max. 2 mg) and bleomycin 10 mg/m2 every 2 weeks IV. Modality of administration for vincristine is as described for single agent. For bleomycin IV give slowly over a period of 10 minutes.	60-75%	As described for single agents
ABV doxorubicin/ bleomycin/vincristine	Doxorubicin 20 mg/m^2 ; bleomycin 15 units and vincristine 2 mg every 21 days. Administer vincristine and bleomycin IV as described previously. For doxorubicin push slowly through sidearm of free flowing IV normal saline or D5W This regimen may be given every 14 days but would increase the severity of side effects.	70-90%	Doxorubicin: • cumulative dose not to exceed 450 mg/m^2; assess cardiac function clinically or by ECG/ECHO before giving drug • avoid extravasation; • reduce dose by 50% if bilirubin 1.5 – 3.0; reduce to 25% for bilirubin > 3.0

Notes: * the response rates "RR" of various KS regimens are indicatory only as they were derived from different studies which did not necessarily use similar end-points

In conclusion, combination chemotherapy for Kaposi's sarcoma is feasible in Malawi and should be made available more widely. A randomized clinical trial to compare HAART alone, vincristine alone, bleomycin alone, oral etoposide alone, combination chemotherapy and perhaps surgery in KS in Malawi would be helpful and informative.

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