PALLIATIVE TREATMENT FOR HIV-RELATED KAPOSI'S SARCOMA

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Objective. To evaluate palliative treatment with chemotherapy and/or radiotherapy in patients with HIV-related Kaposi's sarcoma (KS). The primary end-point was symptom relief; the secondary end-point was tumour response to treatment and overall survival.

Methods. This study includes 100 patients with HIV-related KS. Combination chemotherapy was administered with ABV (doxorubicin, bleomycin and vincristine) (33 patients), or vinblastine and bleomycin (Vbl-B) (48 patients), depending on the CD4+ count at presentation. Radiotherapy was administered to 31 patients.

Results. Symptomatic relief was noted within 4 weeks of chemotherapy and response after 8 weeks. Twenty-nine patients (29%) had partial responses, 8 patients (8%) achieved complete responses, and 37 patients (37%) had stable disease. Twenty-six patients (26%) had disease progression. The response rate was 37%, with clinical benefit achieved in 74% of patients. Patients who received radiation therapy for bleeding and painful ulcers had complete responses. Twenty-seven patients (27%) received 8 Gray (Gy) single fractions. Two lower-half bodies (8 Gy) and one upper-half body (6 Gy) were irradiated. Five patients received a course of radiation for nasopharyngeal and skeletal lesions (20 Gy), rectal lesions (30 Gy) and an eyelid lesion (12 Gy). Forty-two patients (42%) are alive, with a median survival of 11.2 months (range 2 - 49 months). Fifty-eight patients (58%) died due to progression of HIV disease or associated opportunistic infections with a median overall survival of 8.8 months (range 1 - 31 months).

Conclusion. In the absence of antiretroviral therapy the care and prognosis of HIV-related Kaposi's sarcoma remains dismal. However, symptomatic relief and an improved quality of life can still be offered.

People with AIDS are at considerably higher risk of developing cancer than the general population. Frisch *et al.*[1] reported that most of the cancers observed in HIV/AIDS patients were those already considered to be AIDS-defining cancers (87%), notably Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL).

The HIV situation has changed since antiretroviral therapy (ART) became available: deaths from AIDS-related illnesses have been reduced by 75%. A projected reduction in new KS cases of 50 - 90% and regression of existing KS is now a recognised benefit of ART.[2] The clinical response correlates with a decrease in the HIV viral load and an increase in the CD4+ count.[3]

This ongoing study evaluated the effectiveness of palliative treatment in patients with HIV-related KS in the absence of ART.

METHODS

Optimal or standard therapy for AIDS-related KS has not been defined. The major goals of treatment are palliation of symptoms, shrinkage of tumour to alleviate oedema and psychological stress, and prevention of disease progression.

Our study included 54 males and 46 females with HIV-related KS, who were seen and treated between April 1995 and November 2002. The mean age for the group as a whole was 35.8 years (range 21 - 60 years), the mean age for females being 34.2 years (range 21 - 58 years) and the mean age for males 37.1 years (range 21 - 60 years). Of the patients 69 were black, 27 of mixed racial origin and 4 white. The male/female ratio was 1.1:1. Sixty-one patients (61%) presented with KS as their AIDS-defining illness and 39 developed KS during the course of their HIV disease. Ten patients (10%) were homosexual men. Fifty-three patients (53%) were treated for concomitant pulmonary tuberculosis (PTB) (Table I).

All patients presented with generalised mucocutaneous KS lesions and 56 had additional generalised lymphadenopathy. Fifteen patients had systemic disease

TABLE I. PATIENT CHARACTERISTICS

	Male	Female	Total
Number	54	46	100
Age (years)			
Mean	37.1	34.2	
Range	21 - 60	21 - 58	
Ethnic group			
Black	33	36	69
Mixed race	17	10	27
Caucasian	4	-	4
KS presentation			
AIDS-defining	37	24	61
HIV late presentation	17	22	39
Staging			
Good risk	19	7	26
Poor risk	35	39	74
CD4+ count (cells/µl)			
Beginning			
Mean	214	125	
Range	2 - 750	0 - 409	
End			
Mean	171	105	
Range	3 - 769	0 - 409	
Systemic involvement			
Lung	6	3	9
Rectum	2	-	2
Spleen	1	-	1
Liver	1	-	1
Skeletal	1	-	1
Pericardiac effusion	-	1	1
Opportunistic infections			
Tuberculosis	22	31	53
Candidiasis	4	6	10
Herpes zoster	4	-	4
C. neoformans	-	2	2
Pneumocystis carinii	-	2	2

that involved the liver (1 case), spleen (1), lung (9), rectum (2), pericardial effusion (1) and skeletal involvement (1) (Figs 1 and 2).

Because of the multicentric nature of KS, the standard tumour-node-metastases (TNM) staging system used for solid tumours cannot be applied to KS. Patients were assigned to receive treatment according to the AIDS Clinical Trial Group (ACTG) staging system developed by the National Institute of Allergy and Infectious Diseases. Patients were classified in good or poor risk groups based on tumour extent, immune status measured by the CD4+ count (>/< 200 cells/µl), and evidence of HIV-associated systemic symptoms.[4,5] In this patient population there were 26 patients (26%) with good risk status while 74 (74%) presented with advanced poor risk KS. All patients with a CD4+ count < 200 cells/µl received sulphamethoxazole + trimethoprim (Bactrim) as part of *Pneumocystis carinii* prophylaxis.

Patients received chemotherapy with either the combination ABV (doxorubicin 10 mg/m², bleomycin 10 mg/m² and vincristine 2 mg) every 2 weeks if the CD4+ count was > 100 cells/µl, or the combination vinblastine 6 mg/m² and bleomycin 10 mg/m² (Vbl-B) every 2 weeks if

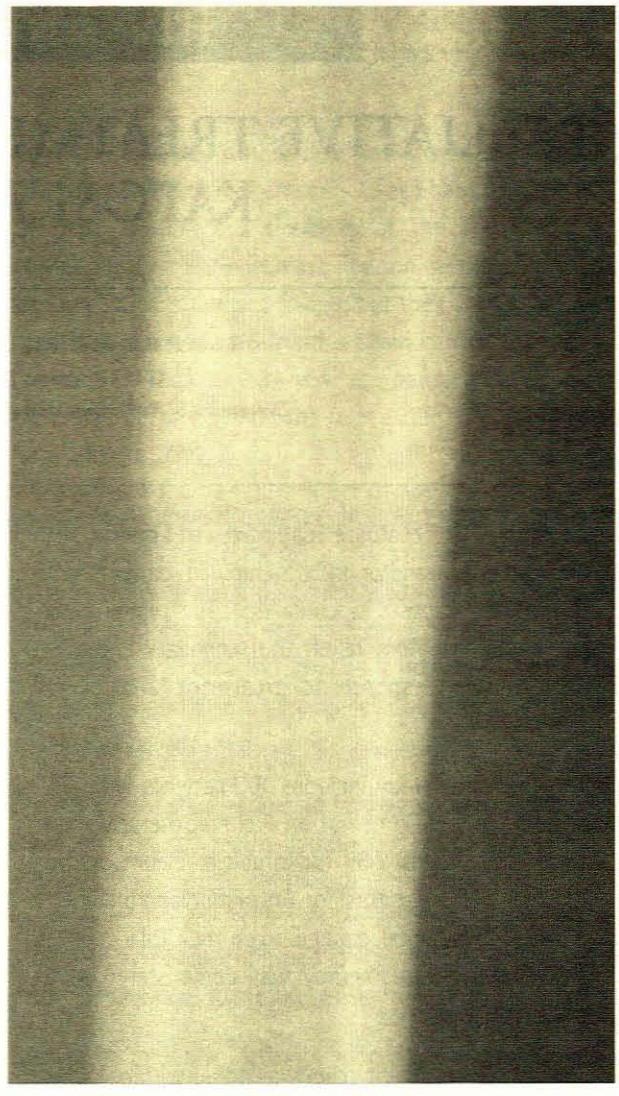


Fig. 1. KS: X-ray image of skeletal involvement.

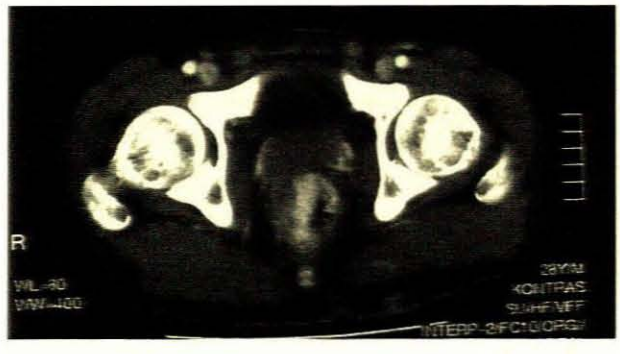


Fig. 2. KS: CT scan image of rectal mass.

the CD4+ count was between 30 and 100 cells/µl. ABV was administered to 33 patients, as first-line therapy in 23 cases and as second-line treatment for fulminating and progressive disease in 10. Forty-eight patients received the Vbl-B combination. A cycle of treatment consisted of day 1 and day 15 every 4 weeks. A median of 5 cycles was administered (range 1 - 15 cycles). A total of 206 cycles of chemotherapy was administered over the study period.

Radiotherapy was offered to patients with CD4+ counts < 50 cells/µl, performance status 2 - 3, bleeding, painful ulcerative lesions, and generalised, painful limb oedema. Thirty-one patients received concomitant radiation therapy

while 9 had radiation therapy as their only form of treatment. Single 8-Gray (Gy) fractions were given in 27 patients and were repeated in 9 patients on day 28. Two lower-half bodies (8 Gy) and one upper-half body (6 Gy) were irradiated. A protracted course of irradiation with cobalt-60 was administered to 5 patients: 1 with bleeding rectal KS received 30 Gy (3 Gy x 10 fractions); 2 with bleeding nasopharyngeal KS received 20 Gy (4 Gy x 5 fractions); 1 with humerus involvement received 20 Gy (4 Gy x 5 fractions); and 1 with eyelid involvement received consolidation radiation with 12 Gy (3 Gy x 4 fractions) electrons, after a partial response to 4 cycles of ABV.

RESULTS

The CD4+ count was done at the start of treatment and repeated after every second cycle of cytotoxic treatment. The mean CD4+ count was 172.8 cells/µl (range 0 - 750 cells/µl) at onset, and a depletion of 18.8% of the CD4+ count was observed by the end of treatment, with a mean of 140.3 cells/µl (range 0 - 769 cells/µl). The study suggested that women present at a younger age (mean 34.2 years, range 21 - 58 years) and with more advanced disease (mean CD4+ count 125 cells/µl, range 0 - 409 cells/µl) than males, for whom the median age at presentation was 37.1 years (range 21 - 60 years) and the mean CD4+ count 214 cells/µl (range 2 - 750 cells/µl).

The ACTG Oncology Committee evaluates tumour responses on the basis of total-body cutaneous lesion counts, changes in lesion character (flat or raised) and bidimensional measurements of marker lesions. Partial responses (PR) are based on a 50% reduction in the total number of lesions or a 50% decrease in the number of raised lesions. Response is never based on improvement of symptoms or visceral disease alone.[4,5]

All 100 patients are evaluable for response and 58 patients for overall survival. All patients receiving treatment had symptomatic relief within the first two administrations (4 weeks) and responses within the first two cycles (8 weeks) of chemotherapy. Patients generally tolerated chemotherapy well. Haematotoxicity requiring treatment delays were observed in 6 patients with grade 3 neutropenia. All 27 patients receiving 8 Gy fractions responded for the indications of pain and bleeding ulcers. Five patients receiving a protracted course of irradiation all had complete responses. Three patients receiving half-body radiation had partial symptomatic relief. Two patients who received radiation therapy for bleeding oropharyngeal lesions experienced prolonged radiation-induced mucositis, grade 3 (World Health Organisation). The duration of response for complete responders was 9.1 months (2.5 - 30 months), while the duration of symptomatic relief was 4.1 months (1 - 8 months).

Twenty-nine patients (29%) had partial responses, while 26 (26%) experienced disease progression. Eight patients (8%) achieved complete responses and 37 (37%) had stable disease, with an overall response of 74%.

In this study 61% of patients presented with KS as their AIDS-defining illness. Thirty-nine patients developed KS as part of the natural course of HIV, a mean of 31.6 months after diagnosis (range 6 - 120 months).

Forty-two (42%) of this patient population are currently alive, with a median survival of 11.2 months (range 1 - 49 months). Fifty-eight patients (58%) died due to progression of their HIV disease or associated opportunistic infections – pneumonia (10 cases), *Cryptococcus neoformans* meningitis (2), *Mycobacterium tuberculosis* (6), systemic candidiasis (3) and fever of unknown origin (2), with a median overall survival of 8.8 months (range 1 - 31 months) (Fig. 3).

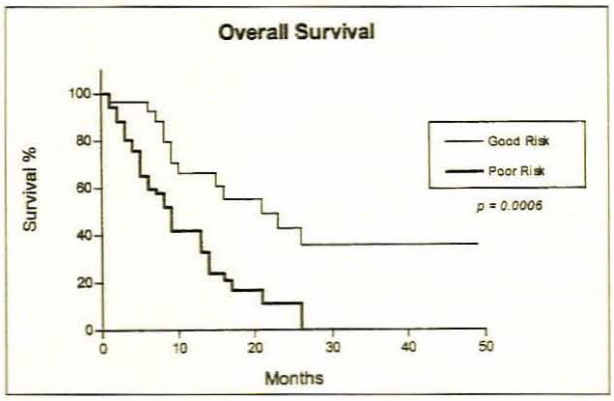


Fig. 3. Overall survival of 100 patients with HIV-related KS stratified according to good and poor risk groups.

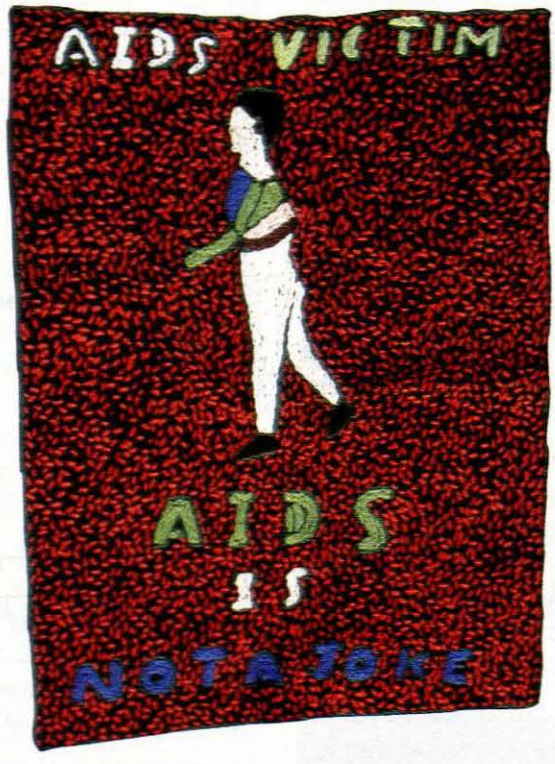
DISCUSSION

KS is the most common malignancy associated with HIV. The single most important risk factor for the development of AIDS-related KS is immune suppression.[6,7] The recognition that effective antiretroviral regimens are associated with both a decrease in new AIDS-defining KS cases and a regression in the size of existing KS lesions resulted in the recommendation that HIV-positive patients be treated with antiretroviral drugs. ART prolongs the time to treatment failure of anti-KS therapies. In particular, since the use of protease inhibitors a 30 - 50% reduction of KS has been observed in the USA and Europe.[8,9] The resolution of immune suppression with ART might also affect KS.[7-11] It is thought that protease inhibitors may inhibit the KS-associated herpesvirus proteins, but it is more likely that KS regression is linked to a decrease in the HIV replication with an associated decrease of cytokine levels leading to the restoration of immune function.[2]

Because of the unpredictable responses of KS to ART, specific local and/or systemic therapy is often instituted.

Optimal ART with maximal viral suppression, prevention and treatment of opportunistic infections is an essential element of KS treatment.

Many chemotherapeutic agents are active against KS, both as single agents and in combination. In most series, the overall response rates range from 25% to 76%, although most have been partial responses.[10,11] In our series, an overall clinical benefit rate of 74% was observed with chemotherapeutic agents, even though the current systemic treatment for KS revolves around liposomal anthracyclines and paclitaxel. Neither ART nor liposomal anthracyclines are standard treatment in the public health sector. The absence of ART is reflected in the overall survival of AIDS-related KS patients, with a median overall survival of 8.8 months (range 1 - 31 months).



The absence of improved survival rates for AIDS-related KS patients is generally attributed to the decline in CD4+ count. Chemotherapy can deplete CD4+ counts by up to 50% independent of HIV and thus limit the CD4+ protective effect of ART.[12] This study showed a decline of 18.8% in the CD4+ count from a mean of 172.8 cells/µl to a mean of 140.3 cells/µl.

In spite of significantly improved overall survival rates for patients with AIDS, the survival of patients with KS has remained poor. A European AIDS cohort study reported a median survival of 17 months for patients with KS.[13] Fernandez Guerrero *et al.*[9] reported that the median survival of patients with KS on ART was 49 months in comparison with 12 months for patients who did not receive ART. In our study 42% of patients are alive with a median survival of 11.2 months (range 2 - 49 months). Four patients with a median survival of 29.5 months are on ART. Fifty-eight patients (58%) died due to progression of their HIV and HIV-related illnesses, with a median overall survival of 8.8 months (range 1 - 31 months). Thirty-nine per cent of deaths were due to opportunistic infections: pneumonia, *C. neoformans* meningitis, systemic candidiasis and *M. tuberculosis*. Twelve patients died of progressive KS.

The high proportion of patients (61%) presenting with KS as their AIDS-defining illness reflects the ignorance and stigma about HIV/AIDS that still persist in communities. This emphasises the need for continuous education and information as a priority of HIV/AIDS prevention. Despite the high frequency of KS, the referral system seems inadequate as a limited number of patients are referred for treatment. Factors that could account for this include physician perception of the disease, or patients with poor performance status and advanced disease at presentation.

Survival rates are still failing to improve among our patients owing to advanced disease, accompanied by opportunistic infections, and the absence of ART. However, symptomatic relief and an improved quality of life can still be offered to a patient population that largely remains marginalised.

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