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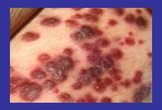
Determinants of Mortality and Disease Progression of Kaposi Sarcoma in a Primary Care ART Programme in Khayelitsha, South Africa



Kathryn Chu [1], Gcina Mahlangeni [1], Sarah Swannet [1], Nathan Ford[1,2], David Stead [1], Andrew Boulle [2] & Gilles Van Cutsem [1,2]

1. **Médecins Sans Frontières**
Cape Town, South Africa
Ph: +27-21-364 5490
Fx: +27-21-361 7051
gillesvancutsem@gmail.com
www.msf.org.za

2. **University of Cape Town**
School of Public Health and Family Medicine
Ph: +27-21-406-6711
andrew.boulle@uct.ac.za
www.ideu.uct.ac.za

ABSTRACT

Background: Kaposi Sarcoma (KS) is the most common HIV-related malignancy. In the developed world, antiretroviral therapy (ART) appears to influence the clinical course of AIDS related KS; partial and complete regressions have been widely reported. Little is known about the evolution of KS on ART in poor resource settings.
Methods: We conducted a retrospective study of patients with KS enrolled on ART in a primary care setting (Khayelitsha Township, South Africa) between May 2001 and January 2007. Site of lesion, grading, treatment, and outcomes on ART are described. Logistic regression was used to model determinants of mortality and disease progression on ART.
Results: Of 15,000 adults enrolled into HIV care in Khayelitsha during the study period, 214 (1.4%) had KS. A folder review was done for 188 (88%) of these patients. Median age was 34 years, median baseline CD4 count 73 cells/µl (IQR, 26-171) and the majority (60%) were female. The most common sites of lesions were oral (65%) and the lower extremities (56%); 124 (69%) had T1 and 148 (82%) S1 disease. Forty-five (24%) patients were not treated and 70 (37%) were treated with ART alone. Of the 86 patients referred for further treatment, 55 (64%) received chemotherapy, 45 (51%) received radiotherapy, and 2 (2%) underwent surgery. Seven (5%) of 137 developed symptoms of KS immune reconstitution syndrome on ART. KS outcome data was available for 94 patients (50%). Of these, 18 (19%) had complete remission of lesions, 43 (46%) had partial improvement, 8 (8%) had no change in lesions, and 25 (26%) had progressive disease. Sixty-six (35%) patients had died, 47 (25%) were lost to follow-up, 9 (5%) were transferred out, and 62 (33%) were alive and in care at the end of the study. In multivariate analysis, stage T1 and S1 disease were associated with mortality (OR respectively 7.4, p<0.001 and 18.6, p=0.007) and disease progression (OR 20.7, p=0.011 and 10.1, p=0.037). Chemotherapy was associated with a decreased risk of death (OR 0.3, p=0.027) and disease progression (OR 0.4, p=0.129).
Conclusions: The prevalence of KS among patients starting ART in Khayelitsha was low. However, despite the advent of ART and other treatments for KS, mortality remained very high (60% if losses to follow-up are counted as dead). Loss to follow-up before and after initiating treatment was high. The major risk factors for mortality and disease progression were advanced (T1 or S1) disease. Chemotherapy was associated with a 70% (95% CI 10-90%) reduction in mortality. Improved studies on the effectiveness of accessible chemotherapy regimens and related side-effects in resource-limited settings are needed. Efforts to improve retention in care for patients with KS are also needed.

Background & Setting

- Kaposi Sarcoma (KS) is the most common HIV-related malignancy and is associated with a fourfold increase in mortality of patients on antiretroviral therapy (ART) in Khayelitsha. Little is known about the evolution of KS on ART in poor resource settings.

- Khayelitsha Township is situated 30 km from the city of Cape Town and has a population of more than 500,000, of which the majority lives in informal housing, is very poor and unemployed.
- Prevalence of HIV in adults is 33% and incidence of tuberculosis is above 1600/100,000 per year, one of the highest in the world.
- Delivery of ART at primary care was initiated by MSF in 2001, in collaboration with Provincial health authorities.
- All patients are initiated on a standardized first line regimen of stavudine, lamivudine, and nevirapine. In case of contra-indications zidovudine, tenofovir, and efavirenz can be used. The standard second-line regimen is zidovudine, didanosine, and lopinavir/ritonavir.
- Kaposi Sarcoma is an indication for rapid initiation on ART; patients with stage T1 and/or S1 are referred to tertiary hospital for assessment of need for chemo- and/or radiotherapy.
- The objectives of this study were to describe baseline characteristics, management, outcomes and determinants of mortality and disease progression of patients with Kaposi Sarcoma.

Methods

- HIV infected individuals with Kaposi Sarcoma and older than 18 years who were enrolled in one of three primary care ART clinics in Khayelitsha, South Africa, between May 2001 and January 2007 were included.
- Database and chart reviews from primary and tertiary care were conducted to describe site of lesion, grading according to the AIDS Clinical Trials Group classification, treatment, and outcomes.
- Logistic regression was used to model determinants of mortality and disease progression of patients on ART.

Baseline Characteristics of Patients with Kaposi sarcoma

Table 1: Patient characteristics at baseline

	n=188
Men	76 (40.4%)
Baseline age, years	34 (29-41)
Baseline CD4+ count, cell/µl	73 (26-171)

Continous variables are given as medians (interquartile range).
Ordinal and discrete variables are given as n(%). ART, antiretroviral therapy.

Table 2: Staging of KS Lesions

	n=180
T0	56 (31.1%)
T1	124 (68.9%)
S0	32 (17.8%)
S1	148 (82.2%)

- Kaposi sarcoma was diagnosed in 214 (1.4%) of approximately 15,000 patients enrolled on HIV care
- Of these, 88% (188/214) clinical charts were reviewed.
- 136 (72%) of reviewed patients were started on ART, representing 2.2% of the 6292 patients started on ART during the study period.
- Most patients presented with advanced disease; 105 (58%) patients were staged T1S1 at presentation.

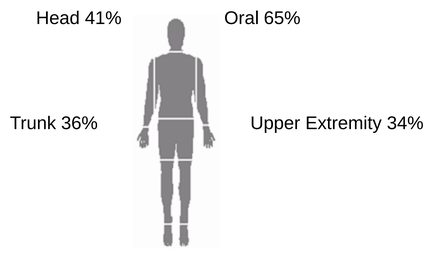
Location of Lesions

Table 3: Site of KS Lesions

	n=188
Disseminated Cutaneous Lesions	72 (38.3)
Site of Lesions	
Oral	122 (64.9)
Head	78 (41.5)
Trunk	68 (36.2)
Upper Extremity	63 (33.5)
Lower Extremity	105 (56.2)
Lymphadenopahthy	42 (22.3)
Lymphoedema	42 (22.3)
Gastrointestinal	4 (2.1)
Lung**	37 (19.7)

*Total more than 188 as each patient could have more than one lesion

- The majority had oral lesions
- Pulmonary KS was suspected in 20%.



Types of Treatment of Kaposi Sarcoma

Table 4: Treatment of Kaposi's Sarcoma

	n=188
No treatment	45 (23.9%)
Antiretroviral Therapy Only	70 (37.2%)
Chemotherapy	55 (29.3%)
Bleomycin	28 (50.9%)
Adriamycin	29 (52.7%)
Vincristine	28 (50.9%)
Vinblastine	26 (47.3%)
Radiotherapy	45 (23.9%)
Surgery	2 (1.1%)

- The majority of patients (136, 72.3%) were treated with ART.
- 55 (29.3%) received chemotherapy
  - 26 (47.3%) received bleomycin, vincristine, and adriamycin.
  - 24 (43.6%) received vinblastine monotherapy
- Of the 45 patients who were never started on ART, 39 (86.7%) were poor risk (stage T1 and/or S1); 2 were transferred out, 13 (30%) died and 27 (63%) were lost to follow-up.
- Out of 55 patients who were treated with chemotherapy, 27 (49.1%) also received radiotherapy.
- Of the 2 patients who underwent surgery, one received chemotherapy and both received radiotherapy.

Kaposi Sarcoma Treatment Outcomes

Table 5: Evolution of Kaposi Sarcoma

	n=94
Complete remission of lesions	18 (19.2%)
Partial Improvement	43 (45.7%)
No change in lesions	8 (8.5%)
Progessive disease	25 (26.6%)

Table 6: Outcomes of Patients with KS

	n=184
Alive and in care	62 (33.7%)
Dead	66 (35.8%)
Lost to Follow-up	47 (25.6%)
Transferred Out	9 (4.9%)

Ordinal and discrete variables are given as n(%)

- 61 (65%) patients improved on treatment whilst 33 (35%) were stationary or progressed.
- More than one third of patients were confirmed dead and more than 25% were lost to follow-up by the end of this study.

Determinants of Mortality and Disease Progression

Table 7: Determinants of Mortality in patients on ART

	Unadjusted			Adjusted		
	OR	95% CI	p	OR	95% CI	p
Age, years	1.0	(0.9-1.0)	0.234	1.0	(0.9-1.0)	0.766
Male	1.2	(0.6-2.3)	0.691	1.4	(0.5-3.4)	0.521
Baseline CD4 count<50 cell/µl	2.2	(1.1-4.5)	0.029	1.5	(0.6-3.7)	0.348
T1 stage (versus T0 stage)	3.8	(1.6-9.0)	0.003	7.4	(2.4-22.8)	<0.001
S1 stage (versus S0 stage)	20.2	(2.6-154.0)	0.004	18.6	(2.2-155.7)	0.007
ART only	1.3	(0.7-2.5)	0.477			
Chemotherapy	0.6	(0.3-1.3)	0.230	0.3	(0.1-0.9)	0.027
Radiotherapy	1.0	(0.5-2.1)	0.971	1.2	(0.5-3.1)	0.7

Table 8: Determinants of Disease Progression in patients on ART

	Unadjusted			Adjusted		
	OR	95% CI	p	OR	95% CI	p
Age, years	1.0	(0.9-1.1)	0.698	1.0	(0.9-1.1)	0.850
Male	0.5	(0.2-1.2)	0.105	0.5	(0.2-1.8)	0.332
Baseline CD4 count<50 cell/µl	1.6	(0.6-4.1)	0.327	1.1	(0.3-3.5)	0.872
T1 stage (versus T0 stage)	10.3	(1.3-81.8)	0.028	20.7	(2.0-213.7)	0.011
S1 stage (versus S0 stage)	10.3	(1.3-81.8)	0.028	10.1	(1.1-89.2)	0.037
ART only	1.8	(0.7-5.0)	0.250			
Chemotherapy	0.8	(0.3-1.9)	0.591	0.4	(0.1-1.3)	0.129
Radiotherapy	0.7	(0.3-1.7)	0.400	0.7	(0.2-2.0)	0.479

ART, antiretroviral therapy.

- Advanced disease (stage T1 and S1) was significantly associated with mortality and disease progression.
- Addition of chemotherapy to ART was independently associated with a 70% (95% CI, 10-90%) decrease in mortality.

Discussion and conclusions

- The prevalence of diagnosed KS among patients starting ART in Khayelitsha was low. However, the high proportion of high risk disease (T1S1) could be explained by a combination of late presentation and under-diagnosis of low risk disease.
- Despite the advent of ART and the availability of chemo- and radiotherapy mortality remained high.
- Loss to follow-up before and after initiation of treatment was higher than in non-KS HIV-infected patients.
- The major determinant for mortality and disease progression was advanced disease (stage T1 or S1), with systemic symptoms (stage S1) being associated with higher mortality and stage T1 with increased disease progression.
- Addition of chemotherapy to ART was independently associated with a 70% decrease in mortality.
- Improved studies on the effectiveness of accessible chemotherapy regimens and related side-effects in resource-limited settings are needed.
- Efforts to improve early diagnosis and retention in care for patients with KS are also needed.