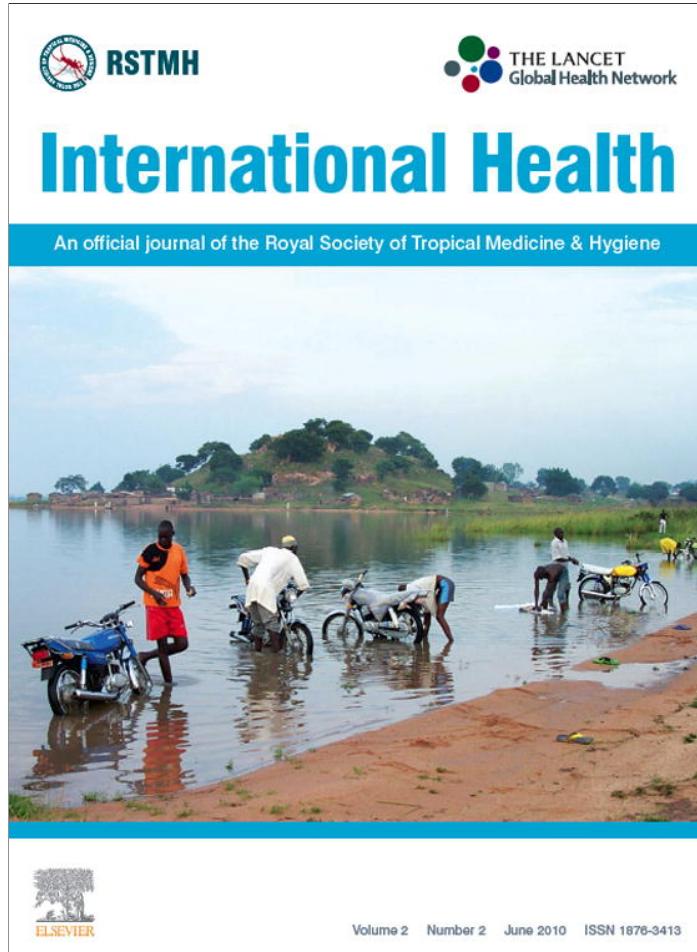


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Risk factors for mortality in AIDS-associated Kaposi sarcoma in a primary care antiretroviral treatment program in Malawi

Kathryn Chu^{a,b,*}, Dalitso Misinde^c, Moses Massaquoi^c, Olesi Pasulani^c, Beatrice Mwagomba^d, Nathan Ford^a, Rony Zachariah^e

^a Médecins Sans Frontières, 49 Jorissen St, Braamfontein 2017, Johannesburg, South Africa

^b Department of International Health, Johns Hopkins M, Baltimore, MD, USA

^c Médecins Sans Frontières, Thyolo, Malawi

^d Ministry of Health, Thyolo, Malawi

^e Médecins Sans Frontières, Medical Department, (Operational Research Unit), Brussels, Belgium

ARTICLE INFO

Article history:

Received 19 November 2009

Received in revised form 25 February 2010

Accepted 7 April 2010

Keywords:

AIDS
Kaposi sarcoma
mortality
risk factors
Africa

ABSTRACT

AIDS-associated Kaposi sarcoma (AIDS-KS) is the most common HIV-related malignancy. The majority of cases are found in sub-Saharan Africa. This retrospective cohort study describes characteristics of patients with AIDS-KS and factors associated with mortality in an antiretroviral treatment (ART) program in rural Malawi. Of 11 122 patients enrolled on ART, 830 (7%) had AIDS-KS. Patients with AIDS-KS were more likely to be lost to follow-up (22% versus 14%, $P < 0.001$) and showed a higher mortality (22% versus 10%, $P < 0.001$) compared to patients without AIDS-KS. A CD4 count <150 cells/ μ l, advanced stage AIDS-KS, and absence of bleomycin chemotherapy were associated with increased mortality. Earlier diagnosis and improved treatment of AIDS-KS are urgently needed in order to reduce mortality.

© 2010 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.

1. Introduction

AIDS-associated Kaposi sarcoma (AIDS-KS) is the most common HIV-related malignancy. The majority of cases are found in sub-Saharan Africa, where the disease is associated with increased mortality.^{1,2} However, there is a dearth of published information on risk factors associated with mortality among AIDS-KS patients.

In the developed world, treatment with highly active antiretroviral therapy (HAART) has led to a sharp decline in the incidence of AIDS-KS³ and to increased survival.⁴ HAART can result in regression and even complete remis-

sion of KS lesions.⁵ Unfortunately HAART is still not widely available in the developing world where AIDS-KS mortality remains high.² Moreover, in many settings KS is a visible and potentially stigmatising sign of AIDS that is known to the community. In this respect, KS-related mortality may undermine public health objectives by supporting the notion that, despite substantial advances, AIDS is still a death sentence.

Data from resource-rich settings suggest that adjuvant systemic chemotherapy can improve outcomes in advanced cases, and newer chemotherapeutic agents such as liposomal anthracyclines and taxanes have improved efficacy and tolerability compared to older drugs such as bleomycin, doxorubicin, vincristine, vinblastine, or Adriamycin.⁶ Unfortunately, these medications are rarely available in sub-Saharan Africa, mainly because of their high cost.

* Corresponding author at: Unit 23B, No 14, Waverly Business Park, Wyecroft Road, Mowbray 7700, Cape Town, South Africa.
Tel.: +27 79 895 2489; fax: +27 21 448 3128.

E-mail address: kathryn.chu@joburg.msf.org (K. Chu).

In this retrospective study we describe characteristics of patients with AIDS-KS and risk factors associated with mortality within a routine HIV/AIDS care program in Thyolo, rural Malawi.

2. Methods

Thyolo District Hospital in southern Malawi has a catchment area of about 500 000 people. HIV-positive patients are managed by Médecins Sans Frontières (MSF) and the Ministry of Health as described before.⁷ All patients starting HAART from the beginning of the program in April 2003 to June 2009 were included in this study.

Initial KS stage was determined using the AIDS Clinical Trials Group staging system which classifies tumor (T), immune (I), and systemic illness (S) into good and poor risk. Immune status was subsequently dropped following a study that found it not to be a good predictor of outcome.⁸ T0 disease was defined as <10 cutaneous lesions and one or fewer oral lesions and T1 disease as >10 cutaneous lesions and/or extensive oral or visceral disease. S0 disease was defined as no history of opportunistic infections, no B symptoms (unexplained night sweats or fever), and a Karnofsky score >70%. S1 disease was defined as history of opportunistic infection, B symptoms, or a Karnofsky score <70%. Patients with T1S1 were considered to have advanced disease. In 2004, bleomycin became available in Malawi for treatment of AIDS-KS patients with T1 disease and this was provided per protocol (15 mg intramuscular injections every two weeks for 10 cycles, then for an additional 10 cycles if there was no improvement).

Information on baseline characteristics, ART, mortality, loss-to-follow-up (LTFU), AIDS-KS diagnosis, KS staging, and chemotherapy were extracted from an electronic database maintained for routine monitoring and evaluation. Baseline characteristics were described using medians and interquartile ranges (IQRs) for continuous variables and counts and percentages for categorical data. Patient time to loss to follow up was calculated from date of HAART initiation. Outcomes were censored on 1 July 2009. Differences between groups were compared using the χ^2 test for categorical variables and the Student t-test for continuous variables. Cox proportional hazards were used to identify risk factors for mortality in AIDS-KS patients. Kaplan-Meier analysis was used to estimate cumulative survival for patients with and without AIDS-KS. Variables

considered in the analysis included age, gender, baseline CD4 count (less or greater than 150 cells/ μ l), KS stage, and use of bleomycin chemotherapy. Factors with a $P < 0.1$ on univariate analysis were included in a multivariate model. All tests and confidence intervals were considered to be significant at a $P \leq 0.05$. All statistical analysis was performed using STATA 10 (College Station, TX, USA).

2.1. Ethics

The study received ethical approval from the Ethics Review Board, Médecins Sans Frontières, Geneva, Switzerland.⁹

3. Results

Of 11 122 patients enrolled on ART during the study period, 830 (7%) had AIDS-KS. Baseline characteristics for patients with and without AIDS-KS are shown in Table 1. The median follow-up for AIDS-KS patients was 397 days (IQR, 118–868) compared to 569 days (IQR, 169–1043) for non-AIDS-KS patients ($P < 0.001$). A greater proportion of AIDS-KS patients were deceased (19%, $n = 161$) and lost to follow-up (16%, $n = 136$) at one year compared to non-AIDS-KS patients (8%, $n = 855$, $P < 0.001$ and 9%, $n = 904$, $P < 0.001$ respectively). Of deaths and LTFU in the first year, 56% occurred in the first three months. Cumulative survival of patients with and without AIDS-KS is shown in Figure 1.

Of those with AIDS-KS, 396 (47%) had advanced (T1S1) disease and 636 (77%) received bleomycin chemotherapy. A CD4 count ≤ 150 cells/ μ l (adjusted HR (AHR) = 1.3, $P = 0.053$), advanced stage KS (AHR = 1.8, $P = 0.002$) and lack of treatment with bleomycin chemotherapy (AHR = 2.0, $P = 0.001$) were associated with increased mortality (Table 2).

4. Discussion

We report on a large series of AIDS-KS patients from a primary care HAART program in Malawi. Overall, the proportion of patients with AIDS-KS that died or were lost to follow up was significantly higher than those without AIDS-KS. It can be expected that the higher lost to follow up is associated with higher mortality, as a tracing study from Malawi demonstrated that 50% patients LTFU in HAART programs had died, most (58%) within the first three months.¹⁰ In sub-Saharan Africa, despite the intro-

Table 1

Characteristics of patients with and without Kaposi sarcoma on antiretroviral therapy in Thyolo, Malawi.

	KS $n = 830$	non-KS $n = 10292$	P value*
Males	485 (58)	3884 (38)	0.001
Age on starting ART, years	33 (28–39)	33 (27–40)	0.696
Median baseline CD4+ count, cell/ μ l	136 (56–243)	147 (70–248)	<0.001
Median follow-up time, days	397 (118–868)	569 (169–1043)	<0.001
Deaths	182 (22)	1028 (10)	<0.001
Lost to follow-up	185 (22)	1427 (14)	<0.001

KS: Kaposi sarcoma. ART: antiretroviral therapy.

Continuous variables are given as medians (interquartile range). Ordinal and discrete variables are given as n (%).

* χ^2 for categorical variables and Wilcoxon rank-sum test for continuous variables.

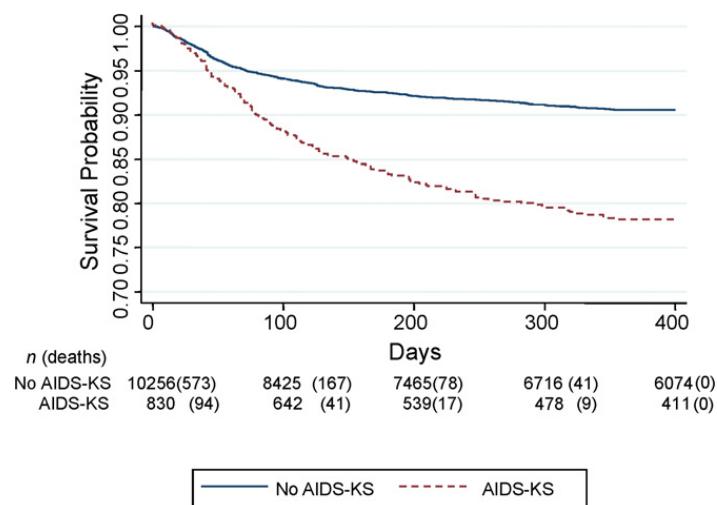


Figure 1. Cumulative survival in patients with and without AIDS-KS.

Cumulative survival in patients with AIDS-KS is lower than those without AIDS-KS. The number at risk at each time point is displayed with the corresponding number of deaths.

duction of HAART, AIDS-KS remains associated with higher mortality.² Contributing factors likely include late diagnosis of KS disease, late access to HAART, and poor availability of chemotherapy. Earlier HIV diagnosis and HAART initiation, and improved retention in care, especially for patients with AIDS-KS, are needed.

Nearly half of the AIDS-KS patients in our study presented with advanced stage KS (T1S1), with corresponding high mortality. Other studies have also demonstrated that patients with advanced KS have a poorer prognosis.¹¹ Lower baseline CD4 was also associated with increased mortality, again pointing to the need for earlier enrolment into HIV care and therefore earlier diagnosis of KS. If AIDS-KS can be detected early in the community and patients come forward for HIV testing and care, the prognosis is likely to improve. The earliest signs of KS which can be

easily diagnosed by patients, family relatives or community volunteers include violet discolouration or plaques in the oral cavity or skin. Individuals could be screened for such a condition at the community level and immediately referred to health facilities for appropriate care as has been suggested recently.¹² Increasing awareness through specific information and education campaigns focused on early recognition of KS at community level would also be helpful.

Our HAART program enrolled more women which reflects the general trend that uptake of HIV services by men is poor.¹³ However, men were more likely to have AIDS-KS than women which is consistent with other studies¹⁴ probably in part because men tend to be diagnosed and treated for HIV at a later stage when prevalence of opportunistic infections is higher. There is a need to increase uptake of services in this vulnerable population.

Table 2
Associations with mortality in AIDS-KS patients.

	Deaths/Total	%	Unadjusted			Adjusted		
			HR	95% CI	P	HR	95% CI	P
Gender								
Female	77/345	(22)	1.00					
Male	175/797	(21)	0.98	(0.73–1.31)	0.876			
Age								
≤18 years	6/33	(18)	1.00					
>18 years	175/797	(22)	0.99	(0.98–1.01)	0.600			
Baseline CD4 count								
>150 cells/ μ l	86/457	(19)	1.0					
≤150 cells/ μ l	95/373	(25)	1.4	(1.0–1.9)	0.029	1.3	(0.99–1.8)	0.053
KS Stage								
Unstaged	48/147	(33)						
T0S0	6/54	(11)	1.0					
T0S1	6/42	(14)	1.4	(0.5–4.4)	0.548			
T1S0	21/191	(11)	1.0	(0.4–2.5)	0.999			
T1S1	100/396	(25)	2.4	(1.1–5.6)	0.034	1.8	(1.2–2.5)	0.002
Bleomycin Chemotherapy								
Yes	132/636	(21)	1.0					
No	49/194	(25)	1.4	(1.0–2.0)	0.032	2.0	(1.4–3.1)	0.001

KS: Kaposi sarcoma. HR: Hazards Ratio.

Chemotherapy has been demonstrated to improve outcomes for patients with advanced AIDS-KS. Liposomal drugs, the backbone of treatment of advanced AIDS-KS in Western settings, are not readily available in sub-Saharan Africa. In our cohort, monotherapy with bleomycin decreased mortality by half suggesting that although this regimen is old, it can still be effective. However, mortality was still high. Currently, studies on efficacy and safety are underway comparing older regimens to newer taxane-based therapies in sub-Saharan Africa. Improving access to more effective adjuvant chemotherapy that can be administered safely in resource poor settings is a priority for reducing KS mortality.

Our study had several limitations. Patients with KS were identified through an electronic database used for routine monitoring and evaluation. Using this methodology, we may have underestimated the number of cases, especially those with early or small lesions. The relatively high lost to follow up and the known high mortality among patients who are lost to care suggest that our mortality estimate is likely to be underestimated. A considerable proportion of patients were also not staged. In addition, the effects of bleomycin therapy and HAART on the change in KS lesions were not analyzed. Further studies are needed to determine the efficacy and safety of currently available therapies on KS disease progression.

Nevertheless, in one of the largest case series of AIDS-KS patients reported in the literature to date, we find that patients tend to present with advanced KS disease and face high mortality despite starting HAART and receiving bleomycin. This points to an urgent need for early diagnosis of HIV, KS and improved treatment of AIDS-KS in an effort to reduce mortality.

Authors' contributions

KC was responsible for the overall design, analysis, and writing of the paper. DM, OP, and MM contributed to the data analysis and interpretation. NF, RZ, and BM contributed to the design of the study and drafting of the manuscript. All authors were involved in critically reviewing the manuscript for its intellectual content and approved the final version. KC is guarantor of the paper

Funding: None.

Conflicts of interest: None declared.

Ethical approval: The study received ethical approval from the Ethics Review Board, Médecins Sans Frontières, Geneva, Switzerland.

References

- Agaba PA, Sule HM, Ojoh RO, Hassan Z, Apena L, Mu'azu MA, et al. Presentation and survival of patients with AIDS-related Kaposi's sarcoma in Jos, Nigeria. *Int J STD AIDS* 2009;20:410–3.
- Makombe SD, Harries AD, Yu JK, Hochgesang M, Mhango E, Weigel R, et al. Outcomes of patients with Kaposi's sarcoma who start antiretroviral therapy under routine programme conditions in Malawi. *Trop Doct* 2008;38:5–7.
- Jones JL, Hanson DL, Dworkin MS, Jaffe HW. Incidence and trends in Kaposi's sarcoma in the era of effective antiretroviral therapy. *J Acquir Immune Defic Syndr* 2000;24:270–4.
- Tam HK, Zhang ZF, Jacobson LP, Margolick JB, Chmiel JS, Rinaldo C, et al. Effect of highly active antiretroviral therapy on survival among HIV-infected men with Kaposi sarcoma or non-Hodgkin lymphoma. *Int J Cancer* 2002;98:916–22.
- Murdaca G, Campelli A, Setti M, Indiveri F, Puppo F. Complete remission of AIDS/Kaposi's sarcoma after treatment with a combination of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. *Aids* 2002;16:304–5.
- Di Lorenzo G, Konstantinopoulos PA, Pantanowitz L, Di Trolio R, De Placido S, Dezube BJ. Management of AIDS-related Kaposi's sarcoma. *Lancet Oncol* 2007;8:167–76.
- Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. *Aids* 2006;20:2355–60.
- Nasti G, Talamini R, Antinori A, Martellotta F, Jacchetti G, Chiodo F, et al. AIDS-related Kaposi's sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart Era—the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naïve From Antiretrovirals. *J Clin Oncol* 2003;21:2876–82.
- Schopper D, Upshur R, Matthys F, Singh JA, Bandewar SS, Ahmad A, van Dongen E. Research ethics review in humanitarian contexts: the experience of the independent ethics review board of Médecins Sans Frontières. *PLoS Med* 2009;6:e1000115.
- Yu JK, Chen SC, Wang KY, Chang CS, Makombe SD, Schouten EJ, Harries AD. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. *Bull World Health Organ* 2007;85:550–4.
- 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;22:399–402.
- Zachariah R, Ford N, Philips M, Lynch S, Massaquoi M, Janssens V, et al. Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. *Trans R Soc Trop Med Hyg* 2009;103:549–58.
- Mills EJ, Ford N, Mugenyi P. Expanding HIV care in Africa: making men matter. *Lancet* 2009;374:275–6.
- Meditz AL, Borok M, MaWhinney S, Gudza I, Ndemera B, Gwanzura L, et al. Gender differences in AIDS-associated Kaposi sarcoma in Harare, Zimbabwe. *J Acquir Immune Defic Syndr* 2007;44:306–8.