**Effect of Highly Active Antiretroviral Therapy on Survival in Patients With AIDS-Associated Pulmonary Kaposi's Sarcoma Treated With Chemotherapy**

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**Purpose:** Kaposi's sarcoma (KS) is the most common AIDS-related malignancy. Pulmonary involvement by KS (PKS) has carried a poor prognosis with median reported survival ranging from 3 to 10 months. We studied whether the introduction of highly active antiretroviral therapy (HAART; triple antiretroviral therapy including a protease inhibitor and two reverse transcriptase inhibitors) has been associated with improved survival for AIDS patients with PKS.

**Patients and Methods:** A retrospective study was performed of 37 consecutive patients with PKS and human immunodeficiency virus infection in the tumor registry at a large municipal hospital in New York City between 1994 to 1997. There were 16 patients from 1994 to 1995 (pre-HAART period) and 21 patients from 1996 to 1997 (post-HAART period). The primary end point was survival, which was defined as time from start of chemotherapy until death from any cause.

**Results:** Patients were analyzed by the date of diagnosis (pre-HAART period) and whether or not they received HAART. Kaplan-Meier analysis showed significantly better survival in patients diagnosed in the post-HAART period ($P = .0025$). Additional Kaplan-Meier analysis indicated that patients on HAART had substantially better survival ($P < .0001$). Cox multivariate analyses showed that HAART therapy was associated with a reduced risk of death (hazard ratio = 0.09; 95% confidence interval, 0.03 to 0.69).

**Conclusion:** In patients with AIDS-associated PKS and undergoing chemotherapy, administration of HAART was associated with increased survival.


Kaposi's sarcoma (KS) is the most common tumor in patients with human immunodeficiency virus (HIV) infection, associated with significant morbidity and mortality, especially in patients with systemic disease. There is a 1,000-fold increase in risk of developing KS in patients infected with HIV. It is reported as the initial AIDS-defining illness in approximately 10% to 20% of cases.1,2

The introduction of highly active antiretroviral therapy (HAART) using a protease inhibitor with two reverse transcriptase inhibitors has shown to reduce the risk of death in patients with HIV infection.4,5 Several investigators have reported a decline in the proportion of persons presenting with KS as an AIDS-defining condition.3,6

Although skin and mucous membranes are the typical sites for presentation for KS, nearly half will have systemic disease with involvement of multiple visceral sites. Pulmonary involvement has been reported in approximately 10% of all AIDS patients and up to 25% of patients with cutaneous KS,7 although the incorporation of HAART in the management of HIV has decreased the incidence of pulmonary KS (PKS).7,8

PKS is the most serious form of KS, with a high fatality rate, and before the advent of HAART, median survival time was reported in the range of 3 to 10 months.9-13 Systemic chemotherapy is the standard treatment for these patients, who often have rapidly progressive pulmonary disease.10 In the 1980s and early 1990s, the most widely used combination chemotherapy regimen for PKS was doxorubicin, bleomycin, and vincristine or vindesine (ABV), with a response rate between 30% and 50% and a median survival of 12 months.10 Because of their efficacy and favorable toxicity profile, liposomal anthracyclines have recently gained favor in the treatment of PKS.14,15 Regardless of the chemotherapy agents used, in the era before HAART, median survival for responders was less than 12 months.
We recently reported a series of six patients with PKS who achieved a clinical remission and prolonged survival after treatment with induction chemotherapy and prolonged HAART maintenance. Chemotherapy in these patients was terminated after induction of clinical remission as evaluated by computed tomography scan and once their viral load was undetectable, suggesting improved immune status. Other investigators have reported similar results of HAART on KS.

Here we report the results of a retrospective analysis of all cases of PKS diagnosed and treated at Bellevue Hospital, a large public medical center in New York City, from 1994 to 1997. The objective of our study is to assess whether outcome for patients with PKS changed with the advent of HAART therapy.

**PATIENTS AND METHODS**

This retrospective study was conducted after obtaining approval from the institutional review board. We reviewed the tumor registry of Bellevue Hospital to identify all cases diagnosed with PKS during the period from 1994 to 1995 (pre-HAART) and 1996 to 1997 (post-HAART). This study reports on 37 consecutive patients with HIV infection and PKS registered in the tumor registry. Five patients did not have complete data or did not receive chemotherapy and were thus excluded from analysis. Characteristics of the 32 patients with complete data are listed in Table 1. There was no significant difference in the demographic characteristics of the study population. All patients were male. Ethnic background and CD4 counts before therapy in both groups were comparable. All patients in the pre-HAART era were treated with some form of standard antiretroviral therapy.

The primary end point of the study was survival, which was defined as the time from the start of chemotherapy until death from any cause. The times to death were analyzed using a two-sided log-rank test. The Kaplan-Meier method was used to construct plots of the probability of survival for patients based on the year of diagnosis or the use of HAART as the group variable.

Multivariate analyses were based on the Cox proportional hazards model for the length of time from start of chemotherapy to death from any cause. The following predictors of time to death were evaluated in stepwise regression analyses as follows: HAART therapy (ever v never); CD4 cell count at the start of chemotherapy (< 100 v ≥ 100); liposomal anthracycline therapy (ever v never); age at diagnosis of PKS (years); and race (white, black, Asian, and Hispanic). Note that HIV RNA level was not included as a covariate because these data were not available for PKS patients diagnosed before 1995. Some reports suggest that the viral load correlates with the CD4 count.

Multivariate analyses were also conducted with the use of exact logistic regression to model the proportion of patients who were alive at the end of follow-up. The results of these analyses were consistent with the results of the Cox model and are, therefore, not presented here. All reported P values are two-sided.

**RESULTS**

At our institution, HAART therapy became widely available in 1996. Thus, the patients were divided according to the year of diagnosis into two groups, 1994 to 1995 (pre-HAART period) and 1996 to 1997 (post-HAART period). Kaplan-Meier analysis of the two groups (Fig 1A)
showed substantially better survival in the post-HAART group ($P = .002$). The estimated median survival was 8.9 weeks (95% CI, 2.4-15.3 weeks) in the pre-HAART period. The median survival could not be estimated in the post-HAART period because the estimated survival function was greater than 0.5 for all $t$.

Some of the patients diagnosed in 1996 to 1997 did not receive HAART. In addition, one patient in the 1994 to 1995 period received HAART as part of a clinical trial. Thus, the survival was analyzed according to whether or not they received HAART (HAART $v$ no HAART). Kaplan-Meier analysis (Fig 1B) showed significantly better survival in the HAART group ($P < .001$). The estimated median survival time for the no HAART group was 13.0 weeks (95% CI, 4.0 to 22.0 weeks). The median survival could not be estimated for the HAART group.

In the multivariate analysis, only HAART was an independent predictor of survival (Table 2). Patients on HAART had a risk of death that was 0.09 times that of the subjects who were not on the therapy (95% confidence interval, 0.02 to 0.41). Liposomal anthracycline treatment, which was a predictor in the univariate analysis, was not independently predictive after adjustment for HAART, possibly because of the strong association between these two variables. In an analysis that included only those patients who received liposomal anthracycline, HAART was also a significant predictor of survival (relative risk, 0.12; 95% confidence interval, 0.02 to 0.57). Kaplan-Meier analysis of this subset of patients also demonstrated significantly better survival in the HAART group ($P < .001$) (data not shown). None of the other factors described in Patients and Methods was found to be a predictor of survival in either the univariate or multivariate analyses.

**DISCUSSION**

This study reports on a cohort of patients with PKS who were treated with chemotherapy concurrently with HAART and have achieved long-term survival. Anecdotal experiences of HAART as the only treatment modality for KS have been reported in the literature, but no long-term survival of patients with PKS has so far been reported. From our analysis, the HAART regimen is a strong independent predictor of survival.

Results of this study supplement the experiences of other investigators that adequate control of HIV disease may result in regression of malignant processes in patients with AIDS-associated malignancies. Dupin et al. reported five patients with PKS who were treated with HAART therapy concurrently with chemotherapy. Four of the five patients had a response, and the median survival for the group was 15 months.

In our study, 90% of the patients in the pre-HAART period died of progressive pulmonary KS, which is in agreement with published data, as compared with 47% in the post-HAART period, showing a significantly improved overall survival (Fig 1A). We believe it is likely that HAART is responsible for the improved survival reported here for the following reasons. Further analysis of the study sample based on HAART treatment indicated significantly improved survival in those patients who received HAART (Fig 1B). It should be noted that in the post-HAART period, we do not have the information regarding the decision to use HAART. Thus, the HAART versus no HAART comparison may introduce a bias. However, we have not been able to detect any differences in the patient characteristics we recorded among the patients in the 1996 to 1997 period between those who did versus those who did not receive HAART.

In addition, the use of liposomal anthracyclines preceded the introduction of HAART at our institution by several months, and thus, HAART use correlated with liposomal anthracycline use. HAART remained a strong predictor of survival in the patients who received liposomal anthracyclines (see Results). Thus, taken together, these data suggest that HAART is responsible for the improved survival reported here.

It is to be noted that both cohorts of patients were severely immunocompromised, with pretreatment CD4 counts of less than 100 cells/$\mu L$ in more than 90% of the patients. Because the efficacy of chemotherapy regimens used and the demographic data in both the cohorts are comparable, the only significant variable is the treatment of HIV with HAART.

Newer antiretroviral regimens have clearly improved the control of HIV disease and incidence of Kaposi’s sarcoma in HIV population. Our report complements yet another positive impact of HAART in HIV patients and suggests that in the era of HAART, PKS is no longer a rapidly fatal disease and that prolonged survival is possible for the majority of patients.

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<th>Variable</th>
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<td>HAART</td>
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Abbreviation: CI, confidence interval.

*All other variables listed in Patients and Methods were not associated with an increased risk of death ($P > .10$).
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REFERENCES


