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Impact of Highly Active Antiretroviral Therapy in the Treatment of HIV-Infected Patients with Systemic Non-Hodgkin's Lymphoma

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Twenty cases of systemic non-Hodgkin's lymphoma (NHL) in HIV-infected patients were reviewed over a 10-year-period, divided into Group A, including 13 NHL cases treated before the highly active antiretroviral therapy (HAART) era, and Group B, including 7 patients who received HAART. A Kaplan–Meier survival curve was performed and log-rank was applied to assess statistical differences between the groups. In group A, the median CD4 count was 36 cells/mm^3. No complete remission was found. In group B, the median CD4 count was 137 cells/mm^3. Four patients (57.0%) are still alive and in complete remission. Group A had a median survival of 5 months and group B 31 months ($p = 0.0032$). Our results are in agreement with recent reports in that a higher CD4 count and better immune status achieved with HAART is predictive of a better outcome. We found that HAART in combination with chemotherapy improves overall survival of NHL patients without increasing adverse effects.

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It is clear that individuals who are immunosuppressed or suffer from immune dysregulation experience higher rates of cancer than expected. These populations include patients with inborn defects in immunity, organ transplant recipients, and HIV-infected individuals (1–3). Certain cancers occur more frequently in HIV-infected patients than in any other immunosuppression states. Kaposi's sarcoma (KS) has been associated with the AIDS epidemic since the first HIV cases were reported (1, 4, 5). HIV patients also present a 50-fold increase in the incidence of non-Hodgkin's lymphomas (NHL) (4–6). Other malignancies have also been reported to occur more often in HIV-infected individuals, although much less commonly than lymphoma or KS (1, 5). Therapy for HIV has improved in the past 10 years because of different combinations of drugs, particularly those including a protease inhibitor. The widespread use of the so-called HAART (highly active antiretroviral therapy) since 1996–1997 has resulted in a greater reduction in HIV viral load, fewer opportunistic infections, and reduced mortality compared with nucleoside analog therapy alone (5, 7–10). The US Centers for Disease Control and Prevention (CDC) reported that AIDS-related deaths decreased for the first time in 1996 (11). These changes in the AIDS epidemic are largely attributable to the effects of HAART (6, 9). The incidence rate of AIDS-related NHL has decreased with the use of HAART, particularly NHL of the primary central nervous system, but the magnitude of the decrease appears to be less than that observed in AIDS-associated opportunistic infections and KS (4). The aim of this study was to evaluate the impact of HAART on the response to treatment and overall survival in HIV-positive patients with systemic non-Hodgkin's lymphoma.

MATERIAL AND METHODS

We retrospectively reviewed the cases of systemic NHL in HIV-infected patients treated at Hospital São Paulo over a 10-year-period, from January 1990 to December 1999. Hospital São Paulo is a university hospital affiliated with the Federal University of São Paulo, Brazil. The medical charts of 20 HIV patients who developed NHL were reviewed and information on age at diagnosis, sex, CD4 count, NHL stage and chemotherapy used were retrieved.

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All tumor biopsies were reviewed by an experienced pathologist and were classified according to the WHO classification for NHL (12). All patients were staged prior to treatment, using the Ann Arbor staging system (13). The patients were treated with an anthracycline-based chemotherapy protocol with the exception of one patient with early-stage disease who received radiation therapy alone. The treatment protocols used were in accordance with a recent report on the treatment of aggressive NHL (14). Patients who died before the beginning of chemotherapy and AIDS-related primary central nervous system NHL cases were excluded from our analysis. The patients were divided into two groups (A and B), according to the use of HAART. Group A included 13 patients who used mono or dual antiretroviral therapy diagnosed between January 1990 and July 1997. One patient who received ritonavir along with AZT (zidovudine) and ddI (didanosine) was included in group A, since this drug combination is no longer considered effective when given without another protease inhibitor (15). Group B included 7 patients on a triple-drug regimen, including a protease inhibitor (HAART), diagnosed between August 1997 and November 1999. In group B a colony-stimulating factor was indicated when the absolute neutrophil count fell below 500 cells/mm^3 or, if there was any evidence of infection, when the absolute neutrophil count was below 1000 cells/mm^3. The response to chemotherapy was based on the International Workshop to standardize response criteria for NHL (16). Survival time was calculated from diagnosis to time of death, or to the date when the patient was last seen. Survival was estimated with the Kaplan–Meier method. Comparisons of survival were analyzed by using the log-rank test. The significance level used was 5%.

RESULTS

Table 1 shows the baseline characteristics of group A. The majority (92.0%) of patients were male with a median age of 36 years. The median CD4 lymphocyte count at NHL diagnosis was 36 cells/mm^3. Only five (38.0%) individuals were being treated with antiretrovirals, and discontinued them while receiving chemotherapy. Most of the patients in this group (85.0%) presented with diffuse, large B-cell lymphoma (DLCL). Chemotherapy was the treatment of choice for 12 patients (92.0%) and local radiation was used

Table 1

Clinical and laboratorial features of Group A

Patient #	Age/Sex	HIV therapy	CD4 count*	NHL diagnosis	Stage	LDH*	Chemotherapy/ Radiotherapy**	Follow-up
1	29/M	AZT ddI	23	DLCL Feb/96	IVB	365	CHOP	Dead 1 month
2	50/M	None	36	DLCL Dec/95	IVB	357	CHOP	Dead 2 months
3	32/F	None	15	DLCL Mar/95	IIA	348	Radiotherapy	Dead 3 months
4	28/M	None	129	DLCL May/95	IVA	400	ProMACE-CytaBOM	Dead 5 months
5	36/M	None	14	DLCL Dec/90	IVB	389	CHOP	Dead 11 months
6	32/M	None	36	BL July/96	IVB	354	CHOP	Dead 6 months
7	29/M	AZT ddI	110	DLCL July/96	IVB	700	CHOP IT Chemo	Dead 8 months
8	42/M	None	40	DLCL Aug/94	IVB	633	CHOP IT Chemo	Dead 8 months
9	37/M	AZT DdI	10	DLCL Nov/95	IBE	245	CHOP	Dead 3 months
10	40/M	AZT ddI Ritonavir	94	DLCL Nov/96	IVB	919	CHOP IT Chemo	Dead 5 months
11	37/M	AZT	36	LL July/94	IVB	10,591	BFM/83	Dead 1 month
12	28/M	None	75	DLCL Sep/91	IIA	181	CHOP	Dead 5 months
13	36/M	None	48	DLCL Feb/94	IIB	193	CHOP	Dead 2 months

Abbreviations: AZT = zidovudine; ddi = didanosine; DLCL = diffuse large B-cell lymphoma; BL = Burkitt's lymphoma; LL = lymphoblastic lymphoma, IT = intrathecal; LDH = lactate dehydrogenase; NHL = non-Hodgkin's lymphoma.

* CD4 and LDH at NHL diagnosis.

** CHOP regimen with 25% reduction in cyclophosphamide and doxorubicin.

Table 2

Clinical and laboratorial features of Group B

Patient #	Age/Sex	HIV therapy	CD4 count*	NHL diagnosis	Stage	LDH*	Chemotherapy	Follow-up
1	31/M	d4T 3TC Indinavir	50	DLCL Aug/97	IIIB	300	CHOP IT Chemo	Alive in CR 49 months' follow-up
2	39/M	Saquinavir ddI d4T	210	DLCL Oct/97	IIA	263	CHOP IT Chemo	Alive in CR 46 months' follow-up
3	47/F	ddI d4T Nelfinavir	36	DLCL Nov/98	IIA	586	ProMACE- CytaBOM	Dead 7 months' follow-up
4	21/M	d4T 3TC Indinavir	395	BL April/99	IIB	378	CHOP IT Chemo	Dead 5 months' follow-up
5	30/M	D4T 3TC Nelfinavir	110	DLCL March/99	IIA	480	CHOP	Alive in CR 29 months' follow-up
6	30/M	d4T 3TC Indinavir	394	DLCL May/99	IVB	780	CHOP	Dead 8 months' follow-up
7	43/M	d4T ddI Indinavir	137	DLCL Nov/99	IIIB	245	CHOP IT Chemo	Alive in CR 21 months' follow-up

Abbreviations: D4T = stavudine; ddI = didanosine; 3TC = lamivudine; DLCL = diffuse large B-cell lymphoma; BL = Burkitt's lymphoma; LDH = lactate dehydrogenase, IT = intrathecal, CR = complete remission; NHL = non-Hodgkin's lymphoma.
* CD4 and LDH at NHL diagnosis.

in one patient. Among the patients receiving chemotherapy, 10 (77.0%) were treated with reduced-dose CHOP (25% reduction in cyclophosphamide and doxorubicin) and 3 received intrathecal chemotherapy with methotrexate and dexamethasone. No complete remission was found in group A. Table 2 shows the baseline characteristics of group B. All patients were on antiretroviral therapy or had started it soon after diagnosis of NHL. The antiretrovirals were given throughout chemotherapy. All regimens consisted of a triple-drug therapy with a protease inhibitor. The median CD4 lymphocyte count was 137 cells/mm^3. Six patients (86.0%) received full-dose CHOP, 1 patient (14.0%) received full-dose ProMACE-CytaBOM and 4 (57.0%) received intrathecal chemotherapy with methotrexate and dexamethasone. Three patients (43.0%) died within 8 months of diagnosis, but 4 patients (57.0%) are still alive and in complete remission. The Kaplan–Meier survival curve for group A and B patients is presented in the Fig. 1. The survival time differences between group A (5 months, 95% CI 3–6 months) and group B (31 months, 95% CI 15–46 months) were statistically significant (log-rank test; $p = 0.0032$).

DISCUSSION

We found that HIV patients who received HAART during treatment for NHL had a median survival rate at least six times higher than that of HIV patients with NHL before the HAART era, 31 and 5 months, respectively. The recent advent of HAART has resulted in notable improvement on survival and has dramatically reduced the incidence of

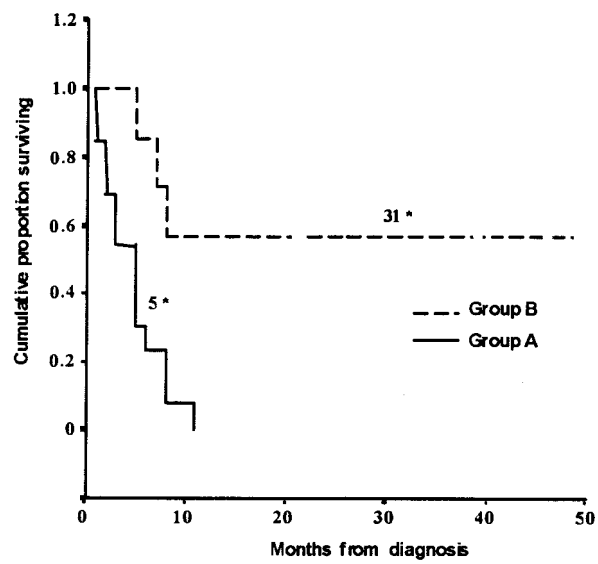

Fig. 1. Kaplan–Meier estimated survival rates of patients with systemic non-Hodgkin's lymphoma (NHL). Group B corresponds to patients who received highly active antiretroviral therapy (HAART) and Group A corresponds to patients who did not receive HAART. *Median survival (months). Log-rank test: $p = 0.0032$.

opportunistic infections in HIV-infected individuals (5–7, 17). Although the prognosis of patients with AIDS-related lymphoma remains poor, some subgroups of patients have a significantly better outcome (18–22). The CD4 lymphocyte count at the time of NHL diagnosis seems to be the best prognostic factor for patients with AIDS-related lymphoma (18–20, 22). Levine and colleagues reported the use of a low-dose m-BACOD regimen in 35 patients with HIV-associated NHL and a median CD4 count of 150/mm^3 (23). Sixteen individuals (46.0%) achieved complete remission, and the median survival was 6.5 months. These results were similar to those of other studies using standard CHOP-like regimens (24, 25). Tirelli and colleagues, using the same dose regimen in individuals with a median CD4 count of 35 cells/mm^3, found that only 19.0% achieved complete remission with median survival of only 3 months (26). Clearly, these results confirm the importance of a good immune function in the prognosis of AIDS-related lymphomas. In our patients a similar outcome was found. Among the 13 patients in Group A with a median CD4 count of 36 cells/mm^3, no complete remission was found, and the median survival was only 5 months. In Group B, the median CD4 count was 137 cells/mm^3, and 57.0% of patients achieved complete remission, with a median survival of 31 months. This statistically significant difference in survival ($p = 0.0032$) could be explained by a better immune status and a higher CD4 count achieved with HAART in group B patients. We are aware that retrospective studies are prone to pitfalls. However, as NHL is a relatively rare event in HIV subjects, observational retrospective design is an efficient approach and probably the only way to gather a significant number of events. Regarding the dose of chemotherapy used, Tirelli and colleagues (21) showed that patients receiving a full-dose CHOP regimen had a significantly higher complete response rate (63.0%) compared with a low-dose regimen (39.0%). However, overall and disease-free survival rates were not different and full-dose CHOP was associated with an excess of infection-related deaths. It has been demonstrated that full-dose chemotherapy could be safely administered if a colony-stimulating factor (G-CSF or GM-CSF) is given (27–29). It is worthemphasizing that all these reports were concluded before the advent of HAART. In our study all patients in group B received full-dose chemotherapy and concomitant antiretroviral therapy, but 3 out of 7 (42.8%) died. The remaining four patients are alive after 21, 27, 46 and 49 months of follow-up. In an attempt to ascertain whether HAART could be used safely with multiagent chemotherapy, Ratner and colleagues (7) reported on the use of CHOP plus stavudine (d4T), lamivudine (3TC) and indinavir and no excessive toxicity was found. In our patients no serious side effects were detected with this combined approach. AZT (zidovudine) was not used in group B patients, as it is associated with more severe anemia and neutropenia when combined with chemotherapy (7, 15). As recently published in the American Society of Hematology Education Program Book 1999 (19), regardless of the chemotherapeutic approach used, it is strongly recommended that all HIV patients treated with chemotherapy should receive concurrent HAART. This observation highlights the importance of the use of HAART for better control of infections and improvement in bone marrow reserves. Its association with standard-dose chemotherapy and a colony-stimulating factor when required for management of neutropenia might ultimately prove to be the most successful approach in HIV-infected NHL patients (7, 18, 30–32). Although our study included only a small number of patients, our results are in agreement with recently published reports, in that the use of HAART in combination with chemotherapy may improve response rates and overall survival of HIV patients. Further studies are required in this subject, because the battle against HIV and its associated malignancies is still ongoing.

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