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Authors
Diamond, Catherine
Taylor, Thomas H
Im, Theresa
et al.

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Presentation and outcomes of systemic non-Hodgkin's lymphoma: A comparison between patients with acquired immunodeficiency syndrome (AIDS) treated with highly active antiretroviral therapy and patients without AIDS

CATHERINE DIAMOND, THOMAS H. TAYLOR, THERESA IM, & HODA ANTON-CULVER

University of California, Irvine Department of Medicine, USA

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Abstract
We used the San Diego/Orange County cancer registry to identify 64 cases of systemic non-Hodgkin's lymphoma (NHL) with AIDS who received highly active antiretroviral therapy (HAART) at the time of NHL diagnosis or thereafter and 64 NHL controls without AIDS, matched on age, sex, race, time of NHL diagnosis (1994 – 1995 and 1996 – 1999), and hospital type (academic, large community, and small community). We compared cases and controls by chi-squared tests and Kaplan-Meier methods. Thirty-three percent of cases had high grade histology versus 11% of controls ($P < 0.01$); 69% had baseline hemoglobin <13 g/dL versus 35% controls ($P < 0.001$) and 21% had baseline neutrophils $<2{,}000$/mcl versus 4% of controls ($P < 0.001$). Overall median survival was 16 months for cases versus 99 months for controls ($P < 0.01$). Among 40 matched pairs of cases and controls who received chemotherapy, 32% of cases received reduced-dose chemotherapy versus 5% of controls ($P < 0.01$) and median survival was 33 months for cases and 99 months for controls ($P < 0.44$). Patients with AIDS-related NHL who received HAART had high grade histology and baseline cytopenia and received reduced-dose chemotherapy more often than patients without AIDS. However, AIDS patients who received HAART and chemotherapy had survival similar to NHL patients without AIDS, an improvement from the pre-HAART era. Appropriate hematologic support, through growth factors, transfusions, and avoidance of drugs with hematologic toxicity, might allow full dosing of chemotherapy, and perhaps would further improve outcomes among patients with AIDS and NHL.

Keywords: *Lymphoma, AIDS-related, antiretroviral therapy, highly active, survival, chemotherapy*

Introduction

Historically, patients with non-Hodgkin's lymphoma (NHL) and AIDS have been more likely than NHL patients without AIDS to present with extranodal NHL and high grade histology [1]. They have been less likely to respond to chemotherapy, with shorter overall survival than patients with NHL without AIDS [2]. Since the introduction of highly active antiretroviral therapy to the United States in 1996 [3], survival from AIDS-related NHL has improved [4]. However, the presentation and outcomes of patients with AIDS and NHL diagnosed in recent years compared to patients without AIDS is not well described. We report the clinical characteristics, treatment, and survival of patients with NHL and AIDS compared against matched controls with NHL without AIDS.

Methods

We obtained institutional review board approval from the University of California Irvine for this study. In October 2001, we identified all incident diagnoses of NHL ($n = 5{,}255$) between January 1994 and December 1999 from the Orange and San Diego population-based cancer registries (Cancer Surveillance Program of Orange County and San Diego/Imperial Organization for Cancer Control, regions 10 and 7, respectively, of the California

Correspondence: Catherine Diamond, 101 The City Dr S Building, 53 Route, 81 Orange, CA 92868, USA. Tel: 1 714 456 7612. Fax: 1 714 456 7169. E-mail: diamondc@uci.edu

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Cancer Registry) [5,6]. Registry data were complete as of December 1999 but we re-ascertained vital status as of April 2004. We defined evidence of NHL as the International Classification of Diseases for Oncology Second Edition (ICD-O-2) morphology codes 959 and 967-971 [7]. According to the registry's HIV indicator variable, 392 of these patients were HIV-infected at the time of NHL diagnosis.

We selected corresponding controls from the remaining 4,863 NHL patients, who were not known to be HIV-infected according to cancer registry records. Matching on age, sex, race, period of NHL diagnosis, and hospital type, we were able to identify controls for 324 of the 392 cases of AIDS-related NHL; we were unable to find matching controls for the 68 remaining cases. Among the 324 cases, we excluded 36 because the NHL diagnosis or the HIV-status was erroneous in either the case or the control and 91 because either the case or the control had lymphoma of central nervous system (CNS) origin (ICD-O-2 topographic code C72) [7]. In addition, we excluded 35 cases because the medical records of either the case or the control were unavailable. Among the remaining 162 cases, we divided cases into 64 who received HAART at the time of NHL diagnosis or thereafter and 87 who had never received HAART, excluding 11 who had received HAART prior to NHL diagnosis but were not taking it at time of NHL diagnosis. Thus, we report on 64 cases of AIDS-related NHL who received HAART at the time of NHL diagnosis or thereafter and their matched controls without AIDS, as well as 87 cases who had never received HAART and their matched controls. In a subset analysis, we excluded pairs of cases and controls if either or both had not received chemotherapy, effectively matching on receipt of chemotherapy, reducing the number of HAART-treated cases to $n = 40$ and cases who had not received HAART to $n = 37$.

Because HAART became widely available in 1996, we dichotomized the period of NHL diagnosis as pre-HAART (1994–1995) and post-HAART (1996–1999) [3]. We defined the hospital types as small community, academic/Veteran's Administration (VA)/military and large community/health-maintenance organization (HMO) [8]. We matched on hospital type in order to make the cases and controls more similar regarding healthcare access and to limit the number of hospitals for chart abstraction. We defined HAART as the use of two nucleosides and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor [9].

Cancer registrars collected data regarding age, race, NHL site, stage and histology as mandated by California state law [6]. Using a standardized form, trained study abstractors collected: antiretroviral therapy; performance status; B symptoms; CD4 cell, neutrophil, hemoglobin, and platelet counts (using the hematologic value closest to the NHL diagnosis date within 3 months of presentation but prior to chemotherapy), and chemotherapy type, dose, and response. We dichotomized the Karnofsky performance status scale between 0 and 50 and 60 and 100 in which 50 is defined as ''requires considerable assistance and frequent medical care'' [10]. We defined NHL stage and B symptoms by the Ann Arbor staging system [11] and histologic grade according to the ICD-O-2 [7]. We defined chemotherapy type (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] versus other regimens) and dosage (high or usual versus low) from the medical literature [12,13]. We defined complete response to chemotherapy as resolution of disease on radiography or biopsy, or a physician diagnosis of complete response. We compared proportions between cases and controls with chi-square tests; if a cell had an expected count less than five, we substituted Fisher's exact test. We used Kaplan-Meier methods to estimate survival [14].

Results

Among 87 AIDS cases who did not receive HAART, the median age was 42 years (range: 24–77); 86 (99%) were men and 65 (75%) were white. Fifty-three (61%) were diagnosed with NHL in 1994–1995 and 34 (39%) were diagnosed with NHL in 1996–1999; 10 (11%) were diagnosed at small community hospitals, 20 (23%) at academic/VA/military hospitals, and 57 (66%) at large community hospitals/HMOs. The median CD4 cell count was 77/mm^3 (range 0–1345) among 52 cases with recorded values. Survival was four months among AIDS patients who did not receive HAART versus 104 months among controls ($P < 0.001$).

Among 64 AIDS cases who received HAART, the median age was 44 years (range 27–64); 62 (97%) were male and 51 (80%) were white. Fifty-five (86%) were diagnosed with NHL in 1996–1999; 11 (17%) were diagnosed at small community hospitals, 25 (39%) at academic/VA/military hospitals, and 28 (44%) at large community hospitals/HMOs. The median CD4 cell count was 92/mm^3 (range: 2–739) for 51 patients with recorded values and the median log HIV RNA was 4.3 copies/ml (range: <1.7–>5.9) for 34 patients with recorded values. Survival was 16 months among HAART-treated cases and 99 months among controls without AIDS ($P < 0.01$, Figure 1).

Regardless of HAART usage, AIDS patients had more high grade histology and neutropenia, anemia,

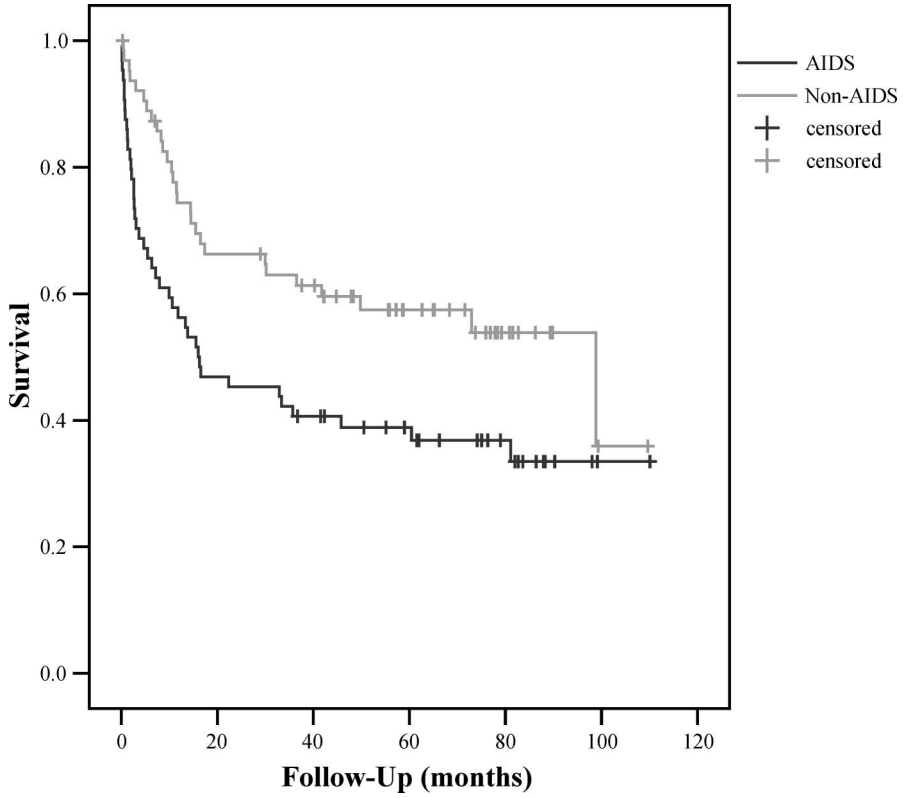

Figure 1. Survival in systemic non-Hodgkin's lymphoma (NHL): 64 patients with acquired immunodeficiency syndrome (AIDS) versus patients without AIDS, matched on age, sex, race, and hospital type, San Diego and Orange County, California, 1994–1999.

and thrombocytopenia than patients without AIDS (Table I); they were also more likely to have low performance status. AIDS patients who did not receive HAART were more likely than matched controls to have B symptoms and less likely to receive chemotherapy. In contrast, the frequency of B symptoms and chemotherapy receipt did not statistically differ between HAART-treated cases and controls. AIDS patients who did not receive HAART were more likely than matched controls to have extranodal and stage IV NHL; however, these differences were not statistically significant after the exclusion of CNS NHL from our analysis.

In a subset analysis of matched cases and controls who received chemotherapy, survival was 7 months among AIDS cases who received chemotherapy but not HAART; 65% of matched controls were alive at most recent follow up (median follow-up time: 64 months) and thus we could not calculate a median survival ($P < 0.001$). Regardless of HAART usage, AIDS patients were more likely than matched controls to have received reduced-dose chemotherapy. AIDS patients who did not receive HAART were less likely to have received CHOP, completed six or more chemotherapy cycles, or have a complete response than matched controls without AIDS (Table II). In contrast, HAART-treated cases had similar use of CHOP, completion of six or more chemotherapy cycles, and chemotherapy response as matched controls. Survival was 33 months among AIDS cases who received HAART and chemotherapy and 99 months among controls ($P < 0.44$, Figure 2).

Although the groups are not matched, to assist the reader in interpreting the data, we compared survival among patients with AIDS-related NHL who received HAART and chemotherapy ($n = 40$) versus those who received chemotherapy without HAART ($n = 37$) [Figure 3]. As described above, the median survival in patients who received HAART and chemotherapy was 33 months versus 7 months among those who received chemotherapy but no HAART ($P < 0.01$). Similarly, we compared patients who received HAART and chemotherapy with patients who received HAART but no chemotherapy ($n = 14$) and found that the median survival in patients who received HAART and chemotherapy was 33 months versus 1 month among those who received HAART without chemotherapy ($P < 0.001$, Figure 4).

Table I. Patients with systemic non-Hodgkin lymphoma (NHL), San Diego and Orange County, California, 1994–1999: Cases with AIDS versus controls without AIDS, matched on age, sex, race, period of NHL diagnosis, and hospital type.

Characteristic	AIDS without HAART $n=87$* # (%)	Controls without AIDS $n=87$* # (%)	P	AIDS with HAART $n=64$* # (%)	Controls without AIDS $n=64$* # (%)	P by chi-square test
Extranodal			0.18			0.14
Yes	28 (32)	20 (23)		11 (17)	18 (28)	
No	59 (68)	67 (77)		53 (83)	46 (72)	
Stage			0.06			0.99
I-III	34 (41)	45 (56)		25 (39)	23 (39)	
IV	48 (59)	35 (44)		39 (61)	36 (61)	
B symptoms at time of NHL diagnosis			0.001			0.20
Yes	53 (66)	27 (36)		29 (47)	22 (35)	
No	27 (34)	48 (64)		33 (53)	40 (65)	
NHL histology			0.01			0.01
Intermediate or low grade, unclassified, or other	57 (66)	72 (83)		43 (67)	57 (89)	
High grade	30 (34)	15 (17)		21 (33)	7 (11)	
Karnofsky performance status			0.001			0.02
0–50	42 (50)	12 (16)		18 (29)	7 (12)	
60–100	42 (50)	61 (84)		44 (71)	51 (88)	
Absolute neutrophil count at the time of NHL diagnosis/mcl			0.001			0.01
$<2{,}000$	22 (29)	1 (2)		12 (21)	2 (4)	
$\geq 2{,}000$	55 (71)	63 (98)		45 (79)	48 (96)	
Hemoglobin at time of NHL diagnosis g/dL			0.001			0.001
<13	66 (81)	30 (42)		41 (69)	19 (35)	
≥ 13	15 (19)	41 (58)		18 (31)	35 (65)	
Platelets/mcl			0.001			0.001
<150	27 (33)	6 (9)		21 (36)	5 (10)	
≥ 150	54 (67)	62 (91)		38 (64)	47 (90)	
Chemotherapy			0.001			0.39
Yes	45 (52)	74 (87)		50 (78)	53 (84)	
No	41 (48)	11 (13)		14 (22)	10 (16)	

*If cells do not add up to sum indicated at top of column, this is due to missing data.

Table II. Patients with systemic non-Hodgkin lymphoma (NHL) treated with chemotherapy, San Diego and Orange County, California, 1994–1999: Cases with AIDS versus controls without AIDS, matched on age, sex, race, period of NHL diagnosis, and hospital type.

Chemotherapy type, dose, number of cycles, and response	AIDS without HAART $n=37$* # (%)	Controls without AIDS $n=37$* # (%)	P by chi-square test	AIDS with HAART $n=40$* # (%)	Controls without AIDS $n=40$* # (%)	P by chi-square test
Type			0.01			0.63
CHOP†	23 (64)	33 (92)		25 (64)	27 (69)	
Other	13 (36)	3 (8)		14 (36)	12 (31)	
Dose			0.05			0.01
Low	7 (19)	1 (3)		12 (32)	2 (5)	
Usual, high, or, unspecified	30 (81)	35 (97)		25 (68)	37 (95)	
Number of cycles			0.01			0.36
1–5	27 (82)	12 (44)		22 (63)	16 (52)	
≥ 6	6 (18)	15 (56)		13 (37)	15 (48)	
Response			0.01			0.25
Complete	7 (22)	18 (60)		19 (51)	12 (38)	
Partial or none	25 (78)	12 (40)		18 (49)	20 (62)	

*If cells do not add up to sum indicated at top of column, this is due to missing data.
†CHOP comprises cyclophosphamide, doxorubicin, vincristine, and prednisone.

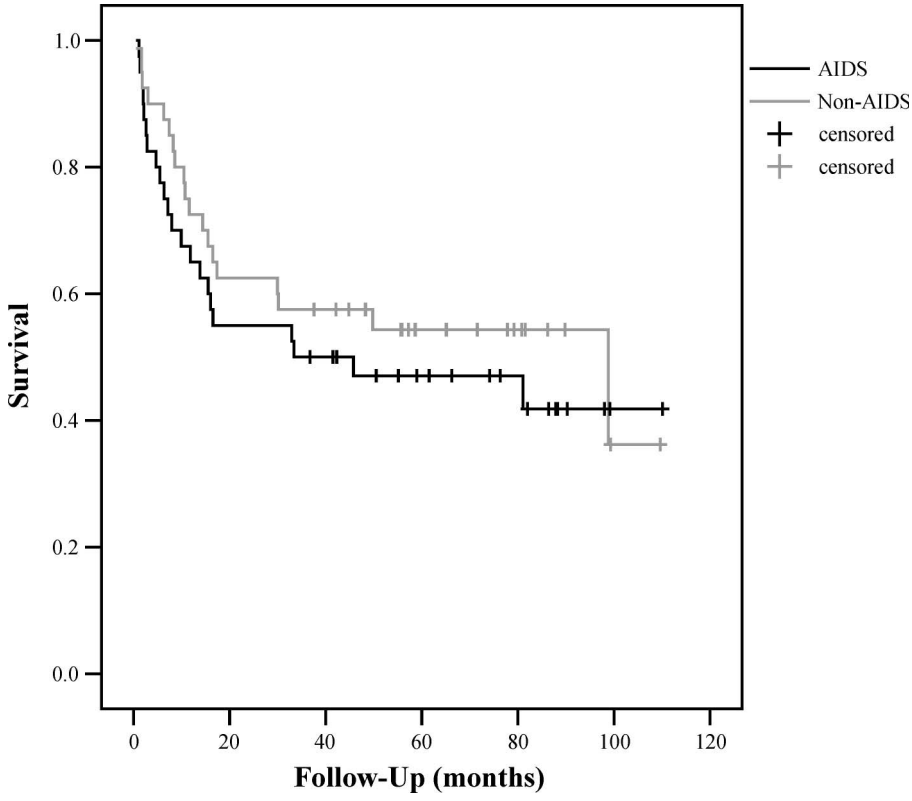

Figure 2. Survival among patients with systemic non-Hodgkin's lymphoma (NHL) treated with chemotherapy: 40 patients with acquired immunodeficiency syndrome (AIDS) who received highly active antiretroviral therapy (HAART) at NHL diagnosis or thereafter versus controls without AIDS, matched on age, sex, race, and hospital type, San Diego and Orange County, California, 1994–1999.

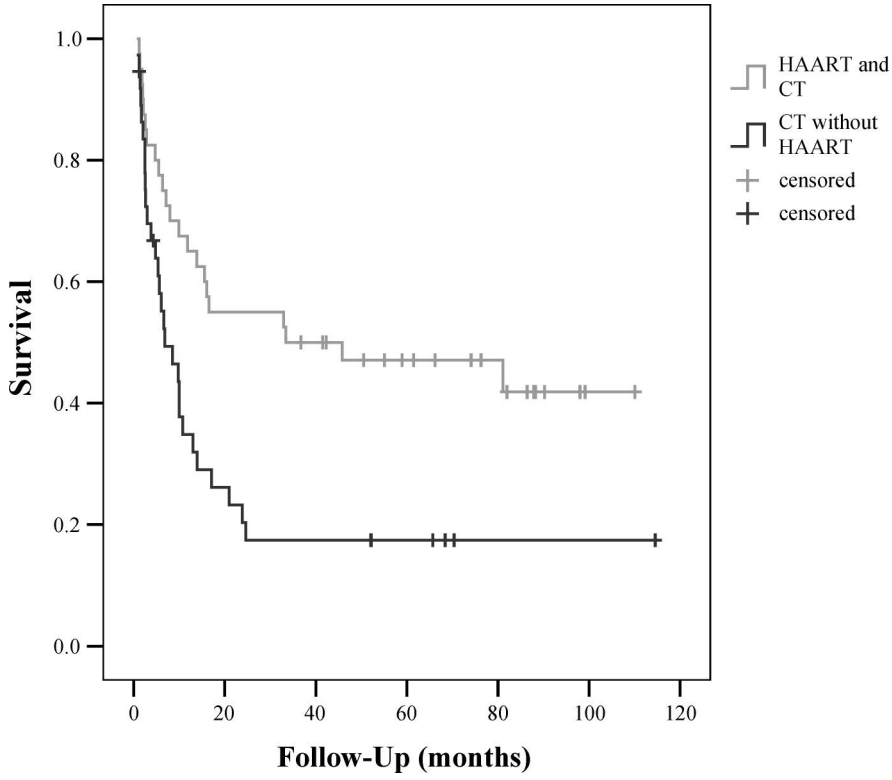

Figure 3. Survival in patients with acquired immunodeficiency syndrome (AIDS) and systemic non-Hodgkin's lymphoma (NHL): 40 patients who received highly active antiretroviral therapy (HAART) and chemotherapy (CT) versus 37 patients who received chemotherapy without HAART, San Diego and Orange County, California, 1994–1999.

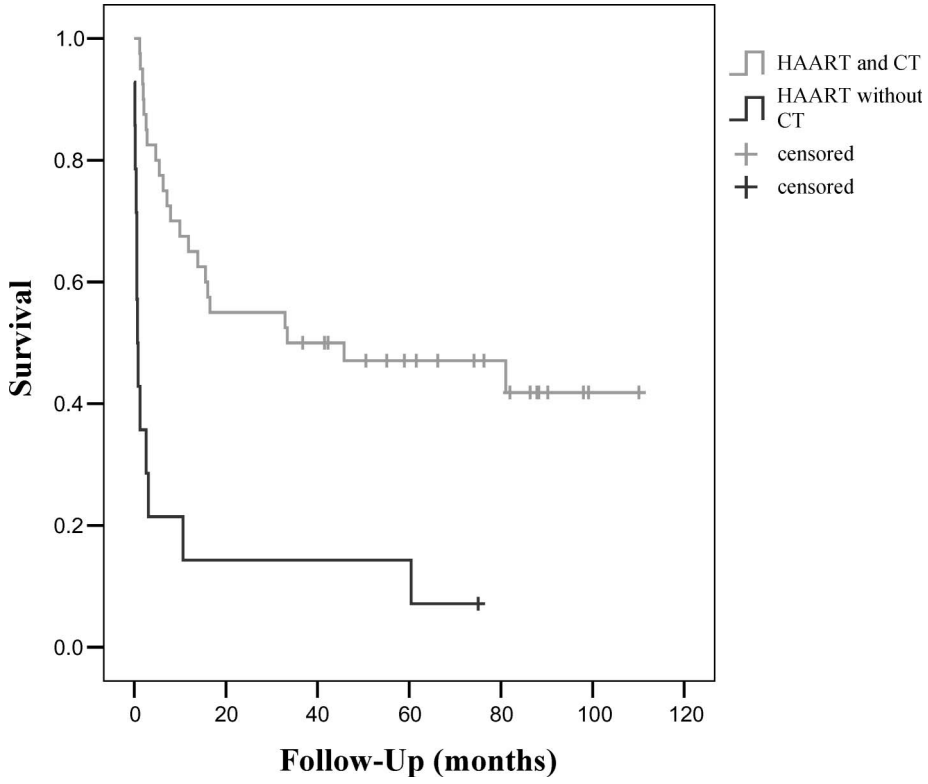

Figure 4. Survival in patients with acquired immunodeficiency syndrome (AIDS) and systemic non-Hodgkin's lymphoma (NHL): 40 patients who received highly active antiretroviral therapy (HAART) and chemotherapy (CT) versus 14 patients who received HAART without chemotherapy, San Diego and Orange County, California, 1994–1999.

Discussion

Like patients with AIDS-related NHL diagnosed in the pre-HAART era, patients with AIDS-related NHL who received HAART had more high-grade histology and baseline cytopenia than matched controls. AIDS patients who received HAART were as likely as matched controls to be treated with chemotherapy, complete at least six cycles of chemotherapy, and have a complete response to chemotherapy. However, AIDS patients were more likely than patients without AIDS to receive reduced-dose chemotherapy. Despite their baseline cytopenia and reduced-dose chemotherapy, AIDS patients who received HAART and chemotherapy had survival similar to NHL patients without AIDS, an improvement from the pre-HAART era.

The baseline cytopenia among AIDS patients may have been the result of bone marrow infiltration with tumor, cytotoxic drugs whether antiretrovirals (e.g. AZT) or prophylactic agents (e.g. trimethoprim/sulfamethazole), or poor nutrition. We do not know whether the use of low-dose chemotherapy in AIDS patients was the treating oncologist's response to patients' baseline cytopenia or related to trends in preferred chemotherapy regimens for AIDS-related NHL; for instance reduced dose m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) was popular during the years under study [13]. HAART-treated patients had improved performance status compared with AIDS patients who did not receive HAART, although their performance status was still significantly worse than matched controls. HAART-treated patients also had B symptoms less frequently than AIDS cases who did not receive HAART, perhaps reflecting less AIDS-related fever and weight loss among the HAART-treated AIDS patients.

In the pre-HAART era, the median survival of patients with systemic AIDS-related NHL was approximately 6 months [13,15–18]. In contrast, a recent study estimated survival among patients with AIDS-related NHL receiving HAART and chemotherapy as 22 months [18], similar to the 33-month medial survival seen with our data. There are multiple possible etiologies of this improvement in survival. Some studies have specifically correlated virologic response to HAART and oncologic response to chemotherapy [16,19,20]. However, even in the absence of complete virologic response, HAART improves performance status and thus enhances patients' ability to tolerate chemotherapy, allowing completion of a full chemotherapy course

and better chemotherapy response. Also, by maintaining CD4 cell counts, HAART may reduce the risk of opportunistic infections, again increasing the likelihood of completing a course of chemotherapy and achieving a complete chemotherapy response [21]. On the other hand, co-administration of HAART with chemotherapy may result in cross toxicity or pharmacokinetic interactions [22]. The best way to co-administer HAART and chemotherapy is a subject for future research.

Positive features of our study include our stringent matching criteria and detailed hematologic information. However, our study has limitations. Some charts were unavailable and others had incomplete data. Also, the number of cases who received both HAART and chemotherapy is relatively small which reduces the power to detect a survival difference between the patients with and without AIDS. Lastly, chemotherapy regimens for AIDS-related NHL are evolving and thus the CHOP regimen is less commonly used now than it was at the time of our study; newer regimens may have improved response rates and survival [23]. Despite these limitations, we are able to conclude that the receipt of HAART and chemotherapy improved survival in AIDS-related NHL. Appropriate hematologic support, through growth factors, transfusions, and avoidance of drugs with hematologic toxicity, might allow full dosing of chemotherapy, and perhaps would further improve outcomes among patients with AIDS and NHL.

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