Original Article

Prognostic Factors for Advanced-Stage Human Immunodeficiency Virus-Associated Classical Hodgkin Lymphoma Treated With Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Combined Antiretroviral Therapy

A Multi-Institutional Retrospective Study

Jorge J. Castillo, MD[1]; Mark Bower, MD[2]; Jérémy Brühlmann, MD[3]; Urban Novak, MD[3]; Hansjakob Furrer, MD[3]; Paula Y. Tanaka, MD[4]; Caroline Besson, MD[5]; Silvia Montoto, MD[6]; Kate Cwynarski, MD[7]; Jeremy S. Abramson, MD[8]; Samir Dalia, MD[9]; Michele Bibas, MD[10]; Joseph M. Connors, MD[11]; Michael Furman, MD[12]; Minh-Ly Nguyen, MD[13]; Timothy P. Cooley, MD[14]; Brady E. Beltran, MD[15]; Jaime A. Collins, MD[16]; Julie M. Vose, MD[17]; Blanca Xicoy, MD[18]; and Josep-Maria Ribera, MD[18]; for the HIV-Associated Hodgkin Lymphoma in the cART Era Study Group

BACKGROUND: The treatment and outcomes of patients with human immunodeficiency virus (HIV)-associated Hodgkin lymphoma (HL) continue to evolve. The International Prognostic Score (IPS) is used to predict the survival of patients with advanced-stage HL, but it has not been validated in patients with HIV infection. **METHODS:** This was a multi-institutional, retrospective study of 229 patients with HIV-associated, advanced-stage, classical HL who received doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus combination antiretroviral therapy. Their clinical characteristics were presented descriptively, and multivariate analyses were performed to identify the factors that were predictive of response and prognostic of progression-free survival (PFS) and overall survival (OS). **RESULTS:** The overall and complete response rates to ABVD in patients with HIV-associated HL were 91% and 83%, respectively. After a median follow-up of 5 years, the 5-year PFS and OS rates were 69% and 78%, respectively. In multivariate analyses, there was a trend toward an IPS score >3 as an adverse factor for PFS (hazard ratio [HR], 1.49; *P*=.15) and OS (HR, 1.84; *P*=.06). A cluster of differentiation 4 (CD4)-positive (T-helper) cell count <200 cells/μL was associated independently with both PFS (HR, 2.60; *P*=.002) and OS (HR, 2.04; *P*=.04). The CD4-positive cell count was associated with an increased incidence of death from other causes (HR, 2.64; *P*=.04) but not with death from HL-related causes (HR, 1.55; *P*=.32). **CONCLUSIONS:** The current results indicate excellent response and survival rates in patients with HIV-associated, advanced-stage, classical HL who receive ABVD and

Corresponding author: Jorge J. Castillo, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, M221, Boston, MA 02215; Fax: (617) 632-4682; jorgej_castillo@dfci.harvard.edu

[1]Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, Massachusetts; [2]Department of Medical Oncology, Chelsea and Westminster Hospital, London, United Kingdom; [3]Department of Medical Oncology and Infectious Diseases, Bern University Hospital and the University of Bern, Bern, Switzerland; [4]Section of Hematology, Emilio Ribas Institute for Infectious Diseases, Sao Paulo, Brazil; [5]Clinical Hematology Unit, Bicetre Hospital, University Paris Sud, INSERM U1012, Le Kremlin-Bicetre, France; [6]Center for Hemato-Oncology, Barts Cancer Institute, London, United Kingdom; [7]Department of Hematology, Royal Free Hospital, London, United Kingdom; [8]Division of Hematology and Oncology, Massachusetts General Hospital, Boston, Massachusetts; [9]Division of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; [10]Department of Clinical Research, Hematology, Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy; [11]British Columbia Cancer Agency Center for Lymphoid Cancer, Vancouver, British Columbia, Canada; [12]Department of Medicine, Rhode Island Hospital/The Miriam Hospital, Providence, Rhode Island; [13]Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia; [14]Division of Hematology and Oncology, Boston Medical Center, Boston, Massachusetts; [15]Department of Oncology and Radiotherapy, Edgardo Rebagliati Martins National Hospital, Lima, Peru; [16]Department of Infectious Disease, Guillermo Almenara Irigoyen National Hospital, Lima, Peru; [17]Division of Hematology and Oncology, University of Nebraska Medical Center, Omaha, Nebraska; [18]Department of Clinical Hematology, Catalan Institute of Oncology-Germans Trias i Pujol Hospital, Jose Carreras Research Institute, Badalona, Spain.

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combination antiretroviral therapy as well as the prognostic value of the CD4-positive cell count at the time of lymphoma diagnosis for PFS and OS. ***Cancer* 2015;121:423-31**. © *2014 American Cancer Society*.

KEYWORDS: human immunodeficiency virus, Hodgkin lymphoma, doxorubicin, bleomycin, vinblastine, and dacarbazine, antiretroviral therapy, CD4 count.

INTRODUCTION

Human immunodeficiency virus (HIV) infection carries an increased risk of developing a variety of malignancies, including the acquired immunodeficiency syndrome (AIDS)-defining cancers non-Hodgkin lymphoma, Kaposi sarcoma, and invasive uterine cervical cancer. HIV infection, however, also increases the risk of developing non-AIDS–defining cancers like Hodgkin lymphoma (HL). On the basis of mounting data, the incidence of HL is increased by 10-fold in individuals with HIV infection compared with the general population in Europe and the United States.[1] A recent analysis of combined European cohorts of HIV-infected individuals has revealed that combination antiretroviral therapy (cART) reduces the incidence of HL.[2]

The optimal treatment for patients with immunocompetent HL continues to evolve. In randomized, controlled studies that include immunocompetent patients with classical HL, it has been demonstrated that the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is effective and is probably less toxic than more intensive regimens.[3,4] A recent study demonstrated an improvement in the outcome of patients with HIV-associated HL compared with their immunocompetent counterparts when treated with standard regimens.[5,6] However, a standard of care in HIV-positive individuals has not been established, because, in general, HIV-positive patients are excluded from clinical trials, and data on their outcomes are rather scant.

One of the most commonly used prognostic tools in immunocompetent patients with advanced HL is the International Prognostic Score (IPS), which uses 7 clinical and laboratory parameters to construct a scoring system that is capable of predicting survival.[7] However, the IPS has not been fully validated in patients with HIV-associated HL. Hence, the objectives of our study were to determine the validity of the IPS, to describe the patients' characteristics and outcomes, and to identify predictive and prognostic factors in a large cohort of patients with HIV-associated, advanced-stage, classical HL who were treated uniformly with ABVD and cART.

MATERIALS AND METHODS

Patient Selection

This was a multi-institutional, retrospective study conducted in 23 centers: 13 from Europe (France, Italy, Spain, Switzerland, and the United Kingdom), 7 from the United States and Canada, and 3 from South America (Brazil and Peru). The institutional review boards at each of the participating institutions approved the current study. Patients were identified through a database search at each of the participating institutions. Patients aged >18 years with HIV infection and a histopathologic diagnosis of advanced-stage, classical HL who received concurrent treatment with ABVD and cART through December 2010 were included in this study. All patients must have received ABVD at standard doses with curative intent. cART was defined as 2 nucleoside reverse-transcriptase inhibitors plus a third agent that was either a protease inhibitor or a non-nucleoside reverse-transcriptase inhibitor.[8,9] Patients were staged by means of computed tomography, positron emission tomography, and/or bone marrow biopsy. Patients with a diagnosis of nodular lymphocyte-predominant HL, stage I or II disease, other concurrent malignancy, or clinical suspicion, but not laboratory confirmation, of HIV infection were excluded. Portions of the data sets from previous studies[5,10,11] are included in this report.

Data Gathering

Clinical data included age, sex, performance status according to the Eastern Cooperative Oncology Group scale, years of HIV infection before HL diagnosis, diagnosis of AIDS, presence of B symptoms, presence of bulky disease (according to the local definition of bulky), clinical stage, response to therapy, receipt of granulocyte-colony–stimulating factor (G-CSF), receipt of anti-infectious prophylaxis, relapse and therapy at relapse, receipt of autologous stem cell transplantation (ASCT), final outcome, progression-free survival (PFS), overall survival (OS), and cause of death. Laboratory data included cluster of differentiation 4 (CD4)-positive (T-helper) cell count, hemoglobin level, white blood cell (WBC) count, absolute lymphocyte count (ALC), and albumin level. Pathologic data included the HL histologic subtype.

Statistical Analysis

Continuous and categorical variables are presented using descriptive statistics. Response to therapy was assessed using revised response criteria whenever possible.[12] Multivariate logistic regression analyses were performed to identify

predictive factors for response to ABVD.[13] The outcome measure was the odds ratio (OR) with 95% confidence interval (CI) for not obtaining a complete response (CR) to ABVD. PFS was defined as the time in months between the date of pathologic diagnosis and the date of progression, death, or last follow-up. OS was defined as the time in months between the date of pathologic diagnosis and the date of death or last follow-up. PFS and OS estimates were obtained using the Kaplan-Meier method.[14] The log-rank test was used to compare survival estimates.[15] Univariate and multivariate hazard ratios (HRs) were calculated using the Cox proportional-hazard regression method.[16] The outcome measure was the HR with 95% CI. For the logistic and survival regression models, univariate analysis (UVA) was performed for each variable, and only the variables with P values $<.1$ were included in the multivariate analysis (MVA). P values $<.05$ were considered statistically significant in the MVA. The categorical variable AIDS violated the proportional-hazard assumption and was not included in the statistical analysis. A cause-specific survival (CSS) analysis was performed with HL-related death and death from other cause as competing factors. HL-related death was defined as death because of disease progression, as it was reported by the investigators. Cumulative incidence function curves were plotted and evaluated using the Fine and Gray method.[17]

The distribution of missing data was as follows: use of prophylaxis, missing for 22% of patients; bulky disease, missing for 21% of patients; albumin, missing for 20% of patients; WBC count, missing for 15% of patients; receipt of G-CSF, missing for 14% of patients; ALC, missing for 14% of patients; hemoglobin, missing for 13% of patients; CD4-positive cell count, missing for 5% of patients; and AIDS diagnosis, missing for 2% of patients. Complete data were available on age, sex, disease stage, the presence of B symptoms, and HL histologic subtype. Although the missing data appeared to be random, we handled missing data by performing multiple imputation analysis in addition to complete case analysis. Multiple imputation analyses for logistic regression and Cox proportional-hazard regression tests were performed after generating 5 imputed data sets using the chained equations method.[18,19] All calculations and graphs were obtained using the STATA 12.1 software package (StataCorp LP, College Station, Tex).

TABLE 1. Clinicopathologic Characteristics of 229 Patients With Human Immunodeficiency Virus-Associated Hodgkin Lymphoma Who Received Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Combination Antiretroviral Therapy

Characteristic	No. of Patients (%)
Age, n = 229	
≥45 y	79 (34.5)
<45 y	150 (65.5)
Sex, n = 229	
Men	198 (86)
Women	31 (14)
CD4-positive count, n = 219	
≥200 cells/μL	102 (47)
<200 cells/μL	117 (53)
AIDS diagnosis, n = 225	
Yes	113 (50)
No	112 (50)
Disease stage, n = 229	
III	70 (31)
IV	159 (69)
B symptoms, n = 229	
Present	187 (82)
Absent	42 (18)
Bulky disease, n = 179	
Yes	8 (4)
No	171 (96)
Histologic subtype, n = 229	
Mixed cellularity	109 (48)
Nodular sclerosis	50 (22)
Lymphocyte depleted	15 (7)
Classic, NOS	55 (24)
WBC count, n = 198	
≥15,000 cells/μL	1 (0.5)
<15,000 cells/μL	197 (99.5)
ALC, n = 197	
≥600 cells/μL	136 (69)
<600 cells/μL	61 (31)
Hemoglobin level, n = 197	
≥10.5 g/dL	99 (50)
<10.5 g/dL	98 (50)
Albumin level, n = 184	
≤4 g/dL	29 (16)
<4 g/dL	155 (84)
IPS risk factors, n = 196	
0	0 (0)
1	13 (7)
2	26 (13)
3	62 (32)
4	43(22)
5	43(22)
6	9 (5)
7	0 (0)

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALC, absolute lymphocyte count; CD4, cluster of differentiation 4 (T-helper cells); IPS, International Prognostic Score; NOS, not otherwise specified; WBC, white blood cells.

RESULTS

Patients' Characteristics

In total, 312 patients were submitted for this study, of which 83 (27%) were excluded; 57 (69%) had early stage disease, 20 (24%) did not receive ABVD, 3 (3%) were diagnosed with HL before their HIV diagnosis, and 3 (3%) had lymphocyte-predominant disease. Therefore, 229 patients met the inclusion criteria and were included in our analysis. The median age at HL diagnosis was 41 years (range, 24-70 years). There was a male

TABLE 2. Multivariate Logistic Regression Analysis for Not Obtaining a Complete Response in 229 Patients With Human Immunodeficiency Virus-Associated Hodgkin Lymphoma Who Received Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Combination Antiretroviral Therapy

	Univariate Analysis		Multivariate Analysis	
Variable[a]	OR (95% CI)	*P*	OR (95% CI)	*P*
Age ≥45 y	2.15 (1.05-4.40)	.04	3.05 (1.35-6.87)	.007
Male sex	0.62 (0.24-1.56)	.31		
Stage IV	3.44 (1.28-9.27)	.01	5.12 (1.43-18.3)	.01
Hemoglobin ≤10.5 g/dL	1.65 (0.78-3.49)	.19		
ALC <600 cells/μL	1.51 (0.70-3.28)	.29		
Albumin <4 g/dL	3.61 (0.81-16.0)	.09	3.44 (0.74-16.0)	.11
CD4-positive count <200 cells/μL	1.61 (0.78-3.32)	.20		
B symptoms	0.58 (0.14-2.45)	.46		
Bulky disease	2.75 (0.62-12.2)	.18		
Use of G-CSF	2.00 (0.85-4.70)	.11		
Prophylaxis	1.34 (0.43-4.20)	.62		
Lymphocyte depleted[b]	0.62 (0.12-3.18)	.56		
Mixed cellularity[b]	0.81 (0.34-1.91)	.63		
Nodular sclerosis[b]	0.68 (0.24-1.97)	.48		

Abbreviations: ALC, absolute lymphocyte count; CD4, cluster of differentiation 4 (T-helper cells); CI, confidence interval; G-CSF, granulocyte-colony-stimulating factor; OR, odds ratio.
[a] A white blood cell count >15,000/μL was not included in the model (n = 1).
[b] Hodgkin lymphoma not otherwise specified was used as the reference group.

predominance of 6.4:1. The median age at HIV infection diagnosis was 33 years (range, 12-69 years). The median time from HIV infection diagnosis to HL diagnosis was 8 years (range, 0-28 years), and 12% of patients (n=34) had a diagnosis of HIV made at the time of HL diagnosis. Laboratory data revealed a median CD4-positive cell count of 180 cells/μL (range, 4-1209 cells/μL), a median WBC count of 4360 cells/μL (range, 300-15,500 cells/μL), a median ALC of 820 cells/μL (range, 89-3500 cells/μL), a median hemoglobin level of 10.5 g/dL (range, 4.1-16.8 g/dL), and a median albumin level of 3.2 g/dL (range, 0.9-5.2 g/dL). The presence of >3 IPS risk factors was reported in 49% of patients (n=95). More detailed clinicopathologic characteristics are listed in Table 1.

Response to Treatment and Predictors of Response

The overall response rate to a median of 5 cycles (range, 3-8 cycles) of ABVD was 91%, the CR rate was 83% (n=183 of 220 patients), and the partial response (PR) rate was 8% (n=18 of 220 patients). Nonresponders comprised 19 of 220 patients (9%). There were no response data available in 9 patients, including 5 (56%) who died before their response could be assessed. Radiation therapy was received by 18 patients (8%). G-CSF support was received by 65% of patients (n=129), *Pneumocystis jiroveci* prophylaxis was received by 74% (n=119), antifungal prophylaxis was received by 31% (n=50), *Mycobacterium avium* complex prophylaxis was received by 27% (n=44), and antiviral prophylaxis was received by 12% (n=19). After a median follow-up of 61 months, 17% of patients (n=38) experienced disease relapse, and 21% (n=49) died. The most common causes of death were HL progression in 47% of patients (n=24), other malignancies such as diffuse large B-cell and Burkitt lymphoma in 27% (n=14), opportunistic infections in 12% (n=6), and other infections in 10% (n=5). In the UVA, age ≥45 years (*P*=.04), stage IV disease (*P*=.01), and an albumin level <4 g/dL (*P*=.09) were selected for MVA. In the MVA, age ≥45 years (*P*=.007) and stage IV disease (*P*=.01) were independently associated with not obtaining a CR with ABVD. Complete results are provided in Table 2. The multiple imputation analysis did not change our results (data not shown).

PFS and Prognostic Factor Analysis

The 5-year PFS rate for patients with HIV-associated HL who received ABVD and cART was 69% (95% CI, 62%-76%) (Fig. 1A). From the UVA, hemoglobin <10.5 g/dL (*P*=.06), ALC <600 cells/μL (*P*=.09), nodular sclerosis subtype (*P*=.06), and a CD4-positive count <200 cells/μL (*P*=.007) were included in the MVA. Patients with CD4-positive counts <200 cells/μL had 5-year PFS rate of 63% compared with 79% for patients with CD4-positive counts ≥200 cells/μL (Fig. 1B). In the MVA, a CD4-positive count <200 cells/μL was the only factor associated with PFS (*P*=.002). Complete results are provided in Table 3. There was a trend toward

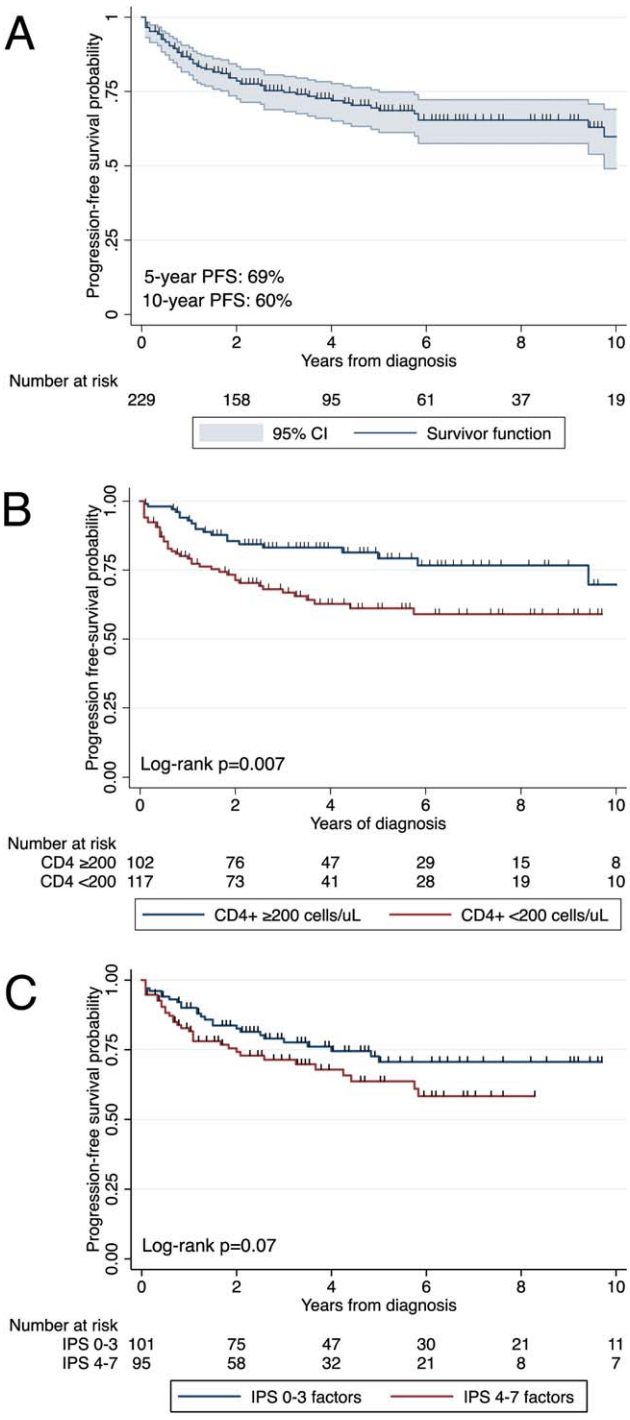

Figure 1. (A) Kaplan-Meier estimates of progression-free survival (PFS) in 229 patients with human immunodeficiency virus-associated Hodgkin lymphoma who received doxorubicin, bleomycin, vinblastine, and dacarbazine plus combination antiretroviral therapy are illustrated according to (B) the cluster of differentiation 4 (CD4)-positive (CD4+) cell count and (C) the International Prognostic Score (IPS).

TABLE 3. Multivariate Analysis for Progression-Free Survival in 229 Patients With Human Immunodeficiency Virus-Associated Hodgkin Lymphoma Who Received Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Combination Antiretroviral Therapy

	Univariate Analysis		Multivariate Analysis	
Variable[a]	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≥45 y	1.43 (0.88-2.32)	.15		
Male sex	1.01 (0.50-2.04)	.98		
Stage IV	1.55 (0.89-2.72)	.12		
Hemoglobin ≤10.5 g/dL	1.76 (1.04-2.97)	.04	1.55 (0.87-2.76)	.13
ALC <600 cells/μL	1.57 (0.93-2.66)	.09	1.23 (0.68-2.21)	.49
Albumin <4 g/dL	1.59 (0.68-3.72)	.28		
CD4-positive count <200 cells/μL	2.09 (1.22-3.57)	.007	2.55 (1.38-4.70)	.003
B symptoms	1.04 (0.39-2.83)	.94		
Bulky disease	1.08 (0.34-3.44)	.90		
Use of G-CSF	0.99 (0.58-1.69)	.96		
Use of prophylaxis	0.94 (0.45-1.93)	.86		
Lymphocyte depleted[b]	0.74 (0.21-2.58)	.64		
Mixed cellularity[b]	1.20 (0.64-2.27)	.56		
Nodular sclerosis[b]	1.92 (0.97-3.81)	.06	1.55 (0.91-2.65)	.11

Abbreviations: ALC, absolute lymphocyte count; CD4, cluster of differentiation 4 (T-helper cells); CI, confidence interval; G-CSF, granulocyte-colony-stimulating factor; HR, hazard ratio.

[a] A white blood cell count >15,000/μL was not included in the model (n = 1).

[b] Hodgkin lymphoma not otherwise specified was used as the reference group.

a relation between >3 IPS risk factors and worse PFS in the UVA (HR, 1.61; 95% CI, 0.96-2.71; *P*=.07). Patients who had >3 IPS risk factors had a 5-year PFS rate of 64% compared with 73% for patients who had ≤3 IPS risk factors (Fig. 1C). When evaluating CD4-positive count and the IPS side by side, a CD4-positive count <200 cells/μL was associated with worse PFS (HR, 2.60; 95% CI, 1.43-4.73; *P*=.002) but having >3 IPS risk factors was not (HR, 1.49; 95% CI, 0.87-2.54; *P*=.15). The multiple imputation analysis did not change our results (data not shown).

OS and Prognostic Factor Analysis

The 5-year OS rate was 78% (95% CI, 71%-83%) (Fig. 2A). From the UVA, age ≥45 years (*P*=.02), hemoglobin <10.5 g/dL (*P*=.07), and a CD4-positive count <200 cells/μL (*P*=.02) were selected for the MVA. Patients with CD4-positive counts <200 cells/μL had a 5-year OS rate of 72% compared with 86% in patients with CD4-positive counts ≥200 cells/μL (Fig. 2B). In the MVA, a CD4-positive count <200 cells/μL was the only independent factor associated

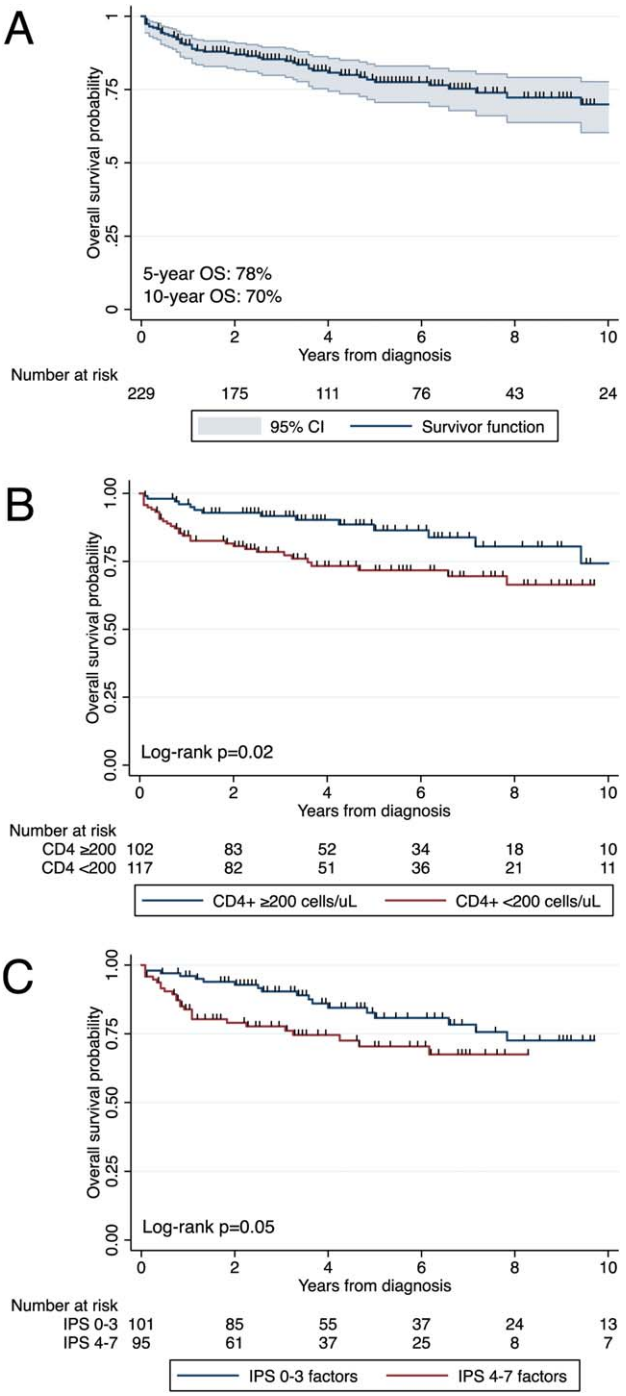

Figure 2. (A) Kaplan-Meier estimates of overall survival (OS) in 229 patients with human immunodeficiency virus-associated Hodgkin lymphoma who received doxorubicin, bleomycin, vinblastine, and dacarbazine plus combination antiretroviral therapy are illustrated according to (B) the cluster of differentiation 4 (CD4)-positive (CD4+) cell count and (C) the International Prognostic Score (IPS).

with OS (P=.03). Complete results are provided in Table 4. There was a trend toward a significant relation between having >3 IPS risk factors, when evaluated alone, and OS (HR, 1.83; 95% CI, 0.99-3.36; P=.05). Patients who had >3 IPS risk factors had a 5-year OS rate of 70% compared with 80% in patients who had ≤3 IPS risk factors (Fig. 2C). When evaluating the CD4-positive count and the IPS side by side, a CD4-positive count <200 cells/μL was associated with worse OS (HR, 2.04; 95% CI, 1.03-4.02; P=.04), but having >3 IPS risk factors was not (HR, 1.84; 95% CI, 0.97-3.48; P=.06). The multiple imputation analysis did not modify our results (data not shown).

TABLE 4. Multivariate Analysis for Overall Survival in 229 Patients With Human Immunodeficiency Virus-Associated Hodgkin Lymphoma Who Received Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Combination Antiretroviral Therapy

	Univariate Analysis		Multivariate Analysis	
Variable[a]	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≥45 y	1.92 (1.09-3.38)	.02	1.78 (0.95-3.34)	.07
Male sex	1.12 (0.48-2.64)	.79		
Stage IV	1.22 (0.65-2.31)	.54		
Hemoglobin ≤10.5 g/dL	1.77 (0.96-3.27)	.07	1.64 (0.8703.11)	.13
ALC <600 cells/μL	1.55 (0.84-2.86)	.16		
Albumin <4 g/dL	1.81 (0.64-5.10)	.26		
CD4-positive count <200 cells/μL	2.14 (1.14-4.02)	.02	2.11 (1.06-4.18)	.03
B symptoms	1.11 (0.33-3.68)	.87		
Bulky disease	0.83 (0.20-3.43)	.79		
Use of G-CSF	0.90 (0.47-1.73)	.75		
Use of prophylaxis	1.11 (0.46-2.68)	.82		
Lymphocyte depleted[b]	1.15 (0.31-4.27)	.83		
Mixed cellularity[b]	1.47 (0.69-3.14)	.32		
Nodular sclerosis[b]	1.39 (0.58-3.36)	.46		

Abbreviations: ALC, absolute lymphocyte count; CD4, cluster of differentiation 4 (T-helper cells); CI, confidence interval; G-CSF, granulocyte-colony-stimulating factor; HR, hazard ratio.
[a] A white blood cell count >15,000/μL was not included in the model (n = 1).
[b] Hodgkin lymphoma not otherwise specified was used as the reference group.

CSS Analysis

We further evaluated the impact of CD4-positive cell counts on survival by performing a CSS analysis evaluating HL-related deaths (n=24) and deaths from other causes (n=25) as competing factors. A CD4-positive count ≥200 cells/μL was not associated with HL-related death (HR, 1.55; 95% CI, 0.66-3.66; P=.32) (Fig. 3A), but it was associated with an increased incidence of deaths from other causes (HR, 2.64; 95% CI, 1.05-6.65; P=.04) (Fig. 3B). The presence of >3 IPS risk factors was not associated with HL-related death (HR, 1.11; 95% CI,

0.46-2.68; P=.81) but was associated with death from other causes (HR, 2.43; 95% CI, 1.05-5.58; P=.04).

DISCUSSION

Here, we present the results from a large study that included 229 patients with HIV infection and classical HL who received uniform treatment with ABVD and cART. There are several important findings. First, our study demonstrates that patients with HIV-associated HL who received ABVD and cART experienced high response rates. Second, patients with HIV-associated, advanced-stage, classical HL who received ABVD and cART experienced high 5-year PFS and OS rates. Third, we observed that a CD4-positive count <200 cells/μL was an independent, adverse prognostic factor for PFS and OS.

Our cohort of patients with HIV-associated HL who received ABVD and cART experienced an overall response rate of 91% and a CR rate of 83%. These results are comparable to recent studies. In a study by Hentrich and colleagues, 108 patients with HIV-associated HL were treated using a risk-adapted approach, which produced a CR rate of 90%.[20] It is noteworthy that there was no difference in CR rates between patients who had early favorable, early unfavorable, and advanced disease, but no predictive factor analysis for response was performed. A study by Montoto and colleagues included 93 HIV-positive patients with HL and reported a CR rate of 74%, which was not statistically different from the rate in HIV-negative patients (79%).[5] However, in that study, no specific factors were independently associated with CR. A Spanish study in 62 patients who received ABVD produced a CR rate of 87%.[11] Finally, a prospective study by Spina and colleagues in 59 patients with HIV-associated HL who received the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) and cART produced a CR rate of 81%.[21] The IPS was significantly associated with obtaining a CR. It is noteworthy that the CR rate to ABVD observed in our cohort was comparable to the response rates to ABVD reported in immunocompetent HL patients with advanced-stage disease.[3,4,22]

After a median follow-up of approximately 5 years, the patients in our cohort had 5-year PFS and OS rates of 69% and 78%, respectively. In the study by Spina et al,[21] patients experienced 3-year freedom from progression and OS rates of 60% and 51%, respectively, and the study by Montoto et al produced 5-year event-free survival and OS rates of 59% and 88%, respectively.[5] Our results are similar those reported by Xicoy et al, with estimated 5-year PFS and OS rates of 71% and 76%, respectively.[11]

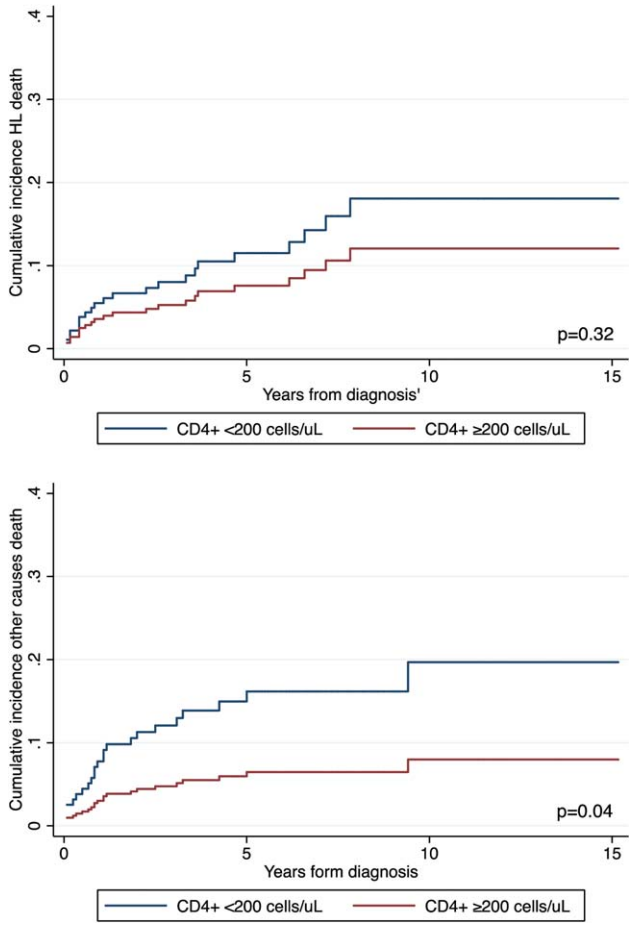

Figure 3. The cumulative incidence of death is illustrated in 49 patients with human immunodeficiency virus-associated Hodgkin lymphoma (HL) who received doxorubicin, bleomycin, vinblastine, and dacarbazine plus combination antiretroviral therapy according to the cluster of differentiation 4 (CD4)-positive (CD4+) cell count for (*Top*) lymphoma-related deaths and (*Bottom*) deaths from other causes.

The results reported by Hentrich et al were also encouraging, with 2-year PFS and OS rates of 92% and 91%, respectively.[20] Most of the studies on HIV-associated HL, however, are hampered by short follow-up periods, which might lead to overestimation of survival rates. For example, in the study by Spina and colleagues, the median follow-up was 17 months, and it was 26 months in the study by Hentrich et al. We believe our study clearly enlarges the current body of literature by providing survival data with longer follow-up. The 5-year PFS and OS rates in our cohort also were comparable to the survival rates reported in immunocompetent patients with advanced-stage HL.[3,4,22]

Few studies have previously analyzed the prognostic value of the CD4-positive cell count. In the study by Hentrich et al, a CD4-positive count <200 cells/μL was not

associated with PFS or OS after adjusting for covariates. However, our analysis revealed that a CD4-positive count <200 cells/μL was an independent, adverse prognostic factor for PFS and OS after adjusting for several relevant covariates. It may be reasonable to hypothesize that there were differences between studies, such as population selection or different therapies. Conversely, we believe our larger sample size had more power to allow a meaningful analysis of prognostic factors. In the study by Hentrich and colleagues, a CD4-positive count <200 cells/μL study was associated with an HR of 2.8 for PFS and an HR of 1.2 for OS. In our study, a CD4-positive count <200 cells/μL was associated with HRs of 2.5 and 2.1 for PFS and OS, respectively, which we consider to be clinically relevant.

Our CSS analysis demonstrated that the CD4-positive cell count was a prognostic factor for death from other causes but not for HL-related death. This finding supports the notion that the CD4-positive cell count, as the best marker of HIV-associated immunodeficiency, plays an important role in driving deaths from HIV-associated HL but has little or no impact on response to HL chemotherapy. Both PFS and OS include deaths from any cause, which may explain why a low CD4-positive cell count plays such an important role in estimating these 2 endpoints. The current findings demonstrate that the CD4-positive cell count is a strong and easy-to-use prognostic factor for survival in patients with advanced-stage, classical HIV-associated HL. However, a low CD4-positive count should not be a contraindication to choosing the best established oncologic treatment. Of course, our findings will need further validation.

The IPS is the most commonly used prognostic tool in patients with advanced-stage HL and comprises 7 clinical factors to prognosticate PFS.[7] The IPS has been evaluated in patients with HIV-associated HL with mixed results. In the study by Montoto et al, the IPS appeared to be prognostic for OS but not event-free survival; Spina et al reported the IPS as prognostic for OS and freedom from progression; and the study by Hentrich et al indicated that the IPS was not prognostic for PFS or OS. A Spanish study also demonstrated limited prognostic value of the IPS for PFS and OS in patients with HIV-associated HL.[23] In our cohort, there was a statistical trend in favor of the IPS as a prognostic factor for PFS and OS, suggesting a prognostic role for the IPS in HIV-associated, classical HL. We should acknowledge that our study may have been underpowered to evaluate the prognostic role of the IPS, because our results indicated a sizable albeit nonsignificant HR.

Our study carries several strengths, because it included 1 of the largest cohorts of patients with HIV-associated, advanced-stage, classical HL to date who uniformly received standard doses of ABVD and cART, and it included longer follow-up than previous studies. However, our study has multiple limitations given its retrospective design, potential heterogeneity in patient selection, missing data, and lack of detailed information on the timing of cART and therapy-associated toxicity. However, we mitigated the impact of those weaknesses by performing a large multicenter study that included consecutive patients. Our findings cannot be translated to HIV-associated HL patients who do not receive concurrent treatment with ABVD and cART. We dealt with missing data by performing multiple imputations for our predictive and prognostic factor analyses. Multiple imputations permit the substitution of missing data with inferred values that would have taken into account the heterogeneity and variance of the original data.[24] A recent review and recommendations for the use and reporting of multiple imputation analyses have been published.[25]

In summary, based on the results from our study, the concurrent administration of ABVD and cART is associated with high rates of response and survival, arguing in favor of this treatment modality outside of clinical trials for patients with advanced-stage, HIV-associated, classical HL. Our study also supports the finding that HIV-infected patients with HL should receive standard doses of ABVD, akin to those received by immunocompetent patients, and that HIV-positive patients with HL also should be included in clinical trials. Finally, the CD4-positive cell count at HL diagnosis has emerged as a prognostic marker for PFS and OS in patients with HIV-associated, classical HL.

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CONFLICT OF INTEREST DISCLOSURES

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