Original Article

Human Immunodeficiency Virus-Associated Plasmablastic Lymphoma

Poor Prognosis in the Era of Highly Active Antiretroviral Therapy

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BACKGROUND: Plasmablastic lymphoma (PBL) is a rare and aggressive B-cell lymphoma strongly associated with human immunodeficiency virus (HIV) infection. The authors conducted a multi-institutional, retrospective study to describe characteristics and determine prognostic factors in HIV-associated PBL. **METHODS:** For this study, the investigators included consecutive, HIV-positive patients diagnosed between the years 2000 and 2010 whose tumors had a plasmablastic morphology, were cluster of differentiation 20 (CD20)-negative, and expressed markers of plasmacytic differentiation. **RESULTS:** Fifty patients from 13 institutions were evaluated. The median age was 43 years, and there was a male predominance. The median count of cells that were positive for CD4 (a glycoprotein expressed on the surface of T-helper cells, monocytes, macrophages, and dendritic cells) was 206 cells/mm^3. At presentation, 90% of patients had extranodal involvement, 69% presented with advanced stage disease, and 27% had oral involvement. Rearrangements of v-myc myelocytomatosis viral oncogene homolog (*MYC*) were detected in 41% of the tested patients. Eighty-five percent of patients received chemotherapy, with 63% receiving cyclophosphamide, doxorubicin, vincristine, and prednisone and 37% receiving more intensive regimens. The complete response (CR) rate was 66%. The median overall survival (OS) was 11 months regardless of the intensity of chemotherapy. In the survival analysis, an Eastern Cooperative Oncology Group performance status $\geq$2, advanced stage, and *MYC* rearrangements were associated significantly with a worse outcome, whereas attaining a CR with chemotherapy was associated with a better outcome. **CONCLUSIONS:** The prognosis of PBL in HIV-infected individuals remains poor in the highly active antiretroviral therapy era. Intensive chemotherapy regimens do not seem to increase survival in patients with HIV-associated PBL. ***Cancer*** **2012;118:5270-7.** © *2012 American Cancer Society.*

KEYWORDS: human immunodeficiency virus, acquired immunodeficiency syndrome, plasmablastic, highly active antiretroviral therapy, chemotherapy.

INTRODUCTION

In 1997, Delecluse and colleagues presented a case series of 16 patients with plasmablastic lymphoma (PBL), an aggressive subtype of diffuse large B-cell lymphoma (DLBCL) with distinct clinicopathologic characteristics.[1] In that case series, the large majority of patients had human immunodeficiency virus (HIV) infection and presented with involvement of the oral cavity. PBL has been included in the World Health Organization (WHO) classification as 1 of the lymphomas observed more commonly in HIV-infected individuals.[2]

It is believed that the cell of origin of PBL is a postgerminal center B-lymphocyte or plasmablast.[3] Hence, the malignant cells in PBL usually do not express cluster of differentiation 20 (CD20) (B-lymphocyte antigen) but do express markers of

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plasmacytic differentiation, such as CD38 (cyclic adenosine diphosphate ribose hydrolase), CD138 (syndecan-1), or multiple myeloma oncogene 1/interferon regulatory factor 4 (MUM1/IRF4), akin to plasma cell myeloma (PCM).[4] However, based on genomic profiling, PBL appears to be more in line with DLBCL.[5] Case reports and small case series have demonstrated that HIV-associated PBL is associated with an aggressive clinical course and poor survival rates with standard therapies.[6,7] PBL, hence, poses a challenge for hematopathologists and oncologists alike. We conducted a multi-institutional, retrospective study to evaluate the characteristics and determine prognostic factors in patients with a pathologic diagnosis of HIV-associated PBL in the era of highly active antiretroviral therapy (HAART).

MATERIALS AND METHODS

Case Selection

Institutions in the United States, Europe, and South America submitted patient-level data on consecutive HIV-positive individuals with a pathologic diagnosis of PBL. This study has been approved by the institutional review board at each of the participating centers. For this study, all patients were required to have plasmablastic morphology, be CD20 negative, and express at least 1 plasmacytic marker (ie, CD38, CD138, and/or MUM1/IRF4). All cases were diagnosed between the years 2000 and 2011 and were reviewed by 2 hematopathologists at the center of initial diagnosis. Cases of primary cutaneous and primary brain PBL and cases of PBL diagnosed in HIV-negative individuals were not included. Three patients have been previously reported.[8] Clinical data included age, sex, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, years of HIV infection before PBL diagnosis, count of cells positive for CD4 (a glycoprotein expressed on the surface of T-helper cells, monocytes, macrophages, and dendritic cells), HIV viral load, receipt of HAART, opportunistic infections, the presence of B symptoms, the number and location of extralymph node sites, disease stage, lactate dehydrogenase (LDH) levels, age-adjusted International Prognostic Index (aaIPI) score, chemotherapeutic regimen, receipt of radiotherapy, response and method of response assessment, final outcome, progression-free survival (PFS), overall survival (OS), and cause of death. Laboratory data included hemoglobin level, white blood cell (WBC) count, absolute lymphocyte (ALC) and platelet counts, and the presence of a monoclonal spike by serum protein electrophoresis. Pathologic data included immunohistochemical expression of CD45 (protein tyrosine phosphatase receptor, type C), CD20, CD4, CD8 (transmembrane glycoprotein, a coreceptor for the T-cell receptor), CD56 (neural cell adhesion molecule), CD38, CD138, MUM1/IRF4, B-cell lymphoma 2 (BCL2), BCL6, anaplastic lymphoma kinase (ALK), Epstein Barr virus (EBV) latent membrane protein-1 (LMP1), human herpesvirus 8 (HHV8) latency-associated nuclear antigen (LANA), and Ki67. Molecular studies included the detection of EBV-encoded RNA (EBER) by in situ hybridization, HHV8 by polymerase chain reaction, and immunoglobulin heavy-chain gene and v-myc myelocytomatosis viral oncogene homolog (*MYC*) rearrangements by standard cytogenetic, fluorescent in situ hybridization or polymerase chain reaction studies.

Statistical Analysis

Continuous and categorical variables are presented using descriptive statistics. Response to therapy was assessed using the revised response criteria whenever possible.[9] PFS was defined as the time between diagnosis and progression, death, or last follow-up. OS was defined as the time between diagnosis and death or last follow-up. Univariate survival analyses were performed using the Kaplan-Meier method and the log-rank test. P values $< .05$ were considered statistically significant. All calculations and graphs were obtained using the statistical software MedCalc (MedCalc Software, Mariakerke, Belgium).

RESULTS

Patient Characteristics

Of 53 patients who were identified in 13 institutions, 50 were included in the current analysis. Two patients who were CD20-positive and 1 patient who had primary brain involvement were excluded. Twenty-four patients (48%) were from Europe, 23 patients (46%) were from the United States, and 3 patients (6%) were from South America. The median age was 43 years (range, 19-66 years). There was a predominance of men (4:1). The median CD4-positive count was 206 cells/mm^3 (range, 5-683 cells/mm^3), and the median viral load at presentation was 261,560 copies/mL (range, from undetectable to 4.7 million copies/mL). PBL was the initial presentation of HIV infection in 29% of patients (n = 13). The median duration between HIV infection and PBL diagnoses was 8.9 years (range, 0-26 years). Twenty-one patients (43%) were receiving HAART at the time of PBL diagnosis. Selected clinical characteristics are listed in Table 1. The most common extralymph node sites of involvement were oral cavity (n = 12; 24%), liver/spleen (n = 8; 16%), gastrointestinal tract (n = 7; 14%), central nervous system (n = 7; 14%), lungs (n = 6; 12%), bone/muscle (n = 5; 10%), skin (n = 3; 6%), and gonads

Table 1. Clinical Characteristics, Treatment, and Outcome of 50 Patients With Human Immunodeficiency Virus-Positive Plasmablastic Lymphoma

Patient Characteristic (No. of Patients With Available Data)	No. of Patients	Percentage
Age (n = 50), y		
>40	36	72
≤40	14	28
Sex (n = 50)		
Male	39	78
Female	11	22
CD4+ count (n = 48), cells/mm^3		
≤200	28	58
>200	20	42
HAART before PBL diagnosis (n = 49)		
Yes	21	43
No	28	57
HAART with PBL diagnosis (n = 49)		
Yes	40	82
No	9	18
B symptoms (n = 42)		
Absent	12	29
Present	30	71
ECOG performance status (n = 34)		
0-1	15	44
≥2	19	56
LDH levels (n = 40)		
Normal	10	25
Elevated	30	75
Clinical stage (n = 48)		
I and II	15	31
III and IV	33	69
No. of extra lymph node sites (n = 48)		
0-1	28	58
>1	20	42
Age-adjusted IPI score (n = 40)		
Low/low-intermediate	10	25
High/high-intermediate	30	75
Lymphoma therapy (n = 40)		
CHOP/CHOP-like	25	63
Other regimens	15	37
Response to therapy (n = 38)		
Complete	25	66
Partial	2	5
None	11	29
Outcome (n = 48)		
Alive	15	31
Dead	33	69
Cause of death (n = 33)		
Lymphoma	24	73
Infection	8	24

Abbreviations: CD4+, positive for cluster of differentiation 4 (a glycoprotein expressed on the surface of T-helper cells, monocytes, macrophages, and dendritic cells); CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; ECOG, Eastern Cooperative Oncology Group; HAART, highly active antiretroviral therapy; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PBL, plasmablastic lymphoma.

Table 2. Pathologic Characteristics of 50 Patients With a Diagnosis of Human Immunodeficiency Virus-Positive Plasmablastic Lymphoma

Marker	No. of Patients Tested	No. Positive for Marker (%)
CD45	31	20 (65)
CD20	50	0 (0)
CD4	17	1 (6)
CD8	11	0 (0)
CD56	25	9 (36)
CD38	9	8 (89)
CD138	30	26 (87)
MUM1/IRF4	25	25 (100)
BCL2	27	6 (22)
BCL6	26	1 (4)
ALK	14	0 (0)
Ki67 >80%	34	28 (82)
EBV LMP1	14	9 (64)
EBER	37	35 (95)
HHV8 LANA	28	0 (0)
HHV8 PCR	5	0 (0)
MYC rearrangement	21	9 (41)

Abbreviations: ALK, anaplastic lymphoma kinase; BCL2, B-cell lymphoma 2; BCL6, B-cell lymphoma 6; CD138, cluster of differentiation 138 (syndecan-1); CD20, cluster of differentiation 20 (B-lymphocyte antigen); CD38, cluster of differentiation 38 (cyclic adenosine diphosphate ribose hydrolase); CD4, cluster of differentiation 4 (glycoprotein expressed on the surface of T-helper cells, monocytes, macrophages, and dendritic cells); CD45, cluster of differentiation 45 (protein tyrosine phosphatase receptor, type C); CD56, cluster of differentiation 56 (neural cell adhesion molecule); CD8, cluster of differentiation 8 (transmembrane glycoprotein, a coreceptor for the T-cell receptor); EBER, Epstein-Barr virus-encoded RNA; EBV, Epstein Barr virus; HHV8, human herpesvirus 8; LANA, latency-associated nuclear antigen; LMP1, latent membrane protein-1; MUM1/IRF4, multiple myeloma oncogene 1/interferon regulatory factor 4; *MYC*, v-myc myelocytomatosis viral oncogene homolog; PCR: polymerase chain reaction.

(n = 3; 6%). The following laboratory were reported: 39% (n = 16) had a WBC count <4.0/μL, 51% (n = 21) had an ALC <1.0/μL, 34% (n = 14) had hemoglobin level <10 g/dL, and 32% (n = 13) had a platelet count <150/μL. Pathologic characteristics are listed in Table 2. The pathologic profile of a patient with HIV-associated PBL is provided in Figure 1.

Therapy and Outcome

Chemotherapy was received by 85% of patients (n = 40), with 63% (n = 25) receiving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and 37% (n = 15) receiving more intensive regimens (8 patients received infusional etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone [EPOCH]; 5 patients received hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [hyper-CVAD]; 1 patient received bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide [VDT-PACE]; and 1 patient received combined

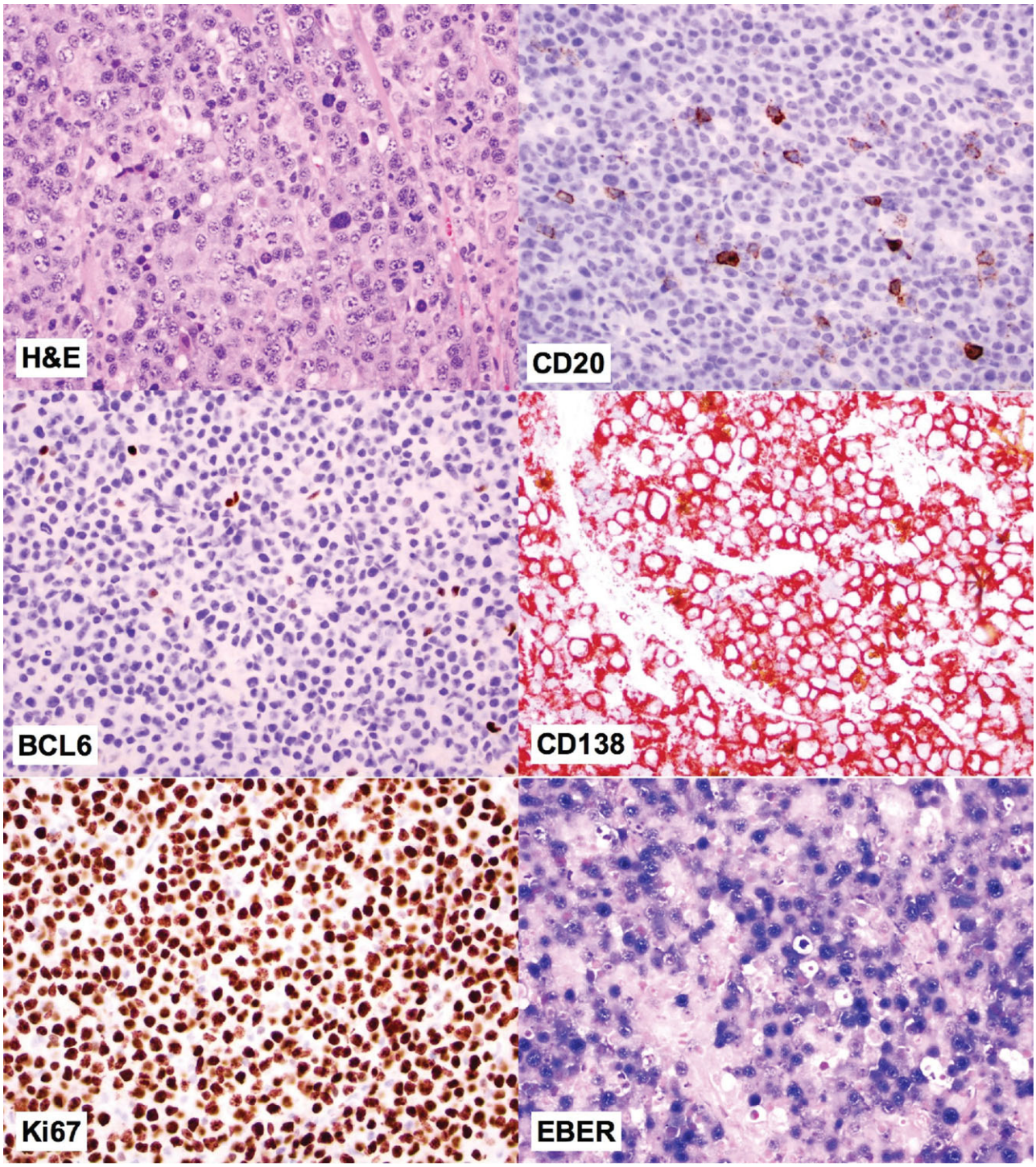

Figure 1. The pathologic profile of a patient with human immunodeficiency virus-associated plasmablastic lymphoma is illustrated. H&E indicates hematoxylin and eosin staining; CD20, cluster of differentiation 20 (B-lymphocyte antigen); BCL6, B-cell chronic lymphocytic leukemia/lymphoma 6; CD138, cluster of differentiation 138 (syndecan-1); Ki67, KI-67 antigen (identified by the monoclonal antibody Ki-67); EBER, Epstein-Barr virus-encoded RNA.

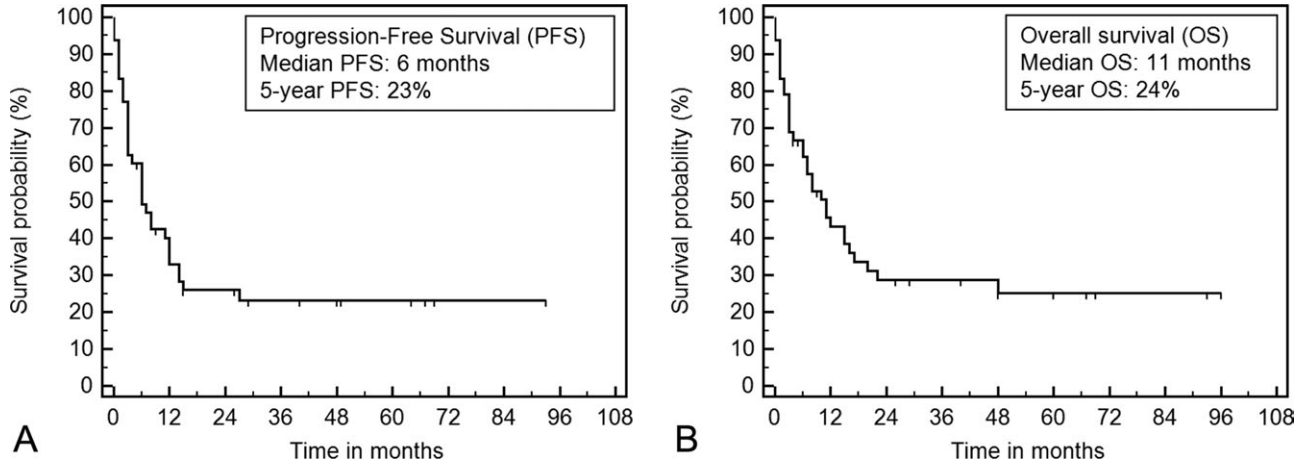

Figure 2. These charts illustrate the median (A) progression-free survival and (B) overall survival of 50 patients with plasmablastic lymphoma.

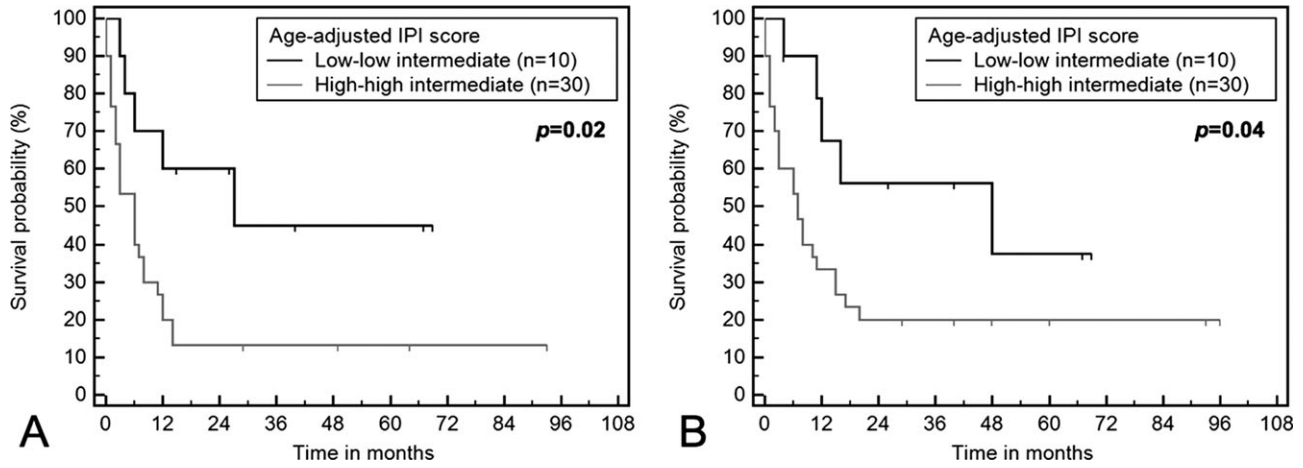

Figure 3. (A) Progression-free survival and (B) overall survival are illustrated according to age-adjusted International Prognostic Index (IPI) scores in 40 patients with plasmablastic lymphoma.

cyclophosphamide, vincristine, doxorubicin, and methotrexate plus ifosfamide, mesna, etoposide, and cytarabine [the Magrath regimen]). Radiotherapy was received by 6 patients (13%), mainly for palliative purposes, because 5 patients had stage IV disease. A minority of patients (n = 4; 10%) underwent autologous hematopoietic stem cell transplantation (HSCT), including 1 patient as part of front-line treatment and 3 patients in the relapsed setting. Response to therapy was assessed by positron emission tomography/computed tomography scans in 9 patients (23%) and by computed tomography scans in 30 patients (77%). A complete response (CR) was obtained in 66% of patients (n = 25), 5% of patients (n = 2) had a partial response, and 29% of patients (n = 11) had no response. Two patients died before response could be assessed and were not evaluable for response. Patients received a median of 2 lines of treatment (range, 1-5 lines of treatment). After a median follow-up of 48 months, 69% of patients (n = 33) had died.

Survival Analysis and Prognostic Factors

The median PFS and OS after diagnosis were 6 months and 11 months, respectively, and the estimated 5-year PFS and OS rates were 23% and 24%, respectively (Fig. 2). Among the patients who received chemotherapy, obtaining a CR was associated with a median OS of 48 months compared with 3 months for patients who obtained less than a CR ($P < .001$). In the survival analyses, an ECOG performance status $\geq$2, advanced stage, and *MYC* rearrangement were associated with shorter median PFS and OS rates. A high/high-intermediate aaIPI score was associated with worse PFS and OS than a low/

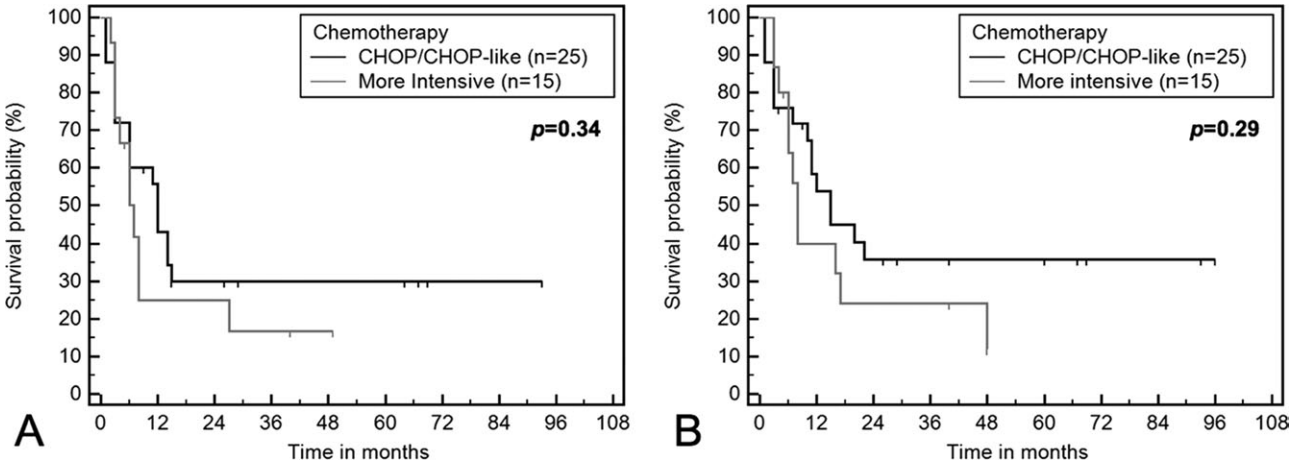

Figure 4. (A) Progression-free survival and (B) overall survival are illustrated according to chemotherapy in 40 patients with plasmablastic lymphoma. CHOP indicates combined cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 3. Univariate Progression-Free and Overall Survival Analyses in 50 Patients With Human Immunodeficiency Virus-Associated Plasmablastic Lymphoma

		PFS		OS	
Variable	No. With Risk Factor/ Total No.	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >40 y	36/50	0.81 (0.37-1.77)	.57	0.82 (0.38-1.78)	.59
Men	39/50	0.81 (0.37-1.81)	.57	0.59 (0.24-1.44)	.16
CD4+ count <200/mm^3	28/48	1.58 (0.80-3.15)	.19	1.84 (0.90-3.75)	.10
Use of HAART during chemotherapy	40/49	0.70 (0.26-1.91)	.41	0.67 (0.24-1.86)	.36
ECOG performance status ≥2	19/34	2.56 (1.21-5.44)	.009[a]	2.80 (1.28-6.13)	.01[a]
Bone marrow involvement	20/46	1.14 (0.57-2.30)	.69	1.26 (0.61-2.61)	.51
Clinical stage III and IV	33/48	2.26 (1.13-4.54)	.03[a]	2.05 (1.00-4.22)	.04[a]
Lymphocyte count <1.0/μL	21/41	1.74 (0.80-3.79)	.11	1.94 (0.87-4.33)	.07
Elevated LDH levels	30/40	2.10 (0.98-4.50)	.08	1.68 (0.75-3.77)	.24
Age-adjusted IPI score	30/40	2.83 (1.35-5.91)	.02[a]	2.49 (1.16-5.36)	.04[a]
Ki-67 >80%	28/34	1.76 (0.65-4.75)	.32	1.67 (0.60-4.64)	.39
MYC rearrangement	9/21	4.61 (1.17-18.1)	.003[a]	6.46 (1.47-28.3)	<.001[a]
More intensive than CHOP	15/40	1.41 (0.63-3.13)	.34	1.50 (0.66-3.41)	.29
CR to chemotherapy	25/38	0.26 (0.10-0.68)	<.001[a]	0.20 (0.07-0.57)	<.001[a]

Abbreviations: CD4+, positive for cluster of differentiation 4 (a glycoprotein expressed on the surface of T-helper cells, monocytes, macrophages, and dendritic cells); CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HAART, highly active antiretroviral therapy; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; *MYC*, v-myc myelocytomatosis viral oncogene homolog; OS, overall survival; PFS, progression-free survival.
[a] This *P* value indicates a statistically significant association.

low-intermediate aaIPI score (Fig. 3). There was a statistical trend toward a worse outcome for patients who had CD4-positive counts <200 cells/mm^3 and ALC <1.0/μL. There was no PFS or OS benefit from chemotherapy regimens more intensive than CHOP (Fig. 4). Complete univariate PFS and OS analyses are provided in Table 3.

DISCUSSION

PBL is an aggressive, CD20-negative B-cell lymphoma that is diagnosed more frequently in HIV-infected individuals.[2] In a recent review of the literature, no more than 150 cases of HIV-associated PBL were reported[10]; however, most of the data available consist of case reports and small case series.[11] Furthermore, current data do not discern between the pre-HAART era and the HAART era. Given the scarcity of cases, it is understandable that there have been no prospective studies in this specific population.

The current study in a larger set of patients confirms previous findings from smaller studies. Clinically, HIV-associated PBL is more likely to present in young men and is characterized by advanced stage, elevated LDH levels, extralymph node involvement, and high aaIPI scores. Pathologically, EBER expression, *MYC* rearrangements, and a Ki67 level >80% are common features of HIV-

associated PBL. With regard to therapy and outcome, most patients in our study received CHOP or more aggressive regimens; and, despite a 69% CR rate to chemotherapy, the median PFS and OS remained poor at 6 and 11 months, respectively. Not surprisingly, obtaining a CR to chemotherapy was associated with longer OS in patients with HIV-associated PBL. Finally, the most common cause of death in these patients was progression of the lymphoma.

Our study also provides new information on the biology, clinical behavior, pathology, therapy, and prognosis of HIV-associated PBL in the HAART era. First, the median CD4-positive count at the time of PBL diagnosis was 206 cells/mm$^{3.}$ This is likely a reflection of the higher proportion of patients on HAART at presentation in our cohort. This is a new finding, because other, more common HIV-associated lymphomas, such as DLBCL, primary central nervous system lymphoma, and primary effusion lymphoma, classically present with lower CD40-positive counts. Conversely, the risk of the more aggressive Burkitt lymphoma does not appear to be associated with such severe immunosuppression.[12] The reasons behind these patterns are yet to be fully explained.

Second, *MYC* rearrangements were detected in 41% of the patients (n = 9 of 22 patients) in our cohort, and its presence was associated with worse PFS and OS. Our study confirms that *MYC* rearrangements are frequent in PBL.[8,13] The number of patients tested in our study, however, was small, and these findings should be taken with caution. It is noteworthy that *MYC* rearrangements have been associated with a worse prognosis in other aggressive B-cell lymphomas,[14,15] although most of the lymphomas associated with *MYC* rearrangements have had a germinal center phenotype.[15] In the case of PBL, the cell of origin is a plasmablast, a postgerminal center B-lymphocyte that has undergone class-switching recombination and hypersomatic mutation but has not fully developed into a plasma cell.[3] Further studies are needed to understand the mechanism of acquisition and maintenance of *MYC* rearrangements in postgerminal center lymphomas.

Third, there was a difference between the original study by Delecluse and colleagues,[1] who reported 100% oral cavity involvement, and ours, in which we observed 24% oral cavity involvement. This proportion is similar to a recent report in patients with HIV-negative PBL in which 21% presented with oral cavity involvement.[16] Potential explanations for this discordance include the possibility that none of the patients on the study by Delecluse et al were receiving HAART, suggesting that HAART may have changed the scope of the disease or that, because of an increased clinical suspicion, more PBL cases that otherwise would have gone undiagnosed or misdiagnosed were identified. Currently, the mechanisms are unclear by which PBL would have a tropism for the oral cavity of HIV-positive individuals.

Fourth, in our survival analysis, an ECOG performance status $\geq$2 and advanced clinical stage were statically significant, adverse prognostic factors for PFS and OS. This has been reported previously in patients with HIV-associated aggressive B-cell lymphomas but provides additional data supporting use of the aaIPI score as a prognostic tool in patients with PBL. CD4-positive counts $<$200 cells/mm^3 and ALC $<$1.0/μL had a trend toward significance, likely reflecting the potential role of the immune system in the prognosis of patients with HIV-associated PBL. Lymphopenia has been variously associated with a worse prognosis in other systemic non-Hodgkin lymphomas,[17-19] but its prognostic role in PBL should be evaluated more extensively. Although the receipt of HAART did not seem to confer a survival advantage in our cohort, CRs to HAART have been reported in patients with HIV-associated PBL,[20] and the initiation of HAART should be advised.

A most important finding here is that patients with a diagnosis of HIV-associated PBL have a poor prognosis regardless of the therapy received. In patients with aggressive lymphoid malignancies, the lack of CD20 expression,[21] a plasmablastic morphology,[22] and the presence of *MYC* rearrangements[14] identify tumors that are refractory to chemotherapy and confer a worse outcome. In our cohort, the median OS of the 25 patients who received CHOP or CHOP-like regimens did not differ significantly compared with the 15 patients who received more intensive regimens, such as hyper-CVAD or the Magrath regimen. This supports findings from a previous literature review in which no survival benefit was reported from regimens that were more intensive than CHOP.[23] It is understandable that, given the poor results observed with CHOP-like regimens and the presence of *MYC* rearrangements in patients with PBL, the National Comprehensive Cancer Network would recommend more intensive regimens.[24] Although the results from our study do not support such a recommendation, future prospective studies are needed to address the effect of therapeutic regimens on survival.

There are several potential therapeutic options for patients with PBL. Recently, a small case series in HIV-negative PBL suggested that autologous HSCT in first remission was associated with an improved survival in such patients.[25] In our study, 1 patient underwent autologous HSCT in first CR, and 3 patients underwent autologous HSCT in the relapsed setting. At the time of this report, none of the patients who underwent

transplantation remained alive. Other options include borrowing agents from the antimyeloma armamentarium. A few case reports have suggested that the proteasome inhibitor bortezomib (Velcade; Millennium Pharmaceuticals, Cambridge, Mass) may be active in PBL.[26,27] In addition, recent data indicate specific activity of bortezomib in patients with postgerminal center DLBCL.[28] Immunomodulatory agents like lenalidomide (Revlimid; Celgene, Cambridge, Mass) also have demonstrated activity in PBL, although only at the level of case reports.[26]

In conclusion, in the HAART era, patients with HIV-associated PBL have a poor prognosis. The survival of patients with PBL does not appear to improve with more intensive chemotherapeutic regimens. Although the results are preliminary, it appears that *MYC* rearrangements are frequent in HIV-associated PBL and confer a worse prognosis. Because novel therapies are needed to treat these patients, we believe the current article should increase awareness of this rare lymphoma. Multi-institutional collaboration is warranted.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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