Prognostic factors in patients with HIV-associated peripheral T-cell lymphoma: A multicenter study

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HIV infection has been associated with an increased risk of developing several types of malignancies, including aggressive peripheral T-cell lymphomas (PTCL). However, this is a rare occurrence with no more than a hundred cases reported in the literature. The purpose of this multicenter study is to describe the characteristics and to identify prognostic factors in patients with HIV-associated PTCL. Data from HIV-positive patients with a pathological diagnosis of non-primary cutaneous, non-leukemic PTCL were gathered retrospectively and are reported using descriptive statistics. Univariate and multivariate survival analyses were also performed. Fifty one patients were included in our analysis. Median age was 38 years with a 5:1 male-to-female ratio. Patients presented with a median $CD4^+$ count of 173 cells mm^{-3}, and a median HIV viral load of 334,787 copies ml^{-1}. The median time from HIV diagnosis to PTCL diagnosis was 4.5 years. About 75% of patients presented with advanced clinical stage and 66% with B symptoms. The most common subtypes were PTCLU (61%) and anaplastic large cell lymphoma (ALCL, 22%). None of the ALCL patients tested expressed ALK. The median overall survival (OS) for the group was 12 months. In the multivariate survival analysis, the use of HAART and patients' performance status were independently associated with OS. HIV-associated PTCL presents predominantly in young men with low $CD4^+$ counts and high HIV viral loads. Both HIV-related and lymphoma-related factors were associated with OS. Am. J. Hematol. 86:256–261, 2011. © 2010 Wiley-Liss, Inc.

Introduction

Infection with the human immunodeficiency virus (HIV) is associated with a several-fold increased risk of developing aggressive B-cell lymphomas accounting for 70–90% of all the lymphoma cases seen in HIV-positive patients [1,2]. Epidemiological studies have demonstrated that HIV infection also increases the risk of developing other lymphoma subtypes, such as Hodgkin and peripheral T-cell lymphoma (PTCL).

Biggar et al. showed that HIV infection was associated with a 15-fold increase in the incidence of PTCL [3]. In this study, individuals infected with HIV had an increased risk of developing primary cutaneous as well as systemic PTCL. However, data on HIV-associated PTCL are largely limited to case reports [4–13] and small case series [14–17]. Hence, data on clinicopathological characteristics and prognostic factors in HIV-associated PTCL are lacking. A comprehensive review of the literature including 85 patients has recently been published [18]; however, due to the lack of pertinent data, potentially relevant prognostic indicators, such as the International Prognostic Index (IPI) and the Prognostic Index for PTCL, unspecified (PIT) score, were not evaluated.

The main objective of this study was to identify prognostic factors for survival in patients infected with HIV who have developed systemic PTCL. A secondary objective was to report original clinicopathological data on patients with HIV-associated PTCL.

Patients and Methods

Case selection. Patients were identified from the medical records of each participating institution. Cases with a serologically confirmed HIV infection that subsequently had a pathological diagnosis of anaplastic large cell lymphoma (ALCL), angioimmunoblastic lymphoma (AITL), NK/T-cell lymphoma (NKTCL), hepatosplenic T-cell lymphoma, enteropathy-type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma and PTCL, unspecified (PTCLU) were included. Each pathological sample was reviewed by a hematopathologist at the center of initial diagnosis and was reclassified according to the 2008 WHO Classification of Lymphoid Neoplasms [19]. The protocol was reviewed and approved by the Institutional Review Board of each of the participating institutions.

Because of their distinct characteristics, therapy and prognosis, primary cutaneous and leukemic variants such as primary cutaneous ALCL, mycosis fungoides, Sézary syndrome, and adult T-cell leukemia/lymphoma (ATLL) were excluded from the study.

Data gathering. Data on each case included country of origin, age at lymphoma diagnosis, gender, ethnicity, $CD4^+$ count at lymphoma diagnosis, use of highly active antiretroviral therapy (HAART), presence of B symptoms, PTCL subtype, expression of anaplastic lymphoma kinase (ALK), presence of EBV-encoded RNA (EBER) detected by an *in situ* hybridization (ISH) technique, Ki-67 expression (%), presence of T-cell receptor (TCR) gene rearrangement by polymerase chain reaction (PCR), primary site of disease, number of extranodal sites involved, bone marrow involvement, Ann Arbor clinical stage, ECOG perform-

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ance status, lactate dehydrogenase (LDH) levels, frontline therapy, response to frontline therapy, use of hematopoietic stem cell transplantation (HSCT), final outcome, overall survival (OS), and cause of death.

The age-adjusted IPI (aaIPI) score in each case was calculated using three variables, performance status ECOG $\geq$2, high LDH levels, and clinical Stage 3 or 4 [20]. The PIT score was calculated using four clinical variables, age $\geq$60 years, performance status ECOG $>$1, high LDH levels, and bone marrow involvement [21].

Statistical analysis. All the patients were included in the clinicopathological analysis while only chemotherapy-treated patients were included in the survival analysis. Clinicopathological variables were dichotomized to facilitate analysis and are presented using descriptive methods. The OS time was defined as the time in months elapsed between the date of diagnosis and the date of death or last follow-up. Univariate analysis was performed using Kaplan–Meier survival estimates [22], which were compared using the log-rank test [23]. The Cox proportional-hazard regression test was used for the multivariate analysis [24]. *P*-values of less than 0.05 were considered statistically significant. Calculations and graphics were obtained using the statistical software MedCalc version 11.4.2.0 (Mariakerke, Belgium).

Results

A total of 53 patients were initially submitted for this study. Two patients were excluded due to a diagnosis of primary cutaneous ALCL and ATLL, respectively. Fifty-one patients were finally included in this analysis. Nine cases have been previously published [16], but new and updated data are presented here.

Clinical characteristics

The main clinical characteristics of HIV-associated PTCL are shown in Table I. The median age at presentation was 38 years (range: 16–63 years), and 50 patients (98%) were younger than 60 years. The male-to-female ratio was 4.7:1. Twenty-six cases (51%) were reported from Europe, 14 cases (27%) from Latin America, 8 cases (16%) from the United States, and 3 cases (6%) from Asia. By ethnicity, 21 patients (42%) were Caucasian, 20 patients (40%) were Hispanic, 5 patients (10%) were Black, and 4 patients (8%) were Asian. The ethnicity of one patient was unknown.

With regard to HIV-related characteristics, the median $CD4^+$ count was 137 cells mm^{-3} (range: 4–604 cells mm^{-3}) and the median HIV viral load was 343,787 copies ml^{-1} (range: undetectable to 1.1 million copies ml^{-1}). The time from diagnosis of HIV infection to diagnosis of PTCL was available in 39 patients, with a median of 55 months (range: 0–231 months). Twelve patients (32%) had a diagnosis of AIDS and 10 (25%) were on HAART prior to their diagnosis of PTCL. Twenty two patients (54%) received HAART after the diagnosis of PTCL was made.

Among the lymphoma-related characteristics, 75% of patients presented with advanced clinical stage, 68% had elevated LDH levels, 66% presented with B symptoms, and 69% had at least one extranodal site involved. High aaIPI scores (two to three factors) were seen in 62%; scores of 0, 1, 2, and 3 were seen in 3 (8%), 11 (30%), 10 (27%), and 13 (35%) patients, respectively. High PIT scores (two to four factors) were seen in 51% of the patients; scores of 0, 1, 2, and 3–4 were seen in 7 (20%), 10 (29%), 13 (37%), and 5 (14%) patients, respectively.

Pathological characteristics

The main pathological characteristics of HIV-associated PTCL are shown in Table II. According to the 2008 WHO Classification of Lymphoid Neoplasms, 31 patients (61%) had PTCLU, 11 patients (22%) had ALCL, 7 patients (14%) had NKTCL, and 2 patients (4%) had AITL. No cases of hepatosplenic, enteropathy-type, or subcutaneous panniculitis-like PTCL were identified. Seven ALCL cases tested did not show ALK expression by immunohistochemistry. From the eight cases that were positive for EBER by ISH, 4 (50%) were NKTCL, 3 (37.5%) were PTCLU, and 1 (12.5%) was ALCL. The average expression of Ki67 was 60%, with a range of 10–95%; PTCLU, NKTCL, and AITL had an average expression of Ki67 of 75, 50, and 25%, respectively. TCR gene rearrangements were identified in 56% of the patients tested.

TABLE I. Clinical Characteristics of 51 Patients with HIV-Associated Peripheral T-Cell Lymphoma

Characteristic (n = cases with available data)	Number/median	Percentage/range
Age, years (n = 51)	38	16–63
Sex (n = 51)		
Male	42	82%
Female	9	18%
CD4+ counts (n = 38)		
$<$200 cells mm^{-3}	27	71%
$<$100 cells mm^{-3}	21	55%
$<$50 cells mm^{-3}	11	29%
Performance status (n = 49)		
ECOG 0-1	26	53%
ECOG $\geq$2	23	47%
LDH levels (n = 37)		
Normal	12	32%
Elevated	25	68%
Number of extranodal sites (n = 51)		
0–1 sites	27	53%
$>$1 site	24	47%
Clinical stage (n = 51)		
Early stage (I–II)	13	25%
Advanced stage (III–IV)	38	75%
Bone marrow involvement (n = 37)		
Non involved	28	76%
Involved	9	24%
B symptoms (n = 50)		
Absent	17	34%
Present	33	66%
IPI score (n = 39)		
Low/low-intermediate (0–1)	22	56%
High/high-intermediate (2–3)	17	44%
PIT score (n = 35)		
Low (0–1)	17	49%
High ($\geq$2)	18	51%
Lymphoma therapy (n = 42)		
CHOP or CHOP-like	30	71%
Other regimens	12	29%
Response to therapy (n = 42)		
Complete response	18	43%
Partial response	9	21%
No response	15	36%
Received stem cell transplantation	7	17%
Outcome (n = 51)		
Alive	17	33%
Dead	34	67%
Cause of death (n = 32)		
Lymphoma progression	20	63%
Infections	10	31%

PTCL: peripheral T-cell lymphoma, LDH: lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, PIT: Prognostic Index for PTCL, unspecified, CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone.

Treatment and response

Out of 51 patients, 9 did not receive chemotherapy because they died prior to the institution of therapy or best supportive care was pursued. From the 42 patients who received at least one cycle of chemotherapy, 30 patients (71%) received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); the remaining 12 patients received either CDE (cyclophosphamide, doxorubicin, etoposide; n = 5), PVB (cisplatin, vinblastine, bleomycin; n = 2), ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine; n = 1), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine; n = 1), CVP (cyclophosphamide, vincristine, prednisone; n = 1), ICE (ifosfamide, carboplatin, etoposide; n = 1), or ACVB (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; n = 1).

The overall response (OR) rate to chemotherapy was 64% (n = 27/42), with a 43% complete response (CR; n = 18) and 21% partial response (PR; n = 9). Progressive dis-

TABLE II. Selected Pathological Characteristics of 51 Patients with HIV-Associated Peripheral T-Cell Lymphoma

		ALK		EBER		Ki67 >80%		TCR	
Lymphoma subtype	Number of cases	No. tested	No. positive	No. tested	No. positive	No. tested	No. positive	No. tested	No. positive
PTCLU	31	7	0 (0%)	10	3 (30%)	9	5 (56%)	8	4 (50%)
ALCL	11	7	0 (0%)	2	1 (50%)	0	NA	5	3 (60%)
NKTCL	7	2	0 (0%)	6	4 (67%)	3	1 (33%)	2	1 (50%)
AITL	2	2	0 (0%)	2	0 (0%)	2	0 (0%)	1	1 (100%)
Total	51	18	0 (0%)	20	8 (40%)	14	6 (43%)	16	9 (56%)

AITL: angioimmunoblastic lymphoma; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase, EBER: Epstein Barr virus-encoded RNA, NKTCL: NK/T-cell lymphoma; PTCLU: peripheral T-cell lymphoma, unspecified; TCR: T-cell receptor gene rearrangement.

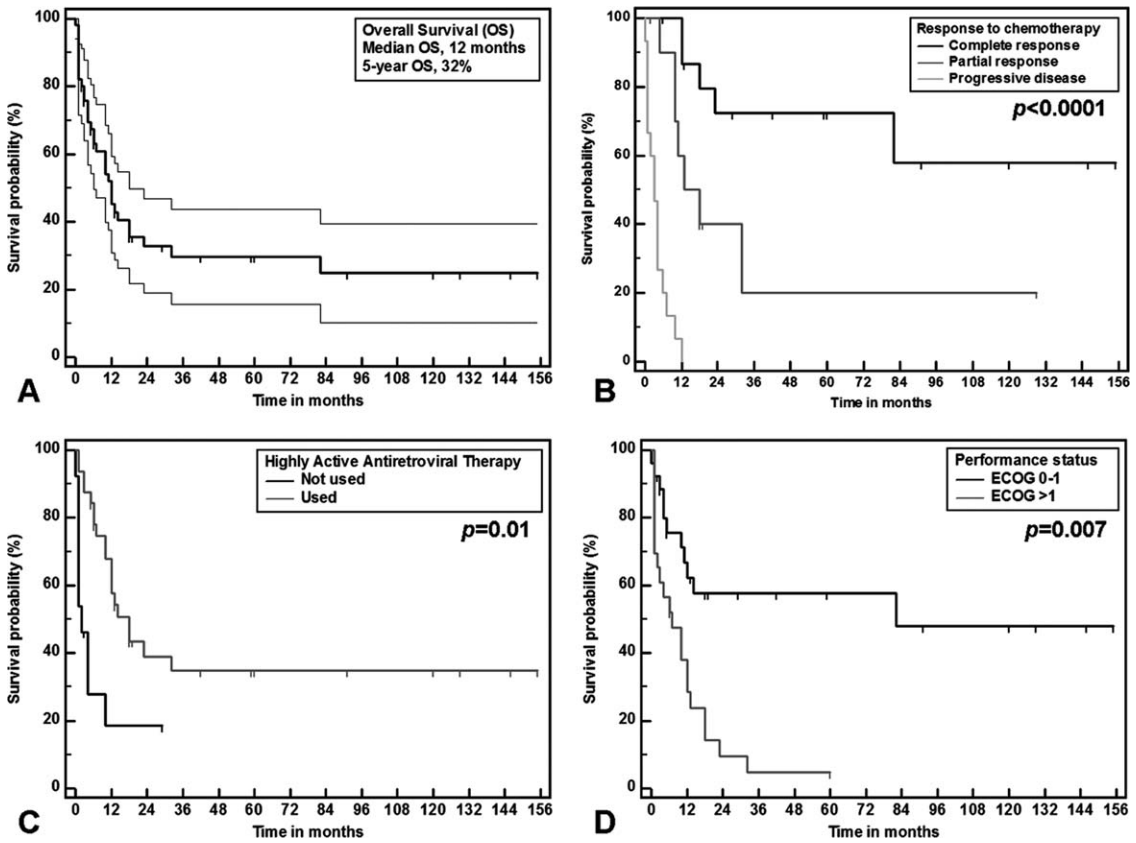

Figure 1. Kaplan–Meier survival estimates in 51 patients with HIV-associated peripheral T-cell lymphoma for the whole group (A), and according to response to chemotherapy (B), use of HAART (C) and performance status (D). A shows 95% confidence intervals.

ease (PD) was seen in 36% of patients ($n = 15$). Seven patients (17%) underwent autologous HSCT, five patients as part of frontline therapy, and two patients in the salvage setting. At the time of this report, after a median follow-up of 59 months (range: 3–146 months), 17 patients (33%) were still alive without disease while 34 patients (67%) were deceased. Causes of death included lymphoma progression (63%), infectious complications (31%), and cerebrovascular accidents (6%). Two of the infectious deaths (20%) occurred during chemotherapy.

Survival analysis

Survival data were available in 48 patients, from which 41 received at least one cycle of chemotherapy; survival time was not available in one patient treated with CHOP. The median OS for the entire group was 12 months and the 5-year OS was 32% (Fig. 1A). Among the patients who received chemotherapy, the median OS has not been reached in patients achieving a CR ($n = 18$), while patients who achieved PR ($n = 9$) or experienced PD ($n = 14$) had a median OS of 18 and 3 months, respectively ($P < 0.0001$; Fig. 1B).

In the univariate analysis (Table III), performance status ECOG ≥ 2 and $CD4^+$ counts <200 cells mm^{-3} at PTCL diagnosis were associated with a worse OS. The use of HAART was associated with a better OS. High aaIPI and high PIT scores were also associated with a better OS (data not shown). Other factors such as age, sex, ethnicity, B symptoms, extranodal and bone marrow involvement, advanced clinical stage, elevated LDH levels, and histological subtypes were not associated with OS. Because of the small sample size, survival analyses using EBER or Ki67 expression were not attempted.

In the multivariate analysis (Table III), the use of HAART was independently associated with a better prognosis (median OS 18 vs. 2 months; Fig. 1C) and a performance status ECOG ≥ 2 was independently associated with a worse survival (median OS 82 vs. 7 months; Fig. 1D). No other variables were retained in the model. The multivariate analysis did not include aaIPI or PIT scores since age, LDH levels, clinical stage, and bone marrow involvement did not show an association with median OS.

TABLE III. Univariate and Multivariate Survival Analysis in 51 Patients with HIV-Associated Peripheral T-Cell Lymphoma

	Univariate analysis		Multivariate analysis[a]	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male sex	1.1 (0.5–2.9)	NS		
$CD4^+$ count <200 cells mm^{-3}	3.4 (1.4–8.1)	**0.03**		
Use of HAART	0.3 (0.1–0.9)	**0.003**	0.3 (0.1–0.8)	**0.01**
Presence of B symptoms	2.0 (0.9–4.2)	NS		
Performance status ECOG ≥ 2	3.1 (1.5–6.7)	**0.001**	3.4 (1.4–8.1)	**0.007**
>1 extranodal sites	1.2 (0.6–2.5)	NS		
Bone marrow involvement	0.5 (0.2–1.4)	NS		
Clinical stage 3–4	1.0 (0.4–2.2)	NS		
Elevated LDH levels	0.9 (0.3–2.5)	NS		
aaIPI score 2–3	2.5 (1.0–6.1)	**0.025**		
PIT score 2–4	3.9 (1.5–10.0)	**0.004**		

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HAART: highly active antiretroviral therapy; HR: hazard ratio; LDH: lactate dehydrogenase; aaIPI: age-adjusted International Prognostic Index; PIT: Prognostic Index for PTCL, unspecified; NS: not significant.

[a] The multivariate analysis did not include aaIPI or PIT scores since clinical stage, LDH levels and bone marrow involvement were NS.

Survival in patients undergoing autologous HSCT

From the five patients undergoing autologous HSCT as part of their frontline regimen, three were in CR, one in PR, and one in PD. The latter died of lymphoma progression 10 months after diagnosis while the other four patients were alive at the time of this report with survivals of 5, 18, 42, and 129 months. Furthermore, the median OS of the five patients treated with frontline autologous HSCT has not been reached (data not shown). The two patients undergoing autologous HSCT as salvage therapy died 13 and 18 months after their PTCL diagnosis; one patient died of lymphoma progression and the other from infectious complications.

Discussion

PTCLs are rare lymphoproliferative disorders characterized by the dysregulated growth of malignant NK or T-cells, accounting for ~10–15% of all the cases of NHL [19]. Recent published data from the International Peripheral T-cell Lymphoma Project showed that these entities carry a poor prognosis despite modern therapeutic approaches [25]. HIV infection has been associated with an increased risk of developing aggressive subtypes of NHL; however, data on HIV-associated PTCL are largely limited to case reports [4–13] and small case series [14–17]. Here we present data on 51 patients with HIV-associated PTCL with a median follow-up of 59 months, and this is, to the best of our knowledge, the largest study reported to date.

Among the most salient clinical findings was that HIV-associated PTCL presented in individuals with a median $CD4^+$ count of 137 cells mm^{-3}. Furthermore, the median HIV viral load at diagnosis of PTCL was >300,000 copies ml^{-1}. These findings are similar to prior reports on aggressive B-cell lymphomas in HIV infected persons, such as DLBCL [26] and plasmablastic lymphoma [27], and suggests a relationship between immunosuppression and T-cell lymphomagenesis. The median age of PTCL diagnosis at 38 years and the male-to-female ratio (5:1) at presentation of PTCL are similar to other lymphoma subtypes in HIV-positive individuals [27]. In a similar fashion, HIV-associated PTCL patients tend to present frequently with advanced stage, extranodal involvement, and B symptoms.

Interestingly, the time from HIV diagnosis to PTCL diagnosis was ~4.5 years. Few studies have focused on the latency time between HIV infection diagnosis and the development of lymphoma. In the pre-HAART era, it was estimated that the median time between HIV infection and diagnosis of lymphoma was ~50 months [28]. However, this observation may need to be re-evaluated in the HAART era.

One of our pathological findings was the high proportion of patients with a pathological diagnosis of PTCLU (61%), which is not surprising since PTCLU is also the most common PTCL subtype seen in immunocompetent individuals. A second interesting finding was that, in our study, all the ALCL patients tested for ALK expression were negative. Patients with ALK-negative ALCL tend to be older and have a worse OS compared with their ALK-positive counterparts [29]. This finding is consistent with a recently published literature review of 37 cases of HIV-associated ALCL [30]. Based on this finding, one could theorize that the pathogenesis of ALCL in HIV-positive individuals is less dependent on ALK. Finally, the expression of EBER by ISH was found within the malignant cells in 50% of the NKTCL patients tested and also in a number of patients with PTCLU and ALCL. Although the pathogenetic role of EBV in NKTCL has been demonstrated [31], its relationship with PTCLU and ALCL remains unclear. For example, Dupuis et al. showed that 40% of immunocompetent patients with PTCLU expressed EBER mainly in CD20-positive cells within the tumors, although EBER was also expressed in rare CD2-positive cells [32]. In contrast, a study on immuncompetent patients with ALCL showed a complete absence of EBER expression in all 64 cases [33]. The pathogenetic role of EBV in PTCL needs to be further investigated.

With regard to response to therapy, the results from our study are consistent with prior reports in immunocompetent patients with PTCL, in which the OR rate to chemotherapy ranges from 50 to 70% [25]. Not surprisingly, patients who achieved a CR with chemotherapy had a statistically significant survival benefit. Although there is no standard of care for the initial treatment of PTCL, ~70% of the patients reported here received CHOP as part of their initial therapeutic regimen. A previous study has challenged the efficacy of anthracycline-containing regimens in PTCL [25]; however, 37 patients (88%) in the present series received anthracycline-based chemotherapy. Because of the small sample size, no further statistical analyses were attempted in this regard. The role of autologous HSCT is under investigation in patients with PTCL. In our series, five patients underwent HSCT as part of their frontline therapy with encouraging results, although prolonged survival was not seen in the two patients receiving HSCT as salvage therapy. However, this was a very small subset of patients to draw any definitive conclusions. In the light of a recently published case-control study by the European Group for Blood and Marrow Transplantation Lymphoma Working Party [34], in which similar survival was seen in patients with HIV-associated lymphomas and immunocompetent matched controls, further research is needed to clarify the optimal time for HSCT in HIV-associated PTCL.

The median OS of our patients was 12 months and no statistical differences in survival were observed among different PTCL subtypes (data not shown). This apparent lack of difference in OS could be due to equalization secondary to HIV infection or most likely the small sample of our study. Nonetheless, the median OS (12 months) in patients with HIV-associated PTCL appears shorter than in immunocompetent patients [25]. The 5-year OS (32%), however, seems similar to the one reported by the International T-cell Lymphoma Project [25]. A small case series compared the survival of patients with HIV-associated B-cell lymphoma and HIV-associated PTCL and found no statistical difference [14]; however, in that study, only 15% of the patients received HAART and $CD4^+$ counts were extremely low in both groups. Further studies are needed to clarify these observations in the HAART era.

Several prognostic factors have been described in HIV-associated lymphomas, and they have been subdivided into HIV-related and lymphoma-related factors. Among the HIV-related factors, low $CD4^+$ counts and the use of HAART have been frequently associated with survival [35,36]. Among the lymphoma-related factors, probably the most widely used risk-stratification tool is the IPI score [26,37,38]. It is unclear whether lymphoma-related factors are stronger prognosticators than HIV-related factors; however, it is likely that both play a role in HIV-associated lymphomas. In the univariate analysis, two HIV-related and three lymphoma-related factors were associated with OS. However, due to the lack of association between OS and age, clinical stage, LDH levels and extranodal involvement, the association between OS and the aaIPI and PIT scores likely relied heavily on performance status. Hence, these were not included in our multivariate analysis. In the multivariate analysis, the use of HAART was independently associated with a better OS while a performance status ECOG $\geq$2 was associated with a worse OS.

The use of HAART has not only been associated with a decrease in the incidence, but also an improvement in survival in HIV-associated lymphomas [39]. Furthermore, studies have shown that an immunological response to HAART could be the main reason for this survival benefit [40]. Unfortunately, our numbers were too small to evaluate timing of or response to HAART as prognostic factors. Performance status has been previously described as a prognostic factor in patients with a wide variety of HIV-associated lymphomas.

The main strengths of our study include the number of patients (n = 51), since less than a hundred cases have been reported in the literature, the multi-institutional participation, including USA, Europe, Asia, and South America, the ethnic diversity of the cohort, and the relatively long follow-up (5 years). Our study, however, carries several weaknesses, such as the retrospective nature of the investigation and the lack of central pathological evaluation. Retrospective studies are more prone to selection and reporting bias, hence the conclusions could have been potentially achieved by chance rather than a true association. However, several of our findings are consistent with prior reports. The lack of central pathological evaluation could have also affected the classification of our cases, although the cases were reviewed at the center of diagnosis and reclassified according to the 2008 WHO Classification. Despite these shortcomings, we were able to identify statistically significant prognostic factors for survival and describe the clinicopathological characteristics of patients with HIV-associated PTCL.

In conclusion, we present the largest study reporting original data in patients with HIV-associated PTCL, a rare lymphoma that represents a diagnostic and therapeutic challenge for modern clinicians. Our study shows that HIV-associated PTCL presents in young male patients with low $CD4^+$ counts and high HIV viral load. Patients commonly present with advanced stage and extranodal involvement. The most common subtype was PTCLU and we confirmed the lack of ALK expression in HIV-associated ALCL. Both HIV and lymphoma-related factors, namely use of HAART and performance status, respectively, were associated with OS. Further research is needed to clarify the role of HIV infection in the development of patients with PTCL, and to improve the survival of patients with HIV-associated PTCL.

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Erratum to: Prognostic factors in patients with HIV-associated peripheral T-cell lymphoma: A multicenter study

In the above mentioned article (Am J Hematol 2011;86:256–261, DOI21947), an author was inadvertently left off. Authors should have been listed as Jorge J. Castillo,[1*] Brady E. Beltran,[2] Michele Bibas,[3] Mark Bower,[4] Jaime A. Collins,[5] Kate Cwynarski,[6] Jose L. Diez-Martin,[7] Francisco Hernandez-Ilizaliturri,[8] Steven M. Horwitz,[9] Silvia Montoto,[10] Kikkeri Naresh,[11] Liron Pantanowitz,[12] Josep-Maria Ribera,[13] and Julie M. Vose[14]

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We apologize for any confusion this error might have caused.

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