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Outcomes of patients with advanced stage classical Hodgkin's lymphoma and human immunodeficiency virus infection treated with ABVD

Agreda Gladys*

Department of Hematology and Oncology, Responsible for the Lymphoma Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

***Corresponding Author:** Agreda Gladys, Department of Hematology and Oncology, Responsible for the Lymphoma Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico. Tel: 55 3333 3825, E-mail: gladys.agredav@incmnsz.mx

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Abstract

Classical Hodgkin's lymphoma (cHL) is a common neoplasm in persons living with the human immunodeficiency virus (HIV).

The aim of the present study was to determine the association of HIV infection status with treatment response and survival of advanced-stage cHL.

We retrospectively analyzed 77 male patients with advanced-stage cHL (21 patients with HIV infection) from a single institution and compared treatment response and survival rates between persons living with HIV (cHL-HIV) and patients without HIV infection (cHL-HIV negative).

Of the cohort, age was 43.8 ± 15.7 years; the presence of B symptoms (89.6%), stage IV (66.2%) and prognostic score (PSI) ≥4 (66.2%) was documented in higher proportion. 93.5% of patients received first-line treatment with a complete response (CR) rate of 65.3%. At last follow-up, 44.2% had active cHL and 27.3% had died, median overall survival (OS) had not been reached.

In the analysis of the cohort divided according to HIV infection status, the treatment response rate was similar. OS and event-free survival (EFS) did not demonstrate statistically significant differences (p=0.551 and p=0.483 respectively).

In patients with cHL-HIV, the median time between HIV diagnosis and cHL diagnosis was 3.4 years (0.4 - 6.9), the median CD4 reported was 109 cells/μL (41 - 239) and the median viral load was 50 copies/mL (40 - 147.25). Of the patients, 90.5% were receiving antiretroviral therapy (ART).

None of the variables analyzed showed an association with treatment response. In a multivariable analysis, only IPS ≥4 proved to be a risk factor for mortality [HR 6.3, (95% CI 0.5-26.8), p=0.013], whereas OS and EFS were higher in patients with IPS <4 (p=0.005 and p=0.040 respectively).

Finally, the results demonstrated that the HIV infection status is not a prognostic factor in male patients with advanced stage cHL.

Keywords: Hodgkin's lymphoma, HIV infection, ABVD, IPS

Introduction

Classical Hodgkin's lymphoma (cHL) accounts for 90% of all Hodgkin's lymphomas and is responsible for 0.5% of all cancers [1].

In people living with the human immunodeficiency virus (HIV), the incidence of cHL is 5 to 20 times higher compared with the general (HIV negative) population. The introduction of antiretroviral therapy (ART) and CD4 count >200 cells/μL appear to increase the risk, with the period of highest risk being the first 6 months after initiating ART [2-4].

The median age at diagnosis of cHL in people living with the HIV (cHL-HIV) is between 40 and 45 years, higher than that observed in the general population [3]. It is also more common in males (76% - 89%) than in females [2].

cHL-HIV is characterized by more aggressive clinical findings, higher frequency of B symptoms (85% vs. 43%), advanced stage disease (80% vs. 42%), extranodal disease (67% vs. 32%), and a high-risk prognostic score (68% vs. 26%) compared to the general population [2,5].

The most frequent histopathological subtype is mixed cellularity and about 90% of cases are associated with the Epstein-Barr virus (EBV) [2, 3].

With standard treatment and ART, the complete response (CR) rate ranges from 74% to 87%, while the estimated 5-year event-free survival (EFS) and overall survival (OS) are around 59% to 71% and 76% to 81%, respectively [6-9].

CD4 count <200 cells/μL, age ≥45 years and high-risk IPS are factors that have been associated with worse progression-free survival (PFS) and OS [5,7,8].

Current recommendations indicate that cHL-HIV should be treated with standard chemotherapy while continuing ART [11].

The aim of this study was to determine the association of HIV infection status with treatment response and survival of advanced stage cHL.

Material and Methods

Retrospective cohort study that included male patients, diagnosed with advanced stage cHL, from January 1, 2004, to December 31, 2018, at a single reference center in Mexico City. Patients with incomplete information were excluded. Due to the lack of female patients in the cHL-HIV group, it was decided to perform the analysis in male patients.

The institutional ethics committee approved the conduct of this study in accordance to the Good Clinical Practice guidelines of the International Conference on Harmonization.

All patients underwent standard clinical evaluation and staging procedures.

Demographic (age), clinical (B symptoms), laboratory [blood cytometry, albumin, lymphocyte-to-monocyte ratio (LMR) cut-off value <1.1] and imaging (number of affected lymph node regions, bulky disease) variables were obtained. Advanced stage was determined according to the Lugano classification and poor prognostic factors were identified according to the IPS [12,13].

In persons living with the HIV, baseline CD4 counts (cells/μL) and HIV-RNA viral load were obtained at the time of cHL diagnosis. Undetectable viral load was considered when HIV-RNA was below the limit of detection in serum (<40 copies).

Treatment consisted of standard ABVD chemotherapy (adriamycin 25 mg/m2, bleomycin 10 IU/m2, vinblastine 6 mg/m2 and dacarbazine 375 mg/m2) administered on days 1 and 15 every 28 days, for 6 cycles [14].

The evaluation of the response to treatment was performed according to the recommendations of the Lugano Classification [12].

OS was considered as the period between the date of diagnosis of cHL and the date of death or last follow-up. EFS was defined from the date from where response to treatment was observed assessment to the presence of relapse, progression and/or death.

For the analysis, the cohort was divided in two groups according to the HIV status (cHL-HIV and cHL-HIV negative). For qualitative variables, Fisher's exact test or Chi-squared-test was used; for quantitative data, Student's t test was used for independent samples and Mann-Whitney U test for non-parametric samples. Welch's correction was performed for age and ESR.

The Kaplan-Meier method was used for OS and EFS, and both were compared appropriately using the long-rank or generalized Wilcoxon test.

Bivariate and multivariate analysis were performed with the logistic regression model to obtain odds ratio (OR) for treatment response and Cox regression was performed for obtaining hazard ratios (Hazard Ratio HR) for mortality and EFS. A p value of <0.05 was considered to be statistically significant. IBM SPSS Statistics® version 26.0 and Jamovi version 2.2.5 were used for the analysis.

Results

Baseline Patient Characteristics

A total of 77 patients were included, with a mean age of 43.8 ± 15.7 years, 49.4% of patients fell within the group of ≥45 years. The presence of B symptoms was documented in 89.6%, 66.2% had stage IV and 66.2% had an IPS ≥4. LMR <1.1 was evident in 41.6%. The most frequent histologic subtype was mixed cellularity, present in 39%. Tissue expression of EBV could be determined in 87% of samples, being present in 76.6%.

A total of 21 patients (27.3%) had HIV infection. In the analysis of the cohort according to HIV status, no differences were found with respect to age, B symptoms, clinical stage III or IV, IPS, histologic subtype and EBV expression.

Bone marrow infiltration, leukocytes >15 x103/μL and LMR <1.1 showed a tendency to occur with higher proportion in cHL-HIV negative patients; only hemoglobin <10.5 g/dL was more frequent in cHL-HIV patients.

Differences in the number of involved nodal regions of 3.5 vs. 4 (p=0.040) and monocytes of 708 vs. 340 x103/μL (p=<0.001) were observed between cHL-HIV negative and cHL-HIV patients, respectively.

Additional baseline characteristics are described in Table 1.

Variables	Totaln=77	HIV negativen=56	HIVn=21	*p*
Age, years Age ≥45 years, *n* (%)	43.8 ± 15.7 38 (49.4)	44.2 ± 17.2 28 (50)	42.9 ± 10.9 10 (47.6)	0.695 0.852
B symptoms, *n* (%)	69 (89.6)	51 (91.1)	18 (85.7)	0.676
Clinical stage, *n* (%) III IV	26 (33.8) 51 (66.2)	18 (32.1) 38 (67.9)	8 (38.1) 13 (61.9)	0.623
Infiltrated bone marrow, *n* (%)	34 (44.2)	27 (48.2)	7 (33.3)	0.242
Lymph node regions, *n*	4 (3-5)	3.5 (2-4.3)	4 (3-6)	0.040
Bulky disease, *n* (%)	15 (19.5)	13 (23.2)	2 (9.5)	0.215
Laboratories, *n* (%) Hemoglobin <10.5 g/dL Leukocytes >15 x10^3/μL Lymphocytes <8% Lymphocytes <600 x10^3/μL Monocytes x10^3/μLMLR <1.1 Platelets x10^3/μL Albumin < 4 mg/dL	32 (41.6) 8 (10.4) 23 (29.9) 33 (42.9) 561 (297-880) 32 (41.6) 262 (141-340) 69 (89.6)	21 (37.5) 8 (14.3) 17 (30.4) 22 (39.3) 708 (424-956) 27 (48.2) 269 (119-348) 51 (91.1)	11 (52.4)0 (0)6 (28.6)11 (52.4)340 (185-544)5 (23.8)231 (152-286)18 (85.7)	0.238 0.099 1.000 0.301 <0.001 0.053 0.723 0.676
ESR mm/hr. *	60 (28-98.5)	63 (33-100)	38.5 (11.8-73.5)	0.217
IPS ≥4, *n* (%)	51 (66.2)	37 (66.1)	14 (66.7)	0.961
Histology, *n* (%) Nodular sclerosis Mixed cellularity Lymphocytic predominance Lymphocytic depletion Not specified	24 (31.2) 30 (39) 1 (1.3) 4 (5.2) 18 (23.4)	18 (32.1) 22 (39.3) 0 (0) 4 (7.1) 12 (21.4)	6 (28.6) 8 (38.1) 1 (4.8) 0 (0) 6 (28.6)	0.445
Report EBV, *n* (%)NegativeAssociatedNot reported	8 (10.4) 59 (76.6) 10 (13)	8 (14.3) 41 (73.2) 7 (12.5)	0 (0) 18 (85.7) 3 (14.3)	0.200
Treatment, *n* (%)ChemotherapyCyclesRadiotherapy	72 (93.5) 6 (6-6) 17 (23.6)	54 (96.4) 6 (6-6) 16 (29.6)	18 (85.7) 6 (6-6) 1 (5.6)	0.122 0.739 0.053
Response to treatment, *n* (%) **CompletePartialStable / ProgressionNot evaluated	47 (65.3) 3 (4.2) 14 (19.4) 8 (11.1)	36 (66.7) 2 (3.7) 10 (18.6) 6 (10.7)	11 (61.1) 1 (5.6) 4 (22.2) 2 (11.1)	0.961
Relapse, *n* (%)	11 (19.6)	9 (21.4)	2 (14.3)	0.711
Activity at last follow-up, *n* (%)	34 (44.2)	21 (37.5)	13 (61.9)	0.055
Mortality, *n* (%)	21 (27.3)	15 (26.8)	6 (28.6)	0.875
Data are presented as medians (Q1-Q3) and number (%).* ESR: Erythrocyte sedimentation rate (*n* = 59)**Response to treatment (*n* = 72)				

Table 1: Baseline characteristics of the total cohort and categorized according to HIV infection status

HIV Status Characteristics

In the 21 patients with cHL-HIV, the median time from diagnosis of HIV infection to diagnosis of cHL was 3.4 years (0.4 - 6.9).

Ninety-five percent were receiving ART at the time of cHL diagnosis. Two patients were not receiving ART due to the loss of the follow-up time from the HIV diagnosis to the cHL diagnosis. All patients on ART were receiving two nucleoside reverse transcriptase inhibitors, 63% were treated with a non-nucleoside reverse transcriptase inhibitor, 21% with two protease inhibitors and 11% with an integrase inhibitor.

The median CD4 count was 109 cells/μL (41 - 239). Viral load data was available for 90.5%, with a median of 50 copies/mL (40 - 147.25). In 4 patients, the diagnosis of HIV infection and cHL was made simultaneously.

In the subgroup analysis by viral load, in patients with a detectable load a tendency could be observed with respect to age (mean age was lower) and lymphocytes <600 x103/μL (i.e., the frequency with which lymphopenia was observed was higher); B symptoms were present in 100%, which resulted with statistical difference (p=0.036) compared to patients with undetectable viral load.

Additional characteristics are described in Table 2.

Variables	Undetectablen= 7	Detectablen= 12	*p*
Age, years Age ≥45 years, *n* (%)	48.4 ± 9.3 5 (71.4)	38.9 ± 10.6 4 (33.3)	0.066 0.170
CD4 cell/μL	180 (113-279)	85.5(39.8-232)	0.261
ART treatment, *n* (%) Drugs 2 3 4	7 (100) 0 (0) 5 (71.4) 2 (28.6)	10 (83.3) 1 (10) 9 (90) 0 (0)	 0.509 0.154
Symptoms B, *n* (%)	4 (57.1)	12 (100)	0.036
Clinical stage, *n* (%) III IV	3 (42.9)4 (57.1)	4 (33.3)8 (66.7)	1.000
Infiltrated bone marrow, *n* (%)	2 (28.6)	5 (41.7)	0.656
Lymph node regions, *n*	3.9 ± 2.0	4.9 ± 1.7	0.243
Bulky disease, *n* (%)	0 (0)	2 (16.7)	0.509
Blood cytometry, *n* (%) Hemoglobin <10.5 g/dL Leukocytes >15 x10^3/μL Lymphocytes in <8% Lymphocytes <600 x10^3/μL Monocytes x10^3/μL MLR <1.1 Platelets x10^3/μL	2 (28.6) 0 (0) 0 (0) 1 (14.3) 532 (395-566) 1 (14.3) 288 ± 127	7 (58.3) 0 (0) 5 (41.7) 8 (66.7) 269 (175-435) 3 (25) 228 ± 98	0.350 1.000 0.106 0.057 0.142 1.000 0.269
ESR mm/hr.*	9.5 (5.8-20.8)	48(28.5-83.5)	0.164
Albumin <4 mg/dL, *n* (%)	5 (71.4)	11 (91.7)	0.523
IPS ≥4, *n* (%)	3 (42.9)	9 (75)	0.326

Histology, *n* (%) Nodular sclerosis Mixed cellularity Lymphocytic predominance Not specified	1 (14.3) 3 (42.9) 1 (14.3) 2 (28.6)	5 (41.7) 4 (33.3) 0 (0) 3 (25)	0.514
Report EBV, *n* (%) Associated Not reported	6 (85.7) 1 (14.3)	11 (91.7) 1 (8.3)	1.000
Treatment, *n* (%) ChemotherapyCycles Radiotherapy	7 (100) 6 (5.5-6) 0 (0)	10 (83.3) 6 (6-6) 1 (1)	0.509 0.183 1.000
Response to treatment, *n* (%) Global Complete Partial Stable / Progression Not evaluated	4 (57.2) 3 (42.9) 1 (14.3) 1 (14.3) 2 (28.6)	7 (70) 7 (70) 0 (0) 3 (30) 0 (0)	0.170
Relapse, *n* (%)	0 (0)	1 (12.5)	1.000
Activity at last follow-up, *n* (%)	3 (42.9)	8 (66.7)	0.377
Mortality *n* (%)	1 (14.3)	3 (25)	1.000
In two patients, viral load values were not available at diagnosis of cHL and were therefore excluded from this subanalysis.Data are presented as means ± SD, medians (Q1-Q3) and number (%).*ESR: Erythrocyte sedimentation rate (n = 11), Welch´s correction was used.			

Table 2: Baseline characteristics of patients with HIV infection categorized by viral load

Treatment Outcomes and Survival

93.5% of the cohort received first-line treatment with ABVD, with a median of 6 cycles. In 5 patients no treatment was administered, 3 died at the time of diagnosis due to cHL and 2 did not accept treatment.

The overall response rate (ORR) was 69.5% and the CR rate was 65.3%.

In the analysis of the cohort divided according to HIV infection status, a tendency was observed in the proportion of patients who received treatment, which was higher in patients with cHL-HIV negative (96.4% versus 85.7% p=0.122). No differences were found with respect to response rate (Figure 1).

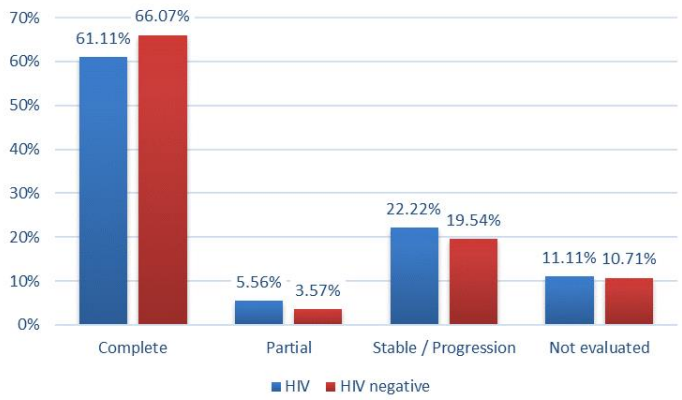

Figure 1: Clustered bars for treatment response categorized according to HIV infection Status

Relapse was documented in 19.6% and the mortality was 27.3% (Table 1), with no differences observed according to HIV infection status.

The most common cause of death was lymphoma in 66.7% (10 in cHL-HIV negative and 4 in cHL-HIV patients).

In the survival analysis of the cohort, divided according to the HIV infection status, the estimated 3- and 5-year OS was 73.1% and 62.5% in cHL-HIV patients vs. 71.2% and 65.1% in cHL-HIV negative patients (p=0.551) (Figure 2A). The median was not reached in both groups. When the analysis was performed according to IPS, the estimated OS at 3 and 5 years was 94.7% and 88.8% in patients with IPS <4 vs. 60.8% and 57.4% in patients with IPS ≥4 (p=0.005) (Figure 2B).

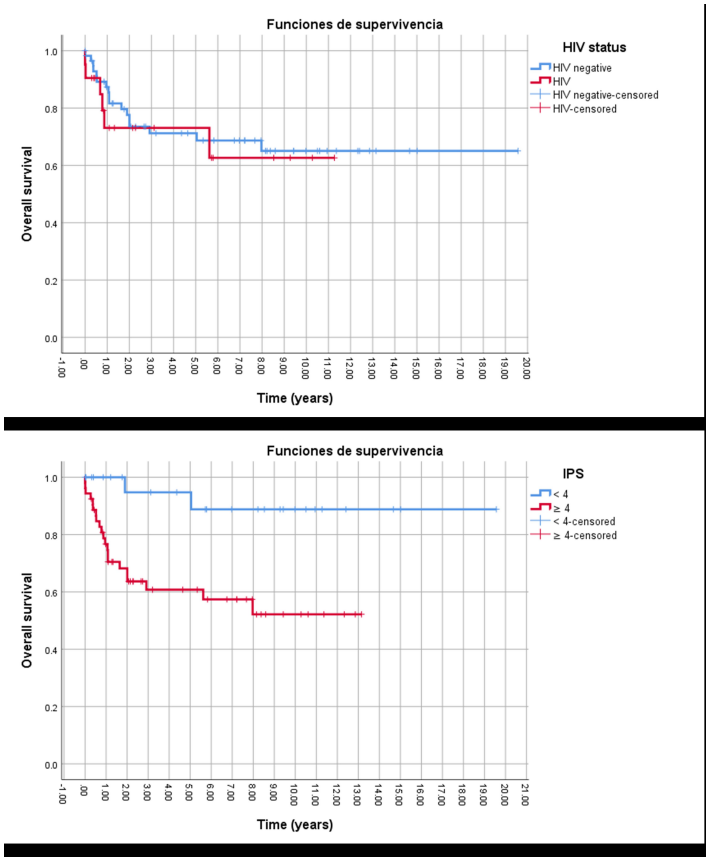

Figure 2: Kaplan-Meier for OS of the total cohort. A) Categorized accordingly to HIV infection status (p=0.551). B) Categorized according to IPS ≥ 4 (p=0.004)

The estimated 3- and 5-year EFS was 48.7% in cHL-HIV patients vs. 52.7% and 47.9% in cHL-HIV negative patients (p=0.483) (Figure 3A), with a median of 2.6 years vs. 4.4 years, respectively. When the analysis was performed according to IPS, the estimated 3 and 5 years EFS was 71.8% in patients with IPS <4 vs. 43% and 37.3% in patients with IPS ≥4 (p=0.040) (Figure 3B), with a median of 2.4 years in patients with IPS ≥4.

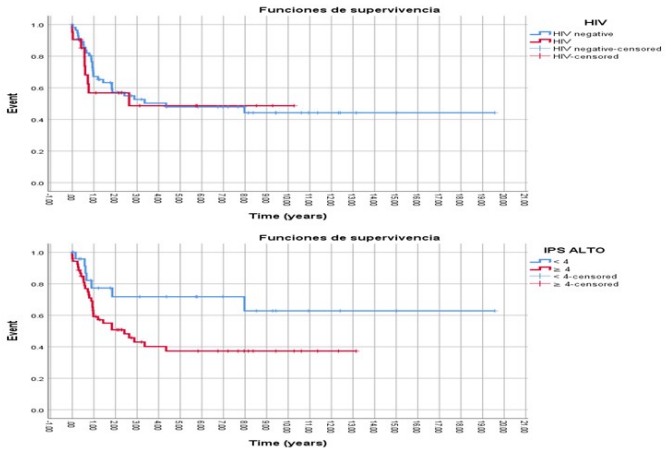

Figure 3: Kaplan-Meier for EFS of the total cohort. A) Categorized according to HIV infection status (p=0.483). B) Categorized according to IPS ≥ 4 (p=0.040)

In the bivariate analysis, HIV status was not a risk factor for treatment response [OR 1.3, (95%CI 0.4-4.4), p=0.682], mortality [HR 1.2, (95%CI 0.5-3.1), p=0.675] and EFS [HR 1.1, (95%CI 0.5-2.4) p=0.756]. IPS ≥4, on the contrary, proved to be a risk factor for mortality [HR 6.3, (95%CI 1.5-26.8), p=0.013] and EFS [HR 2-3, (95%CI 1.01-5.3), p=0.047] (Table 3).

Variables	Response to treatment		Mortality		EFS	
	OR (IC 95%)	*p*	HR (IC 95%)	*p*	HR (IC 95%)	*p*
HIV status	1.3 (0.4-4.4)	0.682	1.2 (0.5-3.1)	0.675	1.1 (0.5-2.4)	0.756
IPS ≥4	1.4 (0.4-4.7)	0.559	6.3 (1.5-26.8)	0.013	2.3 (1.01-5.3)	0.047
MLR ≥1.1	0.8 (0.3-2.5)	0.721	0.6 (0.3-1.4)	0.256	0.7 (0.4-1.3)	0.256
Logistic regression for the analysis of treatment response and Cox regression for the analysis of mortality and event-free survival (EFS).						

Table 3: Bivariate analysis of total cohort (n = 79)

In the multivariable analysis, IPS ≥4 remained as a risk factor for mortality [HR 6.3, (IC95% 1.4-27.6) p=0.016] and only a tendency for EFS (Table 4).

Variables	Response to treatment		Mortality		EFS	
	OR (IC 95%)	*p*	HR (IC 95%)	*p*	HR (IC 95%)	*p*
HIV status	1.4 (0.4-5.1)	0.606	1.6 (0.6-4.3)	0.337	1.4 (0.6-3.0)	0.423
IPS ≥4	1.4 (0.4-4.7)	0.613	6.3 (1.4-27.3)	0.016	2.2 (0.9-5.3)	0.067
MLR ≥1.1	0.8 (0.3-2.7)	0.735	0.8 (0.3-1.9)	0.646	0.4 (0.4-1.6)	0.509
Logistic regression for the analysis of treatment response and Cox regression for the analysis of mortality and event-free survival (EFS).						

Table 4: Multivariate analysis of total cohort (n = 79)

Discussion

The introduction of ART in the treatment of HIV infection represents a major change in the incidence of cancer in people living with the HIV. While aggressive forms of non-Hodgkin's lymphoma have decreased, the incidence of cHL has increased and now represents one of the leading causes of non-AIDS-defining neoplasms [3].

There are only a few studies that analyze the clinical characteristics of patients with cHL-HIV and that compare the outcomes of first-line treatment with patients with cHL-HIV negative. These studies have reported that patients with cHL-HIV present more frequent characteristics that confer worse prognosis, findings that differ from study to study. Sorigué et al. [9] reported that functional status, bone marrow involvement and histologic subtype are baseline characteristics of different clinical behavior between patients with cHL-HIV and cHL-HIV negative. Montoto et al, [7] and Besson et al, [5] reported that patients with cHL-HIV have higher risk disease according to IPS. In the present study, two baseline features resulted in different clinical behavior: a higher number of involved lymph node regions and lower monocyte counts in patients with cHL-HIV compared to patients with cHL-HIV negative; the proportion of patients with other clinically aggressive features was similar.

With respect to first-line treatment outcomes, the studies by Montoto et al, [7] and Sorigué et al, [9] have identified that HIV infection status is not associated as a poor prognostic factor for response and survival. In the present study, multivariate analysis performed according to HIV infection status found no differences in CR, EFS and OS rates, thus showing that the HIV infection status is not associated with worse treatment outcome. In contrast, when bivariate analysis was performed according to IPS if differences in SLE and OS rates were found, multivariate analysis identified that only IPS ≥4 is associated with worse OS.

These results are consistent with the findings reported by Montoto et al. for a IPS ≥3 [7]. Therefore, the outcomes of these patients are significantly affected by IPS regardless of HIV infection status. The studies by Castillo et al, [8] and Spina et al, [15] which included only patients with cHL-HIV, also show IPS as a poor prognostic factor PFS and OS, with different cutoff points for IPS (IPS >3 and IPS >2, respectively).

In addition, LMR <1.1 was investigated as a prognostic factor associated with poor survival according to the results of Vassilakopoulos et al, [16] but the present study was not able to demonstrate such association.

Finally, several limitations of the present study are recognized, such as its retrospective and single-centered nature, as well as the sample size; however, its main strength is that it is a cohort that compares patients with cHL-HIV and patients with cHL-HIV negative with similar baseline characteristics.

Conclusion

Treatment outcomes and survival are similar between cHL-HIV patients and cHL-HIV negative patients, HIV infection does not confer a worse prognosis in advanced stage cHL.

Declaration of Interest

All authors declare no competing interests of any nature. All participating investigators conducted this study in the context of their research line of work.

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