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Clinical characteristics and outcomes of HIV positive patients with lymphoma in an oncological reference center in Mexico City

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Abstract

The epidemiology of lymphomas has changed since the use of antiretroviral therapy. The incidence of Non-Hodgkin Lymphomas (NHL) has significantly decreased in high income countries but not in low and middle-income countries where AIDS-related events remain high. This observational study describes the characteristics, infectious complications and main outcomes of patients diagnosed with HIV and lymphoma at the Instituto Nacional de Cancerología.

All adults >18 years diagnosed with HIV and lymphoma from January 2010 to December 2017 were included. Information on HIV and lymphoma was collected, as well as the occurrence of co-infections at diagnosis and during therapy. Multiple regression was done with NHL patients to evaluate independent variables associated to death.

One hundred fifty three patients were included: 127 patients with NHL (83%) and 26 (17%) with Hodgkin lymphoma (HL). Of the NHL, 49 (38%) were diffuse large B cell Lymphomas (DLBCL), 35 (27%) plasmablastic, 28 (23%) Burkitt, 10 (8%) primary DLBCL of Central Nervous system, 3 (2%) T-cell lymphomas, and 2 (2%) pleural effusion lymphoma. Most patients were diagnosed in an advanced stage: 70% of NHL had a high International Prognostic Index (IPI); 68% of patients had <200 cells/mm^3. Almost 25% of NHL patients had an opportunistic infection at lymphoma diagnosis. During chemotherapy, 60% of all patients presented with at least 1 serious non-opportunistic infectious complication, and 50% presented 2 or more infectious complications, mostly bacterial infections. Thirty six percent of NHL and 23% of HL died. After adjusting for confounders, the variables associated with death were IPI and lymphoma type.

HIV positive patients with lymphoma in our institution are diagnosed with an advanced stage and a high burden of infections complications. Death remains high and the variables strongly associated with death are those related to lymphoma prognosis such as lymphoma type and IPI.

Abbreviations: ADC = AIDS defining cancers, ART = antiretroviral therapy, CMV = cytomegalovirus, CNS = Central Nervous System, CT = chemotherapy, DLBCL = diffuse large B cell Lymphomas, ECOG = Eastern Cooperative Oncology Group, HL = Hodgkin lymphoma, INCan = Instituto Nacional de Cancerología, IPI = International Prognostic Index, IQR = interquartile range, NHL = Non-Hodgkin Lymphomas, OI = opportunistic infection, OS = overall survival, PEL = pleural effusion lymphoma, PJP = pneumocytis jirovecii pneumonia, PLWHIV = people living with HIV.

Keywords: AIDS defining cancer, cancer survival in HIV, HIV and lymphoma, infections in lymphoma

1. Introduction

Since the introduction of combined antiretroviral therapies (ART), the epidemiology of AIDS defining neoplasms has changed.[1–3] In most developed countries, the incidence of NHL and AIDS-associated mortality have decreased, while other non-AIDS defining neoplasms, such as Hodgkin's Lymphoma (HL), have increased. However, in low and middle-income countries, there is still a high proportion of late diagnosis in those with low CD4 counts.[4] In Mexico, Non-Hodgkin Lymphoma (NHL) is the most frequent lymphoma, and AIDS defining events

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remain the main cause of mortality.[5] Recent Latin American HIV cohorts have reported AIDS defining cancers (ADC) account for 70% of all cancers in people living with HIV (PLWHIV). NHL represent 30% of all ADC.[6]

Risk factors associated to lymphoma's prognosis in PLWHIV include the International Prognosis Index (IPI) for Diffuse Large B-Cell Lymphoma (DLBCL), the Eastern Cooperative Oncology Group (ECOG) Performance Status, histologic subtype, cytomegalovirus (CMV) infection and CD4 low count.[7,8] Prior studies comparing the outcomes between HIV and non-HIV cohorts have reported inconsistent results. Two US studies found an association between low CD4, previous AIDS defining illnesses, and mortality in NHL.[9,10] Coutinho et al[11] reported high overall survivals in PLWHIV (>70%) in DLBCL, but they excluded all patients not receiving chemotherapy. Calcagno et al[7] reported a high proportion of infections during follow up (42%); particularly, CMV infection, which was associated with mortality. It would appear that PLWH and lymphoma still carry a worse prognosis compared to HIV uninfected individuals, once adjusted by tumor stage and subtype, probably associated to AIDS comorbidity and/or immunosuppression.[10,12]

Few studies have evaluated co-infections in PLWHIV and lymphoma and their impact on clinical outcomes. In Mexico, there have been no publications regarding infectious complications of lymphoma in PLWHIV. We aimed to describe the characteristics, infectious complications and main outcomes of patients diagnosed with HIV and lymphoma in an oncologic reference hospital of Mexico City, between 2010 and 2017.

2. Methods

2.1. Setting

This was a retrospective study in the Instituto Nacional de Cancerología (INCan) in Mexico City, a 150-bed teaching tertiary care hospital in Mexico City serving as a reference center for patients without employment insurance coming mainly from the central part of the country.

Since 2013, all patients coming to the Hematology Department of the INCan are offered an HIV test (4th generation ELISA) as part of the workup of lymphoma diagnosis. Since 2014, a rapid HIV test is also practiced. All positive tests are referred immediately to the Infectious Diseases Department.

2.2. Study participants

All adults older than 18 years with lymphoma and HIV diagnosis from January 2010 to December 2017 were included. HIV infection was defined as 2 positive ELISA tests or 1 positive ELISA plus Western Blot positive test or positive HIV viral load measured by polymerase chain reaction. The lymphoma diagnosis was corroborated by the Hemato-Pathology Department according to the 2008 WHO criteria.[13] Patients with less than 2 follow-up visits to the Hematology or Infectious Diseases department were excluded.

2.3. Study procedures

Electronic files were reviewed for data including age, sex, comorbidities, other sexually transmitted infections, CD4 cell count and HIV RNA viral load. Lymphoma was staged according to Lugano criteria[14] and International prognostic index (IPI). The ECOG performance score was recorded. All AIDS-defining infections prior to lymphoma diagnosis, at diagnosis, and during follow up, were reported. Information regarding chemotherapy, rituximab use and radiotherapy, was collected. In the hematology department, rituximab has been implemented as a standard of care for all CD20+ DLBCL since 2010, but it is not recommended for PLWHIV with <100 CD4 count.

Every infectious event, AIDS-related or not, was recorded from the date the chemotherapy started until one year after the last cycle. We describe overall mortality, infection-related mortality, lymphomas chemotherapy response and relapse, ART response, CD4 cell count and HIV viral load after chemotherapy ended. Lost to follow up included all patients whose death was not registered in the electronic file and with no consultation registered in more than a year.

2.4. Statistical analysis

Data are described as frequencies and measures of central tendency, with medians and interquartile range for quantitative variables, and proportions for qualitative variables. HL and NHL data are separated because the 2 entities have a different prognosis and pathogenesis. For statistical analysis, we used Mann–Whitney tests for quantitative variables and X^2 for qualitative variables. Variables associated with death were evaluated by multiple logistic regression; the model included all variables with a P value $\leq .1$ in the bivariate analysis. Statistical analysis and logistic regression were done only for NHL, due to the small sample for HL. STATA 14.2 was used.

2.5. Institutional review board

The study was approved by the INCan's Ethics Committee (IRB number: INCAN/CI/0606/18).

3. Results

3.1. General characteristics of the sample

One hundred fifty three patients were included: 26 (17%) patients with HL and 127 patients with NHL (83%). The general characteristics are described in Table 1: 90% were men, median age was 40 years (IQR 31–48), and almost 90% had no comorbidities. More than 50% had a history of smoking, 30% reported alcohol abuse and almost 20% had used other illegal substances. A third (32%) of all patients had a positive serology for hepatitis B infection (either past or current): 9.5% had positive Surface Antigen and 22.5% had positive Anticore antibodies. Three percent had hepatitis C antibodies. Kaposi Sarcoma was present in 8.5%, disseminated in 46% of cases. DLBCL was the most frequent NHL (38%), followed by plasmablastic (27%), and Burkitt (23%). Most patients were diagnosed in an advanced stage: 70% of NHL had a high IPI. Bone marrow infiltration was documented in 15% and 23% of NHL and HL respectively. Central nervous system (CNS) infiltration was present in 20% of NHL. More than 80% of NHL and 56% of HL were classified as Ann Arbor IV.

3.2. HIV characteristics at the time of lymphoma diagnosis

The median time from HIV to lymphoma diagnosis was 958 days for HL and 53 days for NHL. Sixty two percent of HL had been diagnosed with HIV for more than 1 year, compared to 34% of

Table 1

Baseline characteristics at lymphoma diagnosis.

	All, n = 153 (%)	NHL, n = 127 (%)	HL, n = 26 (%)
Sex:			
Men	138 (90.2)	114 (89.8)	24 (92.3)
Women	15 (9.8)	13 (10.2)	2 (7.7)
Age in years, median (IQR)	40 (31–48)	40 (31–49)	36.5 (30–45)
Comorbidities:			
None	137 (89.5)	113 (89)	24 (92.3)
Systemic hypertension	3 (2)	3 (2.4)	–
Diabetes Mellitus	2 (1.3)	2 (1.6)	–
Metabolic syndrome	2 (1.3)	2 (1.6)	–
Others	9 (5.9)	7 (5.4)	2 (7.7)
Substance abuse:			
Smoking	79 (51.6)	65 (51.2)	14 (53.9)
Alcohol	45 (29.4)	38 (29.9)	7 (26.9)
Other illegal use	29 (18.9)	26 (20.5)	3 (11.5)
Co-infections*:			
Hepatitis B			
AgS +	14 (9.5)	13 (10.7)	1 (3.9)
Anticore antibodies +	33 (22.5)	26 (21.5)	7 (26.9)
Hepatitis C	5 (3.4)	3 (2.5)	2 (7.7)
Syphilis	24 (22.6)	24 (18.2)	–
Kaposi Sarcoma	13 (8.5)	11 (8.7)	2 (7.7)
Mucocutaneous	7 (53.8)	7 (63.6)	–
Disseminated	6 (46.2)	4 (36.4)	2 (100)
Type of lymphoma:			
Diffuse large B cell Lymphoma		49 (38.6)	NA
Plasmablastic Lymphoma		35 (27.5)	NA
Burkitt Lymphoma		28 (22.0)	NA
Primary central nervous system Lymphoma		10 (7.9)	NA
Pleural effusion lymphoma		2 (1.6)	NA
T cell lymphoma		3 (2.4)	NA
International Prognostic Index:			
Low		27 (21.4)	NA
Intermediate		29 (23.0)	NA
High		70 (55.6)	NA
ECOG performance score:			
1–2	107 (69.9)	84 (66.1)	23 (88.5)
3–4	46 (30.1)	43 (33.9)	3 (11.5)
Bone marrow infiltration*	24 (16.4)	18 (15)	6 (23.1)
CNS infiltration*	20 (18.7)	20 (20.8)	–
Voluminous disease*	53 (35.8)	42 (34.4)	11 (42.3)
Ann Arbor classification:			
I–III	33 (21.8)	22 (17.5)	11 (44)
IV	118 (78.2)	104 (82.5)	14 (56.0)
B symptoms	132 (86.3)	111 (87.4)	21 (80.8)

* The n may vary due to missing values

AgS = Surface antigen hepatitis B virus, CNS = central nervous system, IQR = interquartile range.

Table 2

HIV characteristics of lymphoma patients.

	NHL n = 127	HL n = 26
Time between HIV diagnosis and lymphoma diagnosis in days, median (IQR)	53 (2–727)	958 (9–1650)
CD4, cells/mm^3		
Baseline (at HIV diagnosis)	84 (32–191)	278 (146–382)
At lymphoma diagnosis	98 (35–221)	165 (88–327)
Viral load, $\log_{10}$ copies/mL		
Baseline (at HIV diagnosis)	5.2 (4.8–5.7)	4.6 (4.3–5.0)
At lymphoma diagnosis	4.9 (2.3–5.6)	1.6 (1.6–4.3)
ART prior to lymphoma diagnosis, n(%)	56 (44.1)	17 (65.4)
History of virologic failure, n(%)	11/54 (20.4)	2/17 (11.8)
History of abandon, n(%)	17/54 (31.5)	3/17 (17.7)
ART started at lymphoma diagnosis, n(%)	61 (48.0)	9 (34.6)
Time between lymphoma diagnosis and ART start in days, median (IQR)	19 (8–35)	15 (4–33)

ART = antiretroviral therapy, IQR = interquartile range.

NHL patients. HIV and HL were diagnosed within less than 30 days in 27% of cases, compared to 46.5% of NHL. Eight patients were diagnosed with HIV after initiating chemotherapy. All except one of these patients were diagnosed before 2013, when routine HIV test was still not offered.

Baseline CD4 count at HIV diagnosis was higher in HL than NHL: 278 cells/mm^3, (IQR 146–382) and 84 cells/mm^3, (IQR 32–191) respectively. HIV was diagnosed at an advanced stage (less than 200 cells/mm^3) in 68% of all patients. Half of NHL patients had less than 100 cells/mm^3 (compared to 27% of HL patients, $P = .02$). Baseline viral load was higher in NHL than HL (5.2 log10 copies/ml vs 4.6 log10 copies/ml, $P = .006$), and 56% of HL patients had less than 50 copies/ml at lymphoma diagnosis. Forty four percent of NHL had started ARV prior to their lymphoma diagnosis, and more than half of them had a history of either virologic failure (20%) or stopping treatment (31.5%). In HL patients, 65% had started ART prior to the lymphoma diagnosis; 12% had a history of virologic failure and 18% of stopping treatment (Table 2).

Almost 25% of NHL patients were diagnosed with an opportunistic infection (OI) at the time of lymphoma diagnosis (esophageal candidiasis (31%), *Pneumocystis jirovecii* (PJP) pneumonia (22%), histoplasmosis (11%), CMV disease (17%) and mycobacterial infections (8%)) (Table 3). Four patients with HL (15%) had an OI (esophageal candidiasis, histoplasmosis, PJP and tuberculosis) at lymphoma diagnosis. More than 30% of NHL presented with at least 1 non-opportunistic infection at lymphoma diagnosis: oral candidiasis (22%), skin and soft tissue infections (15%), bacteremia (11%), pneumonia (13%) and urinary tract infection (13%). Overall, 47% of NHL and 35% of HL had at least 1 infection at lymphoma diagnosis, opportunistic or not.

3.3. Lymphoma treatment

Eighty one percent of NHL and 92% of HL started chemotherapy (CT). Patients differed in ECOG performance score: 70% of patients who did not start chemotherapy had an ECOG 3 to 4, compared to 22% in patients who started ($P < .0001$). Patients who did not start CT tended to have lower CD4 count at the time of lymphoma diagnosis (73 vs 125 cell/mm3, $P = .1$) and more infectious complications (opportunistic or not), than the ones who started CT (73% vs 39%, $P = .002$). There were no differences in Ann Arbor Stage or IPI. For the patients who started CT, the median time to start after lymphoma diagnosis was 18 days (IQR 10–39 days). The most common CT given was DA-EPOCH (61%) and CHOP (31%) in NHL, and ABVD (79%) in HL. Of all CD20+ NHL, 45% received rituximab, either with DA-EPOCH of CHOP. Forty eight percent of NHL and 35% of HL started ART after lymphoma diagnosis. The median time to start ART at lymphoma diagnosis was 19 days in NHL (IQR 8–35 days) and 15 days in HL (IQR 4–33 days). This was not modified by the presence of opportunistic infections or any infection at lymphoma diagnosis.

Table 3

Baseline infections (at lymphoma diagnosis).

	NHL n = 127	HL n = 26
Number of patients with opportunistic infections prior to the lymphoma diagnosis[+]	15 (11.8)	1 (3.9)
Number of patients with opportunistic infections at lymphoma diagnosis	31 (24.4)	4 (15.4)
Opportunistic infection at lymphoma diagnosis[*]		
Esophageal Candidiasis	11 (32.3)	1 (25)
P. jirovecii pneumonia	7 (20.6)	1 (25)
Histoplasmosis	4 (11.8)	1 (25)
CMV disease[**]	5 (14.7)	–
Tuberculosis	1 (2.9)	1 (25)
Other mycobacterial infections	2 (5.9)	–
Toxoplasmosis	1 (2.9)	–
Disseminated herpes zoster infection	1 (2.9)	–
Fungal infection (not specified)	2 (1.5)	–
Non opportunistic infections at lymphoma diagnosis		
Non serious infections[***]	17 (37.8)	3 (50)
Fever and neutropenia	3 (6.7)	
Skin and soft tissue infection	7 (15.6)	1 (16.7)
Pneumonia	6 (13.3)	2 (33.3)
Diarrhea	3 (6.7)	–
Bacteremia	5 (11.1)	–
Neuroinfection	1 (2.2)	–
Anal abscess	1 (2.2)	–
Acute abdomen	1 (2.2)	
Varicella	1 (2.2)	–

[+]HL: Tuberculosis (1), NHL: CMV retinitis (1), *Pneumocystis jiroveci* pneumonia (5), Herpes zoster virus (2), Tuberculosis (2), fungal infection (1), atypical mycobacteria (2), meningeal cryptococosis (2).
[*] Some patients had 2 or more simultaneous infections.
[**] includes retinitis, pneumonia, gastrointestinal (colitis) and disseminated CMV.
[***] includes urinary tract infection (not pyelonephritis), upper airway infection, localized herpes simplex, oral candidiasis.

3.4. Infectious complications during treatment

During CT, 60% of all patients presented with at least 1 serious non-opportunistic infectious complication, and 50% presented with 2 or more infectious complications. A detailed description of all infectious complications during CT for NHL patients is shown in Tables 4 and 5. There were 203 non-opportunistic events during treatment, and 20 OI events. Opportunistic infections only represented 10% of all infections occurring during treatment. The most frequent infectious complications were bacteremias (12%), pneumonias (14%), febrile neutropenia (12%), (without microorganism or etiology reported) and diarrheic syndrome or neutropenic colitis (13%), which all together accounted for half of all complications (51%). Another 29% were classified as "non-serious" infections, such as upper airway infection, urinary tract infection, oral candidiasis and localized herpes simplex infection (Table 4).

The microbiologic etiology was identified in 68 non-OI events (35%). *E. coli* was the most common cause of bacteremias (26%). Enterobacterias accounted for 48% of all bacteremias. Other etiologies comprised *S.epidermidis* (11%), *Enterococcus* spp (7%) and *S.aureus* (7%). For pneumonias, etiology was found in 39%. The most common were enterobacteria (14%) followed by *P.aeruginosa* (11%) and *S.aureus* (7%). One diarrheic patient had *Clostridioides difficile* colitis, another had *Cryptosporidium* sp. Four patients with upper airway infection were diagnosed with Influenza A H1N1[3] and H3N2[1] (Table 1 supplement, http://links.lww.com/MD/E924).

Regarding all OI, 60% of them occurred at lymphoma diagnosis and 40% during CT. The most frequent OI were Candidiasis (24%) PJP (22%), histoplasmosis (18.5%), mycobacterial infections (MAC and tuberculosis, 18.5%) and CMV 14%. Regarding PJP, 27% occurred while on prophylaxis with Trimethoprim/sulfamethoxazole. Histopathology and culture (including bone marrow and tissue culture) were useful diagnostic methods for OI, accounting for 24% and 15% of the diagnosis of all OI, respectively, but the diagnostic yield increased when excluding PJP and Candida infections which were usually diagnosed by clinical suspicion or visually by endoscopy, up to 45% and 28% respectively (Table 5).

3.5. Main outcomes

Fifty six percent of NHL and 71% of HL patients that received hematologic treatment had a complete response to first line CT. Overall, 36% of NHL died, with a median time from lymphoma diagnosis to death of 55 days (IQR 19–222); 23% of HL died, with median time from lymphoma to death of 179 days (IQR 33–199). Death was attributed to an infectious cause in 46% of NHL and 50% of HL. Forty percent of NHL who died did not receive CT, compared to 7% of the patients who survived ($P < .001$).

Table 4

Non opportunistic Infectious complications during chemotherapy for Non Hodgkin Lymphoma, by event.

NO. OF EVENT	1° n = 74	2° n = 49	3° n = 36	4° n = 23	5° n = 13	6° n = 8	TOTAL n = 203
Pneumonia	9 (12.1)	6 (12.3)	6 (16.7)	3 (13.0)	3 (23.1)	1 (12.5)	28 (13.8)
Bacteremia	11 (14.9)	5 (10.2)	4 (11.1)	1 (4.4)	3 (23.1)	1 (12.5)	25 (12.3)
Fever and neutropenia[†]	10 (13.5)	9 (18.4)	2 (5.6)	2 (8.7)	1 (7.7)	1 (12.5)	25 (12.3)
Diarrhea/neutropenic colitis	9 (12.1)	8 (16.3)	2 (5.6)	5 (21.7)	–	3 (37.5)	27 (13.3)
Skin and soft tissue infection	9 (12.1)	4 (8.2)	3 (8.3)	3 (13.0)	1 (7.7)	–	20 (9.8)
Herpes Zoster infection	3 (4.1)	1 (2.0)	1 (2.8)	1 (4.4)	1 (7.7)	–	7 (3.5)
Perianal abscess	2 (2.7)	–	–	2 (8.7)	–	–	4 (2.0)
Apendicitis / acute abdomen	–	–	–	–	1 (7.7)	–	1 (0.5)
CNS infection	1 (1.4)	–	1 (2.8)	–	–	–	2 (1.0)
Invasive fungal infection (non OI)	1 (1.4)	–	–	–	1 (7.7)	–	2 (1.0)
Non serious infections[*]	19 (25.7)	16 (32.6)	17 (47.1)	6 (26.1)	2 (15.3)	2 (25.0)	62 (30.5)

[*] upper airway infection, urinary tract infection (not pyelonephritis), oral candidiasis, localized herpes simplex infection.
[†] no etiology found.

Table 5

Characteristics of the opportunistic infections occurring at baseline and during treatment for NHL.

	Aspergillosis N=2	Histoplasmosis N=10	Candida N=13	TB N=6	Atypical mycobacteria+ N=4	CMV N=7	PJP N=12	Total N=54
Timing of infection:								
At lymphoma diagnosis	2	4	11	1	2	6	8	34
During treatment:		6	2	5	2	1	4	20
Diagnosis method:								
Clinical suspicion	–	3	5	1			7	16
Visual			7			2		9
Molecular								
Staining		2		2			1	5
Culture		1	1		4			4
Bone marrow culture		3			1[a]			4
Histopathology	1	1		3	2[a]	5	1	13
Image	1						3	4
Others		1*						
Infection site								
Bloodstream			1					1
Ophthalmic						2		2
Gastrointestinal	1		12		1	3		12
Skin and soft tissue		1						1
Lung	1	2		3	1	1		8
Central nervous system				1				1
Lymph node		1		2	1			4
Disseminated		5			1	1		7

* 1 Urinary antigen positive, from 5 tests.

[a] disseminated cases were diagnosed by multiple methods.

+3 MAC and 1 *M. fortuitum.*

Of the remaining 101 patients whose death was not documented, 63% were still in remission at the moment of the data collection (75% of HL and 60.5% of NHL), and 23% were lost to follow up (10% of HL and 26% of NHL); 86.5% of all patients still on follow up had an undetectable viral load (<40 copies/ml) and 92% had less than 200 copies/ml (n=76).

3.6. Variables associated to death

For the statistical analysis, only NHL were considered. The classification of NHL was simplified, pleural effusion lymphoma (PEL) and primary CNS lymphoma were grouped together, and T cell lymphomas were excluded, due to their different clinical course and histopathology and low representation in our sample (only 3). In the bivariate analysis, there was evidence of an association between death and viral load at lymphoma diagnosis, baseline CD4 count, Ann Arbor stage, IPI, ECOG, bone marrow infiltration, the presence of infections at lymphoma diagnosis (opportunistic and non-opportunistic) and lymphoma type (Table 2 supplement, http://links.lww.com/MD/E925). For the multiple logistic regression, all variables with a P value $\leq .1$ in the bivariate analysis were included in the model, as well as sex and age (Table 6). We excluded all patients lost to follow up, as we could not ascertain if they were alive or not. We excluded Ann Arbor stage and ECOG performance status since these are part of the IPI score. After adjusting for confounders, there was still a strong association between IPI and death: NHL with high IPI had 46 times the odds of dying comparing to NHL with low IPI risk. There was also an association between the type of lymphoma and death: Burkitt and primary CNS or PEL had higher odds of death than plasmablastic lymphomas. The presence of infections was not associated to death.

Table 6

Multivariate logistic regression for variables associated to death in NHL.

	aOR (CI95%)	*P* Value
Sex		
Men	1	
Women	0.29 (0.04–2.09)	.22
Age		
≤40 years	1	
>40 years	0.41 (0.12–1.45)	.17
VL at lymphoma diagnosis		
<100000 copies/ml	1	
≥100000 copies/ml	2.93 (0.89–9.68)	.08
Baseline CD4 count		
≤100 cell/mm^3	1	
>100 cell/mm^3	0.32 (0.08–1.25)	.10
Lymphoma type		
Plasmablastic	1	
DLBCL	3.16 (0.70–14.32)	.14
Burkitt	7.87 (1.25–49.42)	.03
1ary CNS/PEL	27.52 (2.17–349.06)	.01
Infectious complications at lymphoma diagnosis		
No	1	
Yes	1.25 (0.36–4.35)	.73
IPI		
Low	1	
Intermediate	26.03 (1.21–559.57)	.04
High	46.43 (2.62–822.49)	.01
Bone marrow infiltration		
No	1	
Yes	2.67 (0.53–13.46)	.23

CNS = central nervous system, DLBCL = Diffuse B Large Cell lymphoma, PEL = pleural effusion lymphoma, VL = viral load.

4. Discussion

This study describes a sample of PLWHIV and lymphoma, predominantly men (90%), with few chronic comorbidities (only 10%), mainly diagnosed in an advanced HIV and lymphoma stages, with frequent infectious complications, both at baseline and during the chemotherapy.

Both HL and NHL patients had a median CD4 count <200 cell/mm^3 (165 and 98 cell/mm^3 respectively) at lymphoma diagnosis, and NHL had a median <100 cell/mm^3 at HIV diagnosis (84 cell/mm^3). This reflects HIV Latin American epidemiology.[4,15] The CCASANET cohort reported 72% of their cancers to be ADC, with a median CD4 count at cancer diagnosis of 89 cell/mm^3.[6] Late diagnosis also explains the high proportion of opportunistic infections at diagnosis (almost a third of NHL patients). The simultaneous diagnosis of HIV and NHL explains higher HIV viral loads at lymphoma diagnosis, in contrast to HL patients who were usually diagnosed many years after HIV diagnosis, were receiving ART and had an undetectable viral load at lymphoma diagnosis. Interestingly, almost a third of NHL patients who were previously on ART had either a history of virologic failure or stopping treatment; these episodes of uncontrolled HIV and immunosuppression state may have favored the presence of lymphoma.[12,16] All this underscores the necessity to improve access to an earlier HIV diagnosis and better adherence and retention to care once diagnosed.

Similar to what has been described in HIV-NHL subtypes, there was a large proportion of B-cell lymphomas, such as DLBCL, Burkitt and plasmablastic lymphomas,[17] and a high proportion of Ann Arbor stages III or IV, as well as bone marrow and CNS involvement. These findings are comparable to many international reports on PLWHIV.[8,10,11]

There was a high proportion of infectious complications at lymphoma diagnosis and during CT treatment. Opportunistic infections were mostly seen at lymphoma diagnosis (60%). The most frequent infections described (invasive candidiasis, PJP, histoplasmosis, mycobacterial infections and CMV) are similar to what has been reported in CCASANET.[18] This emphasizes the relevance of an exhaustive baseline workup to identify all potential co-infections in HIV patients. In our institute, it is routine for all patients recently diagnosed with HIV and less than 100 cell/mm^3 to undergo bone marrow culture and biopsy, ophthalmologic evaluation, lytic cultures, serum Cryptococcal antigen and serology and urinary antigen for *Histoplasma* spp, simultaneously to the lymphoma workup. Lymph node biopsy culture is also a routine in HIV-associated lymphoma patients, as well as bronchoalveolar lavage culture if any lung abnormality is detected. Up to 45% of our opportunistic infections were diagnosed through histopathology and tissue or bone marrow culture and biopsy. These diagnostic methods were predominantly useful for mycobacterial infections (tuberculosis and MAC) and histoplasmosis. We consider this should be established as a routine for every HIV positive patient with lymphoma. The correct identification of co-infections allows prompt treatment initiation in order to avoid delays in lymphoma treatment. Prophylaxis with trimethoprim/sulfamethoxazole is also routinely administered to all our patients and should be a standard of care for all HIV positive patients receiving chemotherapy, regardless of the CD4 count, considering it will decline during treatment.[19,20]

Non-opportunistic infections were the most frequent infections during CT (90%), mostly bacterial infections such as the ones usually seen in the general hemato-oncological population receiving chemotherapy. Enterobacterias were the most frequent microorganisms identified. This is very similar to what has been reported in HIV negative cohorts and at our own institution.[21–23] The occurrence of infections during CT in those reports varies from 30 to 63%; we report 60%. Literature on infectious complications in PLWHIV during lymphoma treatment is scarce. Calcagno et al[7] also reported a high proportion of complications in their retrospective cohort of 103 patients (43%), and the most common etiology was bacterial infections. We did not find reports comparing the frequency of infections between HIV positive and negative patients.

Median time from lymphoma diagnosis to CT treatment and ART initiation was 18 to 19 days, less than 3 weeks. This probably represents the time needed to complete the workup for both diagnoses. It was not modified by the presence of baseline infections, opportunistic or not, probably because none of the opportunistic infections documented at baseline had an indication for delaying ART, such as meningeal tuberculosis or cryptococcosis. It is shorter than what has been reported in CCASANET (5 weeks in PLWHIV with an opportunistic infection at diagnosis).[18]

Regarding infectious complications, some studies report infection as an independent factor for prediction of death.[22,23] In this sample, 20% of the NHL patients did not receive CT; those patients had more frequent baseline infections than the patients who did receive treatment. There was also an association between infectious complications and death in the bivariate analysis. However, after adjusting for confounders, there was no association between any type of infectious diseases (opportunistic, non-opportunistic, serious or not) and death. We did not find CD4 count less than 100 cells/mm^3 or HIV viremia to be independent predictors of mortality, as others have reported.[7]

Thirty six percent of the NHL patients died, and the median time to death from lymphoma diagnosis was less than 2 months (55 days, IQR 19–222); 40% of the patients who died did not receive CT. If we exclude patients who did not receive CT, mortality was 26%. Previous international publications have reported mortality rates up to 60%.[8–10,24] However, we report a high proportion of lost to follow up, that can be contributing to some bias in the outcome codification. If we consider all the patients lost to follow up (26%) to have died, the survival proportion would be similar to these publications (50%–60%).

There was evidence of a strong association between factors related to lymphoma prognosis, (IPI and lymphoma type) and death. We report a slightly better prognosis and lower proportion of deaths in plasmablastic lymphomas, than Burkitt, PEL or primary CNS lymphomas. There are few reports of plasmablastic lymphomas, but overall 1-year survival (OS) has been reported up to 67% in HIV patients.[17] LYSA group reported a median OS of 32 months in patients treated with anthracycline-based regimens; in this study the IPI was also the most significant independent prognostic factor.[25]

The remission rate was high (63% in NHL and 75% in HL) in the patients who survived. There were also high rates of controlled HIV viremia (>85%). It would seem that after surviving the first 2 months of lymphoma diagnosis, where mortality is higher, patients have good response rates.

This study has strengths and limitations. First, our sample is bigger than most other reports, which allows for a richer population and better statistical analysis. Secondly, the study also includes a more recent sample compared to many publications on

prognosis that include patients up to 2010 to 2012, and it includes information on infectious complications, which almost no previous report has included. However, it is a retrospective study, and we cannot ascertain causality in the association we describe between some variables and death. We did not find HIV-related variables to be associated to death, but we did not compare with a control group (HIV negative) to be able to say that HIV does not play a role in the prognosis of lymphomas. We also report a high proportion of patients lost to follow up which could generate some bias in the results, notably regarding mortality data. Finally, our sample is from 1 single reference center in Mexico City, which could question the generalizability of the results, however patients come from many parts of the country, and we consider the sample represents well the HIV positive population of our country, and have similar findings with the Latin American cohorts to support it.

In conclusion, we report a sample of Mexican PLWHIV with lymphoma diagnosed mostly as an AIDS defining illness, in an advanced stage of both HIV and lymphoma, with a high proportion of infectious complications at baseline and related to chemotherapy. This underscores the need for an exhaustive and early workup for infections in these patients, to avoid delays in treatment. Mortality remains high, mostly in the first 2 months of diagnosis. Despite the burden of these infections, the main and strongest associations with death are variables related to lymphoma prognosis such as lymphoma type and IPI.

Author contributions

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