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AIDS and Non-Hodgkin's lymphoma. Experience at an oncological center in Mexico

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ABSTRACT

Background. Non-Hodgkin lymphoma (NHL) associated with HIV became an AIDS-defining condition early in the epidemic and remains the second most common malignancy in patients with AIDS. With the advent of highly active antiretroviral therapy (HAART), the incidence and mortality of AIDS-related opportunistic infections and Kaposi's sarcoma has fallen dramatically, this trend is not observed so clearly for NHL. Our objective was to review the clinical spectrum of patients with AIDS-associated NHL and to analyze the impact of HAART on survival at an oncological tertiary center. **Material and methods.** We reviewed all medical records and histopathologic tissue of patients with HIV-associated NHL seen from January 1990 to September 2007 at the Instituto Nacional de Cancerologia in Mexico City. Survival or follow-up time was calculated from date of diagnosis to death, or to the date on which the patient was last seen. **Results.** Eighty seven HIV-positive patients were diagnosed with NHL (diffuse large B-cell lymphoma n = 69; Burkitt-like n = 8; pleomorphic large cell n = 7; low-grade n = 2, and angiocentric n = 1). Twenty eight patients never received HAART, and 59 received HAART. Overall, 38 patients (43.7%) achieved complete response to NHL therapy, including only 14.3% patients in the non-HAART compared with 57.6% in the HAART group ($p = 0.0001$). Two patients (7.1%) in the non-HAART were alive compared with 37 (63.8%) in the HAART group ($p \leq 0.0001$). Mean survival time for all patients was 11 ± 16.8 months. Survival was significantly shorter in patients not receiving HAART (4.8 ± 7.6 months) as compared with those who did (14 ± 19.2) ($p = 0.01$). **Conclusions.** Patients with NHL-HIV who were able to receive treatment with HAART and were sufficiently healthy to receive optimal chemotherapy treatment showed a significantly better prognosis.

Key words. Non-Hodgkin lymphoma. Human immunodeficiency virus. Highly active antiretroviral therapy. Survival.

SIDA y linfoma no-Hodgkin. Experiencia en un centro oncológico en México

RESUMEN

Introducción. *El linfoma no-Hodgkin (LNH) ocupa el segundo lugar en frecuencia de las neoplasias asociadas al virus de inmunodeficiencia humana (VIH). El uso de terapia antirretroviral altamente efectiva (TARAA) se ha asociado con disminución en la mortalidad relacionada con sarcoma de Kaposi y con infecciones oportunistas; este beneficio es menos claro para LNH. El objetivo de este estudio es describir las características clínicas de los pacientes con LNH asociado a VIH y analizar el impacto de TARAA en la supervivencia, en un centro oncológico en México.* ***Material y métodos.*** *Se revisaron todos los expedientes clínicos y muestras histopatológicas de los pacientes con LNH-VIH diagnosticados de enero de 1990 a septiembre del 2007 en el Instituto Nacional de Cancerología en la ciudad de México. La supervivencia o tiempo de seguimiento se calculó desde la fecha del diagnóstico hasta la muerte o hasta la última visita.* ***Resultados.*** *Se diagnosticaron 87 pacientes con VIH y LNH (difuso de células grandes n = 69, tipo Burkitt n = 8, pleomorfo n = 7, de bajo grado n = 2, y angiocéntrico n = 1). Veintiocho pacientes no recibieron TARAA y 59 si lo recibieron. Treinta y ocho pacientes (43%) presentaron remisión completa del LNH: 14.3% del grupo sin TARAA y 57.6% del grupo con TARAA ($p < 0.0001$). Dos pacientes del grupo sin TARAA (7.1%) estaban vivos al final del periodo de estudio, comparados con 37 (63.8%) del grupo con TARAA ($p \leq 0.0001$). El tiempo promedio de supervivencia para todos los pacientes fue de 11 ± 16.8 meses; para el grupo sin TARAA fue de 4.8 ± 7.6, para el grupo con TARAA fue de 14 ± 19.2 meses ($p = 0.01$).* ***Conclusiones.*** *Los pacientes con LNH-VIH que se encuentran en condiciones clínicas adecuadas para recibir TARAA y un esquema óptimo de quimioterapia, presentan un mejor pronóstico.*

Palabras clave. *Linfoma no-Hodgkin. Virus de inmunodeficiencia humana. Terapia antirretroviral altamente efectiva. Supervivencia*

INTRODUCTION

Non-Hodgkin lymphoma (NHL) associated with human immunodeficiency virus (HIV) became an acquired immunodeficiency syndrome (AIDS)-defining condition early in the epidemic and remains the second most common malignancy in patients with AIDS.[1] The risk of NHL is 150-250-fold higher among HIV-infected individuals. This malignancy has been associated with advanced HIV disease and low CD4 counts (usually < 100 cells/mm^3), as well as with high-grade histologic subtypes.[2,3] However, up to one quarter of cases of NHL may develop in highly active antiretroviral therapy (HAART)-treated patients with an undetectable HIV viral load.[4,5]

With the advent of HAART, the incidence and mortality of AIDS-related opportunistic infections and Kaposi's sarcoma has fallen dramatically. The decrease in frequency is not observed as clearly for NHL.[2,6-9] In developed countries with open access to HAART, the prognosis of HIV-related NHL appears to be impacted positively by HAART, and at present survival in some groups can be similar to non-HIV infected patients.[4,10] This positive impact on prognosis in HIV-associated NHL has not been described the setting of middle- and low-income countries, where access to HAART cannot be extended to all at-risk individuals.[11]

Our objective was to review the clinical spectrum of patients with AIDS-associated NHL and to analyze the impact of HAART on survival at the Instituto Nacional of Cancerologia (INCan) during the most recent 17-year period.

MATERIALS AND METHODS

We conducted a retrospective analysis of all HIV-infected patients with NHL seen at a tertiary-care referral oncology hospital for adult patients in Mexico City, between January 1990 and September 2007. We included all patients ≥ 16 years of age with proven histopathology of NHL who tested positive for HIV using enzyme-linked immunoabsorbent assay (ELISA), the results of which were confirmed by Western blot analysis. Histopathology staging was performed employing the Revised European-American Classification for Lymphoid Neoplasms (R.E.A.L.) and was reviewed by a single pathologist. Immunophenotyping tissue profiles were determined by immunohistochemical staining of paraffin-tissue sections with monoclonal antibodies to antigens expressed on B lymphocytes, T lymphocytes, and mononuclear phagocytes as described previously.[12]

We retrospectively collected data on age, gender, route of exposure to HIV, date of HIV infection diagnosis, CD4+ count, and HIV viral load at HIV diagnosis at the beginning of antiretroviral treatment and the last CD4 and viral load tested, antiretroviral treatment (ARVT) type, time in months on ARVT, history of Kaposi's sarcoma and other AIDS-defining events, and serologic markers of HCV and HBV co-infection. Regarding information on NHL, we gathered data on presence of B symptoms (night sweats, weight loss, fever), date of diagnosis, histological classification, immunophenotyping, Ann Arbor staging, sites involved, tumor size >10 cm (qualified as voluminous disease), chemotherapy regimens, first- and second-line, number of chemotherapy cycles, percent of dose received, adverse effects related with chemotherapy, and number of episodes of severe neutropenia and fever. For patients who received radiotherapy, we recorded gray (Gy) administered. Laboratory results at time of NHL diagnosis included complete CBC, LDH, β-2 microglobulin, viral load, and CD4 and CD8 cell counts.

NHL response to therapy was classified –at tend of treatment or at the last visit to the hospital (in cases not completing treatment)–as complete response, partial response, progression, relapse, death, or loss of patient to follow-up. Status of the patient was recorded at last hospital visit as either alive, lost to follow-up, or dead. Survival or follow-up time was calculated from date of diagnosis to death, or to the date when the patient was last seen. In case of death, we recorded whether the death was related with NHL, related with HIV opportunistic infection, with chemotherapy toxicity, or unknown.

Statistical analysis

Comparisons among patients were analyzed with Student t test, Fisher exact test, and Mann-Whitney test or χ^2 test as appropriate. Comparisons were performed for non-HAART and HAART patients. We reported odds ratios (ORs) with 95% confidence interval (95% CI).

Kaplan-Meier and the Cox proportional hazards models for time-dependent co-variables were utilized to evaluate overall survival, effect of response to HAART on survival, effect of receiving more than three chemotherapy cycles, and 100% of the corresponding dose, and the effect of clinical complete response (CCR) on survival. Comparisons of survival were analyzed by using log-rank test. Statistical analysis employed was Epi-Info (version 6) and STATA (version 9.1) software.

RESULTS

Patient characteristics

We found 100 patients with HIV infection and a lymphoproliferative disease. Thirteen patients were not included: four had no tissue available for pathologic re-examination, while four patients were diagnosed with Castleman disease and five, with Hodgkin lymphoma. Study analysis was carried out in 87 patients. From 1990-2001, the mean number of NHL cases per year was two; from 2002, we observed an important increase in number of patients with NHL-HIV admitted to the hospital, with a median of 10 cases per year. Data are shown in figure 1.

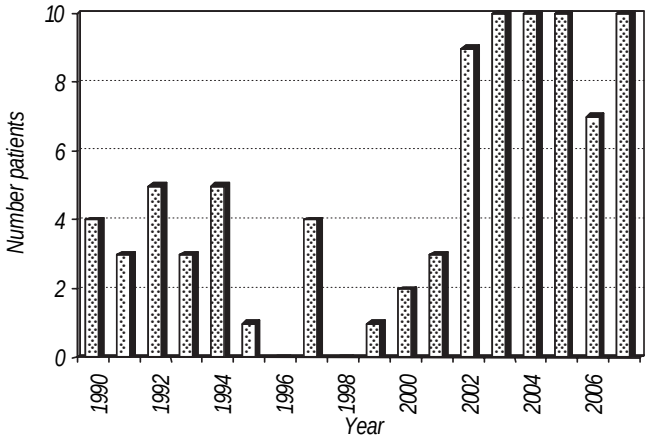

Figure 1. Number of NHL-HIV cases per year.

There were 28 patients (32.2%) included in the non-HAART and 59 (67.8%) in HAART group. Principal demographic characteristics are shown in table 1.

Non-Hodgkin lymphoma characteristics

Overall, 61 patients (70.1%) had systemic B symptoms at diagnosis; advanced stages (III/IV) were documented in 17 (60.7%) of individuals in the non-HAART *vs.* 40 (67.8%) in HAART group (p = 0.518). Immunophenotyping was solely performed in 58 patients (66.7%). B-cell origin was documented in 48 (82.7%) of subjects, T-cell in two (3.5%), and indeterminate in eight patients (13.8%). Sixty four patients (73.6%) presented at least one extranodal site of involvement; digestive tract was the most frequently encountered site (n = 40). Diffuse large B-

Table 1. Demographic and clinical characteristics in patients with NHL-HIV, divided by non-HAART and HAART groups.

Characteristic	All patients (*n* = 87)	Non-HAART (*n* = 28)	HAART (*n* = 59)	P value
Median age ± SD* (years)	35.6 ± 9	33.3 ± 7.9	36.8 ± 9.4	0.09
Gender, male - *N* (%)	71 (81.6)	24 (85.7)	47 (79.7)	0.498
Risk of HIV transmission –*N* (%)				
Homosexual/bisexual	56 (64.4)	20 (71.4)	36 (61)	0.346
Heterosexual	22 (25.3)	4 (14.3)	18 (30.5)	
Transfusión	5 (5.7)	3 (10.7)	2 (3.4)	
Unknown	4 (4.6)	1 (3.6)	3 (5.1)	
HIV diagnosis before NHL (months) †	32.4 ± 46.4	19.7 ± 34.5	38.9 ± 49.8	0.069
NHL diagnosed before HIV – *N* patients (%)	16 (18.4)	5 (17.8)	11 (18.6)	0.929
ARVT therapy‡ – *N* (%)				
PI	14 (16)	n.a.	14 (23.7)	-
NNRTI	43 (49.4)	n.a.	43 (72.9)	
Three NRTIs	2 (2.3)	n.a.	2 (3.4)	
Median CD4+ nadir cell count ± SD (% ± SD)	139.2 ± 138.1 (11.4 ± 9.5)	122 ± 132.5 (9 ± 7.6)	147.1 ± 141.6 (12.6 ± 10.1)	0.528 0.2

* SD: Standard deviation. † Seventy one patients (81.6%): 23 in non-HAART (82.1%) and 48 (81.3%) in HAART group. ‡ARVT: Antiretroviral therapy. PI: Protease inhibitors. NNRTI: Non-nucleoside reverse transcriptase inhibitors. NRTI : Nucleoside reverse transcriptase inhibitors. n.a.: not applicable.

Table 2. Clinical and histopathologic characteraistics of NHL-HIV patients in non-HAART and HAART groups.

Characteristic	All patients (*n* = 87)	Non-HAART (*n* = 28)	HAART (*n* = 59)	P value
Lactate dehydrogenase (U/L) ± SD*	559.5 ± 616	579.6 ± 620.1	550.9 ± 620.1	0.846
Systemic B symptoms – *N* (%)	61 (70.1)	19 (67.8)	42 (71 2)	0.938
Voluminous disease – *N* (%)	22 (25.3)	2 (7.1)	20 (33 9)	0.007
Immunophenotype – *N* (%)†				
B-cell origin	48 (82.7)	7 (77.8)	41 (83.7)	0.645
T-cell origin	2 (3.5)	1 (11.1)	1 (2)	
NulL or indeterminate	8 (13.8)	1 (11.1)	7 (14.3)	
Ann Arbor Stage – *N* (%)				
I/II	30 (34.5)	11 (39.3)	19 (32 2)	0.518
III/IV	57 (65.5)	17 (60.7)	40 (67.8)	
International Prognosis Index – *N* (%)				
0-1	27 (31)	8 (28.6)	19 (32 2)	0.23
2	25 (28.8)	6 (21.4)	19 (32 2)	
3	27 (31)	9 (32.1)	18 (30.5)	
4-5	8 (9.2)	5 (17.9)	3 (5.1)	
Localization of lymphoma – *N* (%)				
At least one extranodal site	64 (73.6)	23 (82.1)	41 (69.5)	0.213
Strictly nodal manifestation	23 (26.4)	5 (17.9)	18 (30.5)	
Extranodal site involvement – *N* (%)				
Digestive tract‡	40 (45.6)	15 (53.6)	25 (42.4)	0.366
Liver	1 (1.5)	0	1 (1.7)	
Leptomeningeal infiltration	3 (3.5)	1 (3.6)	2 (3.4)	
Lung	4 (4.6)	1 (3.6)	3 (5)	
Skin and muscle	7 (8)	2 (7.1)	5 (8.5)	
Other§	9 (10.4)	4 (14.2)	5 (8.5)	
Histopathology – *N* (%)				
DCLS‖	69 (79.3)	24 (85.7)	45 (76.4)	0.459
Burkitt-like	8 (9.2)	2 (7.1)	6 (10.1)	
Pleomorphic large cell	7 (8)	1 (3.6)	6 (10.1)	
Low-grade	2 (2.3)	1 (3.6)	1 (1.7)	
Angiocentric	1 (1.2)	0	1 (1.7)	

*SD: Standard deviation. †: Immunophenotype was performed in 58 patients (66.7%): nine (32.1%) in non-HAART and 49 (83%) in HAART group. ‡: Colon, duodenum, stomach, ileum. §: Bone, uterus, testis. ‖ DCLS: Diffuse large B-cell lymphoma.

cell lymphoma (DCLS) was found in 71 patients (81.6%). Complete data are shown in table 2.

Treatment and survival

Differences between patients receiving antineoplastic therapy and not receiving this therapy in both groups were statistically different: in the non-HAART group, 12 patients (42.9%) received full-dose chemotherapy, six (21.4%), reduced-dose chemotherapy, three (10.7%), only radiotherapy, and seven (25%) received no treatment. In the HAART group, 42 (71.2%) received full-dose chemotherapy, ten (16.9%), reduced-dose, one (1.7%), only surgery, one (1.7%) only radiotherapy, and five (8.5%) received no treatment (p = 0.004). No patient in the non-HAART group received Rituximab; only four patients in the HAART group received Rituximab in all chemotherapy cycles, and one patient received Rituximab in two of eight cycles. Patients not receiving any kind of treatment were gravely ill when they arrived at the hospital, and died soon after diagnosis.

Mean weight lost at NHL diagnosis was 14.4 ± 8.3 kg in the non-HAART and 8 ± 9.4 kg in the

HAART group (p = 0.02). International prognosis index was 2.4 ± 1.1 in the non-HAART, and 2.0 ± 1.0 in the HAART group (p = 0.09).

Among patients who received treatment, we found that in the non-HAART group four patients (13.8%) presented complete clinical remission (CCR), one (3.5%) had progression, two (7%) were lost to follow-up, and 14 (48.3%) died. Among patients in the HAART-group, we found that 24 patients (40.7%) presented CCR, 10 (17.5%) presented partial response, seven (11.8%) progression, one (1.7%) relapse, and 12 (20.4%) died (p < 0.0001) table 3. Mean overall survival was 11 ± 16.8 months for the entire cohort, 4.8 ± 7.6 months (range, 0.5-41 months) in the non-HAART, and 14 ± 19.2 (range, 0.5-84 months) in those receiving HAART (p = 0.01). Kaplan-Meier curve is shown in figure 2.

Multivariate Cox analysis demonstrated that patients not receiving HAART and those receiving a reduced-dose or not receiving chemotherapy had a worse prognosis. Data is shown in table 4.

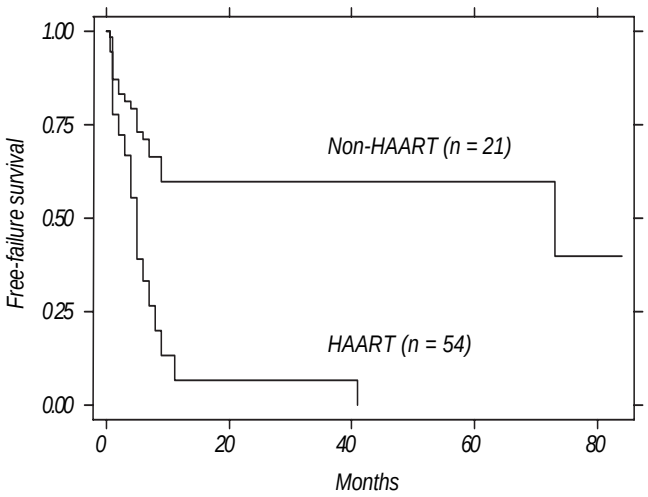

Figure 2. Kaplan-Meier survival curve for NHL-HIV, who recieved NHL treatment stratified according to HAART management or no-HAART.

DISCUSSION

Development of NHL in patients with AIDS is not only more frequent than in non-HIV-infected subjects, but is also associated with a less favorable outcome.[10] The use of HAART can improve survival in this group of individuals, rendering survival similar to that observed in non-HIV infected patients.[10]

This study describes our experience with NHL-HIV over the past 17 years and the impact that HAART management exerted on survival. Protease inhibitors (PI) regimes such as HAART began to be used in 1996 in the majority of developed countries, but extended access for middle-income patients was not the rule. In Mexico, broad access was not available until after the year 2000, when the Mexican government supplied federal funds to broaden access to HAART for HIV-infected patients in need of this.[13] Thus, our study group was divided into patients without and with HAART and not strictly in the pre-HAART and HAART era. Patients in the HAART group could have been treated initially with two nucleoside analogs until PI became available.

We found an increasing number of cases of this HIV-associated malignancy over the last 6 years, probably related with easier access to antiretroviral treatment after the year 2000 which led to an increase in the number of patients presenting for hospital treatment. Additionally, this could actually reflect an increasing trend in the occurrence of these

Table 4. Cox model. Prognostic factors for survival in NHL and HIV*

	OR† adjusted CI 95%	P value
Not receiving HAART	2.5 [1.34-4.7]	0.004
Reduced-dose chemotherapy or no chemotherapy	4.2 [2.09-9.22]	< 0.0001

*Survival or follow-up time was calculated from date of diagnosis to death or date when patient was last seen (in months). †OR: odds ratio.

Table 3. Outcome and survival

Characteristic Response to therapy	All patients (*n* = 87)	Non-HAART (*n* = 28)	HAART (*n* = 59)	P value
Complete clinical remission	38 (43.7)	4 (14.3)	34 (57.6)	0.0001
Progression	9 (10.3)	1 (3.6)	8 (13.6)	
Relapse	2 (2.3)	1 (3.6)	1 (1.7)	
Death	34 (29.1)	20 (71.4)	14 (23.7)	
Lost to follow-up	4 (4.6)	2 (7.1)	2 (3.4)	
Survival	11.08 ± 16.8	4.8 ± 7.6	14 ± 19.2	0.01

malignancies as the HIV epidemic in Mexico grows older and is accompanied by a larger HIV-infected population with an expected increase in patient survival and HAART access.

The majority of our patients were diagnosed with advanced NHL stage (64%). This was less frequent than that reported in other series, in which ~80% of patients had stage IV disease at time of first diagnosis.[1,14] We found gastrointestinal tract as the most frequent extranodal involvement (30.9%), a similar frequency to that reported in other series (25 to 50%).[6,8,15] Contrary to other series, we report a very low occurrence of either primary or secondary involvement of the central nervous system (CNS), as well as bone marrow, lung, and liver.[4,7,15,16] We found only one case of primary brain lymphoma (PBL). This low percentage of PBL can be biased, as patients with neurological symptoms and CNS lesions are referred to the Neurological Tertiary-Care Hospital Center in Mexico City, where the staff saw 17 cases of primary brain lymphoma during the same study period (personal communication, Soto JL).

Immunophenotyping study was performed only in 66.7% of tumors; in the remainder of patients, there was no tissue available to perform this study, as these patients were referred from other hospitals, which sent only biopsy stain slides. Eighty percent of samples studied were B cell-type lymphoma, similar to the U.S. series (60-80%).[14-16]

Only 42.9% of patients in non-HAART received full-dose chemotherapy compared with 71.2% of patients on HAART. Additionally, 25% of patients on non-HAART received no kind of treatment, compared with 8.5% in HAART patients. This was related with worse clinical condition at time of NHL diagnosis, as could be observed in weight loss prior to diagnosis and lower IPI in non-HAART group.

A previous study reported that despite high initial response rates to standard chemotherapy, complete response was 43 to 77%.[17] The majority of patients with NHL-HIV eventually develop refractory lymphoma even during the HAART era; this has not been our finding.[3] For patients in the HAART group, we found that 57.6% achieved complete clinical response, 13% had partial response, and progression was observed in only 1.7% ($p = 0.0001$).

Before HAART, prognosis for HIV-infected individuals with NHL was poor; median survival was 5-8 months as a rule (range, 1.5-18 months), while published median survival in the post-HAART era exceeded 24 months.[3,17-20] We found median survival of 4.8 months in non-HAART as compared with 14 months in HAART group, shorter than described previously. Best response was documented in patients with HAART and a full chemotherapy dose as compared with HAART group and reduced-dose, or non-HAART group with full-dose or reduced chemotherapy dose ($p < 0.0001$).

These results reflect the outcome in developing countries with limited resources and different economic and social conditions than the majority of reports, which are carried out in developed countries with better diagnosis and treatment resources.

Factors that have been associated with poor prognosis in patients with NHL-HIV include CD4+ cells < 100 cells/mm^3, stage III or IV disease, age > 35 years, history of intravenous (i.v.) drug use, elevated LDH, prior AIDS, and extranodal involvement.[15,21-23] One important favorable prognostic factor is response to HAART.[23,24] In this study, factors we found associated with poorer patient outcome were CD4 cells < 200 cells/mm^3 and poor response to antiretroviral treatment.

NHL-HIV patients who received HAART and conventional full-dose chemotherapy presented a better clinical condition, which allowed them to receive optimal chemotherapy and antiretroviral treatments. Therefore, these factors were strong related with survival.

Conflict of interest statement and funding sources

There is none conflict of interest and no founding source.

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