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International Prognostic Index is the best prognostic factor for survival in patients with AIDS-related non-Hodgkin's lymphoma treated with CHOP. A multivariate study of 46 patients

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ABSTRACT

Background and Objective. **The management of non-Hodgkin's lymphomas (NHL) in AIDS is difficult because of the poor bone marrow reserve and immunosuppression of these patients. Combination chemotherapy is the treatment of choice in the subset of patients with good performance status and mild immunosuppression. Several combination chemotherapy regimens have been used in these patients but the results have been poor. We have studied the clinical and biological features, response to treatment, outcome and prognostic factors of 46 patients with NHL and HIV infection, diagnosed in a single institution between January 1988 and June 1997.**

Design and Methods. **Forty-six patients with NHL and HIV infection were treated with CHOP. Patients with previously treated systemic NHL, primary CNS NHL, performance status >2 and active AIDS-defining opportunistic or neoplastic diseases were excluded. The parameters evaluated were: age, sex, risk activity, basic hematologic and biochemical parameters, CD4 lymphocyte count, B symptoms, stage (Ann Arbor), histologic subtype (REAL classification), International Prognostic Index (IPI), response to treatment, relative dose intensity (RDI), relapse free survival (RFS) and overall survival (OS). Uni- and multivariate analyses of prognostic factors were performed.**

Results. **Median age was 35 years and 40 patients were male. CD4 lymphocyte count was lower than 0.1×10^9/L in 18 out of 38 cases, hypoalbuminemia was registered in 24 (52%), serum LDH was higher than 400 U/L in 20 (43%) and β_2-microglobulin was higher than the normal range in 9 out of 20 patients (45%). Complete response was achieved in 18 patients (40%). Twenty-six patients received G-CSF after chemotherapy. Grade 4 neutropenia and fever were significantly more frequent in patients who did not receive G-CSF. Serum LDH >400 U/L and hypoalbuminemia were the only parameters associated with a lower probability to achieve complete response (p=0.015 and p=0.025, respectively). The median RFS was 26 (6-47) months and no variable was found to have statistically significant influence on it. The median OS was 9.2 (4.5-14) months, and IPI score 1 and ESR < 60 mm/h were the only parameters identified as good prognostic factors in the multivariate analysis (p=0.03 and 0.049, respectively).**

Interpretation and Conclusions. **In spite of patient selection, the response to CHOP treatment in patients with NHL and HIV infection remains poor. Episodes of neutropenic fever are less frequent when G-CSF is administered after CHOP. The IPI score 1 is the most important favorable prognostic factor for survival.**

Key words: lymphoma, AIDS, CHOP, prognosis, International Prognostic Index

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Non-Hodgkin's lymphoma (NHL) is one of the most frequent malignancies in patients with acquired immunodeficiency syndrome (AIDS). Primary central nervous system (CNS) lymphoma has been considered as an AIDS-defining condition since the beginning of the epidemic, and high grade B cell systemic NHL were subsequently included in 1985 in the AIDS definition.[1] NHL occurs in approximately 2-5% of all patients infected with the human immunodeficiency virus (HIV). AIDS-associated NHL often involve extranodal sites, are usually diagnosed at advanced stages and have poor prognosis.[2] About 60% of systemic lymphomas are large B-cell lymphomas, 30% are Burkitt's lymphomas, and the rest are of T-cell or non-B, non-T cell origin, including Ki-1 (CD30) anaplastic large cell lymphomas and body-based cavity lymphomas.[3,4]

The management of systemic NHL in AIDS is difficult because of the poor bone marrow reserve of these patients and their underlying immunodeficiency.[5] In spite of these disadvantages, combination chemotherapy is the treatment of choice at least in the subset of patients with appropriate performance status and mild immunosuppression. Several standard combination chemotherapy regimens known to be effective against aggressive NHL in non-HIV patients have been used, but the results have been

poorer in patients with HIV infection.[6-8] In fact, results of treatment have been similar when these standard combination chemotherapeutic regimens have been administered at a lower doses.[8] When administration of standard chemotherapeutic regimens are planned, modern trends in AIDS-lymphoma therapy recommend patient selection. The results of such treatments show that there is a small proportion of HIV-infected patients in which prolonged survival without evidence of lymphoma can be achieved.

In this study, we report the results of CHOP chemotherapy in a series of 46 consecutive HIV-positive patients with NHL treated in a single institution between January 1988 and June 1997.

Patients and Methods

Patients and diagnostic criteria.

Forty-six patients diagnosed with systemic AIDS-related NHL between January 1988 and June 1997 at the *Hospital Universitari Germans Trias i Pujol* of Badalona, Spain, and treated with CHOP chemotherapy were analyzed. Exclusion criteria for the study were: primary CNS NHL, previously treated systemic NHL, performance status >2[9] and active AIDS-defining opportunistic or neoplastic disease.

All patients were evaluated at diagnosis for: age, sex, risk habits, AIDS stage, B symptoms, complete blood cell count, CD4 lymphocyte count, blood chemistry including serum lactate dehydrogenase level (normal range: up to 270 U/L), β_2-microglobulin, histologic subtype, and stage of NHL.

HIV serology was assessed by enzyme-linked immunoabsorbent assay and confirmed by Western blot in all patients. Histopathologic diagnosis of NHL was performed by biopsy study in all cases. Biopsies have been revised for this study and histologic classification was made according to the *Revised European-American Classification of Lymphoid Neoplasms.*[10] *Ann Arbor classification*[11] with the modification proposed by Musshoff for extranodal NHL[12] was used to assess the stage of NHL. In all cases staging procedures consisted of chest radiogram, computed tomography of thorax and abdomen, bone marrow aspirate and trephine biopsy, liver biopsy, and lumbar puncture with cytologic study of cerebrospinal fluid. The *International Prognostic Index* (IPI)[13] was applied to all patients. The revised *Centers for Disease Control (CDC) classification system for HIV infection*[13] was adopted for AIDS diagnosis.

Treatment and criteria for response

The following schedule of chemotherapy was administered: cyclophosphamide 750 mg/m^2 intravenous (IV) day 1, adriamycin 50 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 IV day 1, and prednisone 60 mg/m^2 IV or PO days 1-5. Antiretroviral therapy with zidovudine was discontinued during the treatment. Combination of three antiretroviral drugs (which included two nucleoside analogues and one protease inhibitor) was given to the last 5 patients included in the study and was not discontinued during CHOP treatment. Furthermore, all patients received prophylaxis against *Toxoplasma* and *Pneumocystis carinii* (pirimetamine and aerosolized pentamidine, respectively). The cycles were administered every 21 days or were delayed when the neutrophil count was under 1×10^9/L. Since 1991 patients also received G-CSF from day 6 after treatment until the neutrophil count was over 1×10^9/L. All patients received CNS prophylaxis with methotrexate (12 mg), cytarabine (30 mg) and hydrocortisone (20 mg) in each cycle.

The relative dose intensity (RDI) (the ratio of the actual dose to the expected dose per unit of time) was calculated for each agent as previously reported.[8] Toxicity of treatment was assessed according to WHO scores.

Complete response (CR) was considered as the lack of evidence of NHL after treatment for at least 2 months. Any other situation (partial response, stable disease or progression) was considered as therapeutic failure. Relapse was defined as the presence of NHL in a patient being at least 2 months in CR. Overall survival (OS) was considered as the period of time between the date of diagnosis and the date of death or last control of the patient. Relapse free survival (RFS) was defined as the period between the date of CR and the date of relapse, death, or last control in CR.

Statistical analysis

A descriptive analysis of the different variables was performed. Bivariate tests (Student t-test, Mann Whitney U-test and variance analysis when appropriate) were used to compare quantitative variables and χ^2 or Fisher's exact test was employed to assess differences in proportions. Actuarial curves for RFS and OS were plotted according to the Kaplan-Meier method[15] and were compared by the log rank test.[16] The statistically significant ($p<0.05$) variables or those with borderline significance ($0.05<p<0.1$) identified in univariate studies were included in multivariate analyses. A logistic regression model was used to identify predictive factors for CR achievement and multivariate analyses for RFS and OS were performed using the Cox proportional hazard-regression model.[17] Statistical analyses were carried out using the SPSS (*Statistical Package for Social Sciences*) package, version 6.0 for Windows.

Results

Patient characteristics

Between January 1988 and June 1997, 1,712 patients with AIDS were controlled in our institution and 74 cases of NHL were diagnosed, the frequency being 4.3%. Forty-six patients with systemic NHL were treated with CHOP chemotherapy. The causes of

Table 1. Clinicopathologic characteristics of the 46 patients.

	Number of patients	Percentage
Sex		
Male	40	87
Female	6	3
Risk activity		
IVDU	22	48
Homosexual	12	26
Heterosexual	10	22
Transfusion	1	2
Unknown	1	2
Previous AIDS		
Yes	21	46
No	25	54
Histologic subtype		
Large cell	25	54
Burkitt like	9	20
Anaplastic ki-1	2	4
Peripheral T-cell NHL	1	2
Unclassifiable	9	20
Bone marrow involvement		
Yes	11	24
No	35	76
Stage		
I/I_E	11	24
II/II_E	6	13
III	3	7
IV	26	56

IVDU: intravenous drug users; AIDS: acquired immunodeficiency syndrome.

exclusion of the remaining 28 patients were: previous treatment (4), primary CNS lymphoma (8), active opportunistic or neoplastic diseases (3), performance status >2 (8) and NHL diagnosis at autopsy (5). The median age of the series was 35 years (range 19-62) and 40 patients were male. The main characteristics of the patients are listed in Table 1. The most frequent histologic NHL subtype was large cell lymphoma (54%) and 26 of patients (57%) were in stage IV at diagnosis. B symptoms were present in 29 patients (63%). The main extranodal localizations were: gastrointestinal (13 cases), bone marrow (11), and liver (4). Twenty-one patients (46%) had an IPI score 1 (low risk), 7 (16%) IPI 2 (low-intermediate), 13 (28%) IPI 3 (intermediate-high) and 5 (10%) IPI 4 (high risk).

Table 2 shows the main laboratory parameters. Almost all patients (90%) had anemia. CD4 positive lymphocyte count was lower than 0.1×10^9/L in 18 out of 38 cases (48%). Hypoalbuminemia was registered in 24 (52%), serum LDH was higher than 400 U/L in 20 (43%) and β_2-microglobulin was higher than the normal range in 9 out of 20 cases (45%).

Table 2. Main laboratory parameters of the patients.

Variable	*Mean*	*Standard deviation*	*Range*
Hemoglobin (g/L)	107	242	60-148
CD4 lymphocytes ($x10^9$/L)	0.17	0.18	0.01-0.80
Platelets ($x10^9$/L)	185	87	20-440
ESR (mm/h)	69	38	6-140
Albumin (g/L)	33	5	22-45
Serum LDH (U/L)	974	1,475	122-6,524
β_2 microglobulin (mg/L)	4	2	1.8-9

Response to therapy and survival

Twenty patients were treated with CHOP alone, and 26 received G-CSF after CHOP chemotherapy. Twenty-eight (70%) received RDI of 100%, 13 in the group without G-CSF and 15 in the group with G-CSF (p: ns). Sixteen patients died during treatment and 11 did not respond. CR was achieved in 18 cases (40%) and one is under treatment at the time of this report. Five patients (28%) have relapsed, nine are alive and remain in first CR, and four died in CR for causes not related with NHL: 1 from disseminated toxoplasmosis, 1 from digestive hemorrhage and shock, and 2 from *Pneumocystis carinii* pneumonia. CNS relapse was observed in 3 out of 5 relapsed patients, although they had received CNS chemoprophylaxis.

Factors with influence on CR achievement in univariate analysis were: serum albumin >33 g/L (9 out of 16 patients vs 6 out of 24, χ^2:4, p=0.04), low-risk IPI score, compared with intermediate and high-risk IPI scores (11 out of 20 vs 7 out of 26, χ^2: 3.4, p=0.06), and serum LDH < 400 U/L (11 out of 20 vs 7 out of 20, χ^2:5.22, p=0.02). In the multivariate analysis (Table 3) higher levels of serum LDH and lower levels of serum albumin were the only parameters associated with a lower probability to attain CR.

The median (95% CI) RFS was 26 (6-47) months, with a median follow-up of 8 months (Figure 1). None of the variables were found to be statistically significant in univariate study for RFS.

The median (95% CI) OS was 9.2 (4.5-14) months with a median follow-up of 9.6 months (Figure 1). In the univariate analysis the factors with influence on a longer OS were: low risk IPI score compared with intermediate and high risk IPI scores (p=0.065) (Figure 2), serum LDH < 400 U/L (p=0.023), serum albumin > 33 g/L (p=0.036), and ESR < 60 mm/h (p=0.026). In the multivariate analysis the only parameters identified were IPI score and ESR (Table 3).

Toxicity

Grade 4 neutropenia (absolute neutrophil count < 0.5×10^9/L) and fever developed in 16 out of 70 CHOP cycles in the group of patients not receiving G-CSF and in 10 out of 114 cycles in those treated treated with G-CSF (χ^2:7.09, p=0.008). Grade 3 or 4

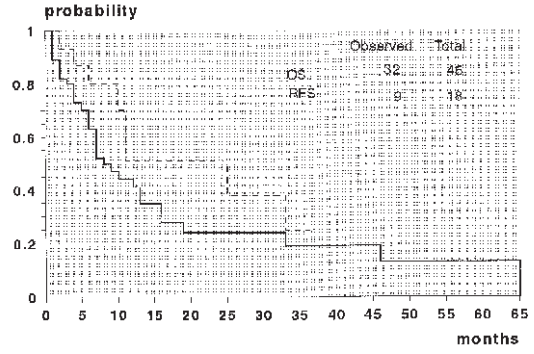

Figure 1. Kaplan-Meier curves for relapse free survival (RFS) and overall survival (OS) for the patients of the series.

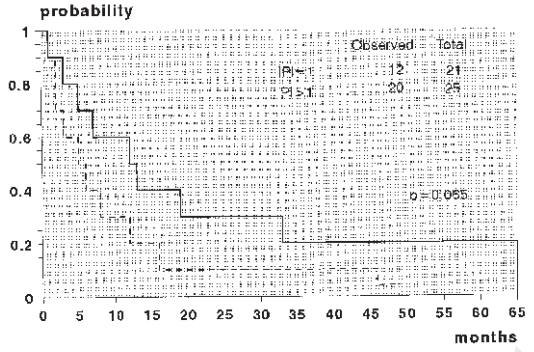

Figure 2. Comparison of survival between patients with International Prognostic Index (IPI) score 1 (low risk) and IPI score >1 (intermediate and high risk).

thrombocytopenia was present in 13 out of 184 cycles of CHOP chemotherapy. Grade 3 and 4 anemia was detected in 10 cycles.

Other remarkable side effects were nausea and vomiting (2 patients), diarrhea (1 case), digestive hemorrhage (3 cases) and neurotoxicity due to vincristine in 2 patients.

Discussion

The prevalence of NHL (4%) in the cohort of HIV patients under control in our hospital is similar to the 3-10% reported by other groups.[3,18,19] In addition, the characteristics of the patients in our series are similar to those referred in others, i.e. high grade of malignancy, B phenotype, advanced stage at diagnosis, B symptoms and extranodal involvement.[20,21]

The type and intensity of the treatment for HIV-related NHL is a matter of controversy. Recently, there is a tendency to treat only the patients with favorable prognostic factors with intensive chemotherapy. These factors usually include good performance status, CD4 lymphocyte count higher than

Table 3. Multivariate analyses for complete remission (CR) attainment and overall survival (OS).

Variable	*β coefficient*	*OR (CI 95%)*	*p value*
CR attainment			
LDH ≥ 400 (U/L)	2.15	8.6 (1.5-48.5)	0.015
Albumin ≤ 33 (g/L)	1.96	7.2 (1.3-40)	0.025
OS			
IPI > 1	0.86	2.3 (1.05-5.3)	0.036
ESR > 60 (mm/h)	2.5	2.5 (1.0-6.5)	0.049

0.1×10^9/L and absence of previous AIDS. Different chemotherapy regimens have been used (i.e. M-BACOD, MACOP-B, CHOP, infusional chemotherapy) with a percentage of CR ranging from 30 to 65%.[5-8,22-24] In our study 40% of CR were achieved, and no differences were found with regard to the RDI administered or to the grade of immunosuppression. Two independent factors with negative influence on CR attainment have been identified: serum LDH higher than 400 U/L and serum albumin level lower than 33 g/L. In addition, it is of note that in our series relapse occurred in CNS in 3 out of 5 relapsed patients, despite adequate CNS prophylaxis.

The use of colony stimulating factors (CSF), such as granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), has been introduced in the last few years in order to reduce bone marrow toxicity and to administer the whole dose of chemotherapy. However, our results show that the administration of G-CSF did not have any influence on the RDI and on the achievement of CR, but the use of this CSF was associated with a lower rate of neutropenic fever, as occurred in previous studies.[25-27]

The administration of antiretroviral therapy during chemotherapy is a controversial question. Some have suggested that zidovudine (AZT) in combination with cytostatic drugs could enhance myelosuppression.[28] In other studies AZT was given concurrently with chemotherapy such as methotrexate to enhance its cytotoxic effect.[23] Didanosine (ddI) has also been used in combination with cytotoxic drugs on the basis of its effect in increasing leukocyte, neutrophil, RBC and platelet counts.[22] On the other hand, ddI, dideoxicytidine (ddC) and stavudine (d4T) must be given with caution in regimens with vincristine, because of their neurotoxicity.[28,29] In our study, the antiretroviral therapy was discontinued during the CHOP treatment except in the last five patients, who received triple antiretroviral therapy during chemotherapy without remarkable side effects. Yet, there is no doubt about the need for prophylaxis of opportunistic infections, which must be continued during NHL treatment, as

was performed in our series.

The results of our study confirm the poor prognosis of NHL in HIV-positive patients, although there is a small subset of patients in which long-term lymphoma-free survival can be achieved, as referred by other authors.[8,22] The recently developed IPI score, was an independent predictor of survival in our series of HIV-related lymphomas. This feature has not been systematically analyzed in chemotherapy trials and, to our knowledge, this is the first study that points out the prognostic significance of the IPI score in HIV-related NHL. We have only found one similar study with similar results published in abstract form.[30] In a recently published study,[31] the adverse prognostic significance of two parameters of IPI, age and serum LDH level, was assessed. In our study, serum LDH was also a prognostic factor in the univariate analysis for OS, and would probably retain its prognostic significance in multivariate study because it is a parameter included in the IPI score, as previously referred.[31] Different from other studies,[31-33] low CD4 lymphocyte count did not predict poorer outcome in our study, probably due to the exclusion of patients with poor performance status and active opportunistic infections, which usually have the lowest CD4 counts.

Despite the poor prognosis of NHL in HIV-positive patients, there is a small subgroup in which long-term disease-free survival (and possibly cure) can be achieved using conventional or lower dose chemotherapy schedules. However, newer chemotherapy schedules,[22,23] as well as improvement in the treatment of HIV infection itself are both required to increase the survival of HIV-positive patients with NHL.

Contributions and Acknowledgments

JMR was responsible for the conception of the study and its design. JTN and JMR wrote the paper. JTN, AO and JG were responsible for data handling and statistical analyses. MV and FM performed and revised the morphologic and immunophenotypic studies. JMR, JR, MB and EF followed the patients clinically.

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Disclosures

Conflict of interest: none.

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Manuscript processing

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