

Malignant Lymphomas

The prognosis of HIV-infected patients with diffuse large B-cell lymphoma treated with chemotherapy and highly active antiretroviral therapy is similar to that of HIV-negative patients receiving chemotherapy

In the era of highly active antiretroviral treatment (HAART), the prognosis of AIDS-related lymphomas might be similar to that of aggressive B-cell lymphomas in human immunodeficiency (HIV)-negative patients. In this study we found that HIV-infected patients with diffuse large B-cell lymphoma treated with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone (CHOP) and HAART showed a similar response rate to chemotherapy, disease-free survival and overall survival as those of HIV-negative patients receiving CHOP.

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Since the introduction of highly active antiretroviral therapy (HAART), the prognosis of AIDS-related lymphomas (ARL) has improved.¹⁻⁴ However, few studies have compared the response to therapy and the survival between human immunodeficiency virus (HIV)-infected and HIV-negative patients.^{5,6}

We compared the clinicobiological characteristics, the response to chemotherapy, overall survival (OS) and disease-free survival (DFS) between a group of HIV-infected and a group of HIV-negative patients, diagnosed with the same subtype of lymphoma and treated with the same chemotherapy.

Two groups of patients from 18 to 60 years of age diagnosed with diffuse large B-cell lymphoma (DLBCL) in a single institution from June 1996 to December 2002, and treated with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone (CHOP) chemotherapy, were studied. Group 1 consisted of 23 HIV-infected patients treated with HAART concomitantly with chemotherapy. Group 2 consisted of 30 HIV-negative patients treated with CHOP. All patients were scheduled to receive 6 cycles of CHOP at 3-week intervals. HIV-infected patients received granulocyte colony-stimulating factor (G-CSF) daily (300 µg subcutaneously) for 7 days, starting the sixth day after chemotherapy, whereas only four HIV-negative patients received this factor, given because of severe neutropenia after the first cycle of CHOP. Central nervous system prophylaxis was administered to all HIV-infected patients in each CHOP cycle, and to those HIV-negative patients with involvement of bone marrow, testicles or paranasal sinuses (n=6). Involved field radiotherapy was planned if bulky or residual masses were present.

Complete remission (CR) was considered as the complete disappearance of clinical, biochemical and radiographic evidence of disease, lasting for at least 1 month after the completion of therapy. OS was considered as the period of time from the date of diagnosis to the date of death or last follow-up. DFS was defined as the period between the date of first CR and the date of relapse of the lymphoma, the date of death in CR or the last follow-up in CR.

Table 1. Comparison of the main clinical characteristics and laboratory parameters of the two groups of patients at lymphoma diagnosis.

	HIV-infected n=23	HIV-negative n=30	P
Gender (Male/Female)	16/7 (70%/30%)	17/13 (57%/43%)	NS
Age, yr.*	42 (9)	42 (10)	NS
Prior AIDS	11 (48%)	—	
Risk group for HIV infection			
Intravenous drugs users	9 (39%)	—	
Homosexual	10 (43.5%)		
Heterosexual	4 (17.5%)		
B symptoms	14 (61%)	7 (23%)	0.006
ECOG ≥2	9 (39%)	15 (50%)	NS
Extranodal involvement	15 (65%)	20 (66%)	NS
CNS involvement	1 (4%)	1 (3%)	NS
Bone marrow involvement	6 (26%)	3 (10%)	NS
Bulky mass	3 (13%)	4 (13%)	NS
Ann Arbor stage >II	15 (65%)	14 (47%)	NS
Age-adjusted IPI score			
0	7 (30%)	10 (33%)	NS
1	6 (26%)	8 (27%)	
2	5 (22%)	7 (23%)	
3	5 (22%)	5 (17%)	
Hemoglobin (g/L)*	118 (38)	116 (21)	NS
Lymphocytes (×10 ⁹ /L)*	1.6 (0.9)	2.4 (1.4)	NS
ESR (mm/h)*	66 (34)	33 (23)	<0.001
Albumin (g/L)*	38.5 (9.0)	36.7 (6.3)	NS
LDH (U/L)*	238 (101)	273 (233)	NS
β2 microglobulin (mg/L)*	4.5 (2.9)	1.8 (0.8)	0.001
CD4 lymphocyte count/µL*	134 (135)	—	
Time from HIV detection and NHL diagnosis (months)*	90 (65)	—	

IPI: International Prognostic Index; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system; NS: not significant; NHL: non-Hodgkin's lymphoma; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; *Results expressed as mean (standard deviation).

The main clinical and laboratory parameters are shown in Table 1. The apparent imbalance in the number of patients in each group (higher than expected in group 1 and relatively lower in group 2) could be explained by the fact that our hospital is a referral center for ARL. Among HIV-infected patients, 11 had a virological response to HAART (undetectable HIV-1 RNA load in plasma), 7 did not respond to HAART and 5 were not evaluated, because of death during chemotherapy.

There were no differences in relative dose intensity (RDI): 19 patients in group 1 (83%) and 29 in group 2 (97%) received a RDI ≥ 95% of cyclophosphamide and

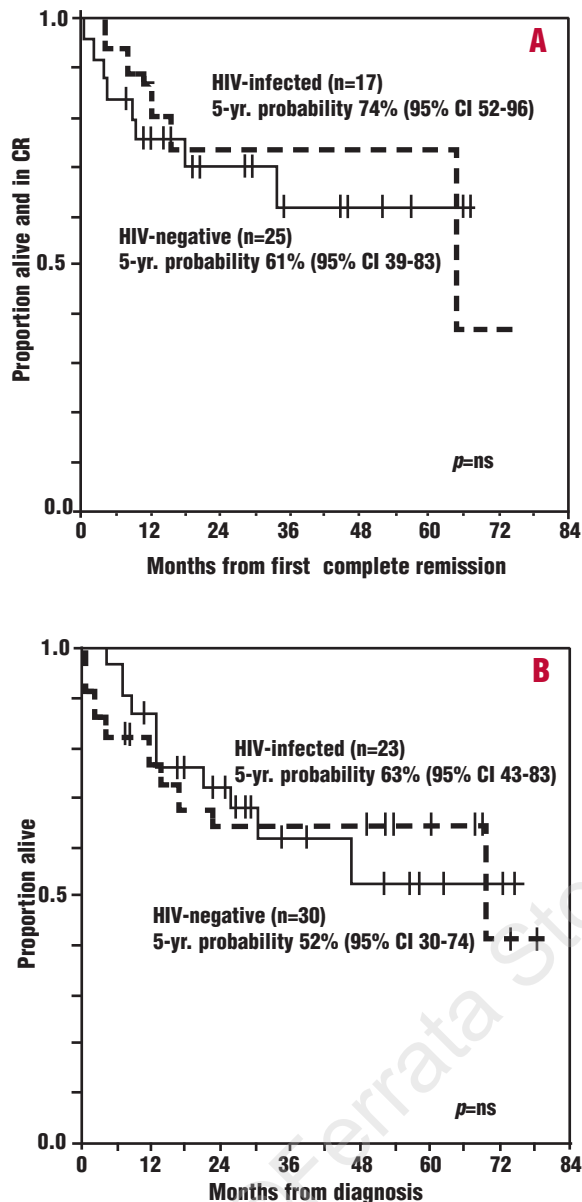


Figure 1. A. Kaplan-Meier curves for disease-free survival in HIV-infected and HIV-negative patients with diffuse large B-cell lymphoma. B. Kaplan-Meier curves for overall survival in HIV-infected and HIV-negative patients with diffuse large B-cell lymphoma.

adriamycin ($p=ns$). Complementary radiotherapy was administered to 8 patients in the HIV-negative group and to 2 in the HIV-positive group. Seventeen out of 23 patients (74%) achieved CR in the HIV-infected group, and 25 out of 30 (83%) in the HIV-negative group ($p=ns$). Among HIV-infected patients, only 1 case relapsed, 7 died due to progression of lymphoma and 2 due to opportunistic infections. Among the HIV-negative group, 8 cases relapsed and, of the 11 patients who died, lymphoma progression was the main cause of death in all.

No differences were found regarding OS and DFS between the two groups (Figure 1). When group 1 was studied separately, no differences were found in CR, DFS, and OS when the patients who were receiving HAART

prior to the diagnosis of lymphoma ($n=13$) were compared with those who started this therapy at the time of lymphoma diagnosis ($n=10$). Moreover, no differences in CR, DFS and OS were found between those who did or did not respond to HAART. Recent studies on ARL have shown that some of the aggressive characteristics of lymphomas are still present in the HAART era.⁷⁻⁹ In the present study, some clinicobiological features reflect more aggressiveness of DLBCL in HIV-infected patients (Table 1). The CR rate was similar in the two groups, which may have several explanations. First, the systematic use of G-CSF in ARL probably contributed to a similar RDI being achieved in the two groups. Second, HIV-infected individuals were selected to receive chemotherapy if they had an ECOG score ≤ 2 , while non-HIV infected patients were not excluded because of their performance status. Finally, HAART could be implicated in the high CR rate in HIV-infected patients.^{3,4,7,10} To our knowledge, there is only one published study comparing the results of CHOP or CHOP-like therapy in patients with aggressive non-Hodgkin's lymphoma, in relation to their HIV infection status.⁶ In that study, the patients with HIV-NHL who achieved CR while receiving doxorubicin-based regimens and HAART showed the same outcome as HIV-negative patients with aggressive NHL.

The results shown in this study, regarding HIV-infected patients with DLBCL treated with CHOP and HAART, support the concept that the treatment of ARL, or at least of DLBCL, in the HAART era should be identical to that given to non-immunocompromised patients.

José-Tomás Navarro,* Natàlia Lloveras,* Josep-Maria Ribera,*
Albert Oriol,* José-Luis Mate,* Evarist Feliu*

*Haematology Department, Institut Català d'Oncologia and °Pathology Department Hospital Universitari Germans Trias i Pujol, Badalona, Universitat Autònoma de Barcelona, Spain

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Correspondence: José-Tomás Navarro, MD, Clinical Hematology Department, Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, d/Canyet s/n. 08916, Badalona, Spain. Phone: international +34.9.34978868. Fax: international +34.9.34978995. E-mail: jnavarr@ns.hugtip.scs.es

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Multiple Myeloma

CD221 (IGF-1R) is aberrantly expressed in multiple myeloma, in relation to disease severity

We investigated the expression of insulin-like growth factor-1 receptor (CD221) in normal, reactive and malignant plasma cells. We show that CD221 is aberrantly expressed on human myeloma cells, that higher levels of CD221 are observed in patients and human myeloma cell lines with the most aggressive 14q32 translocations, and that CD221 expression has a negative prognostic impact in patients with multiple myeloma.

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Recent studies have shown that insulin-like growth factor-1 (IGF-1) is an important survival and growth factor in multiple myeloma (MM).¹⁻³ The studies of IGF-1 and interactions with its receptor IGF-1R or CD221 have mainly involved mouse models of plasmacytomas and/or human myeloma cell lines (HMCL)⁴⁻⁶ but not MM patients, or normal plasma cells (PC). In this study we evaluated the expression of CD221 on normal, reactive and malignant PC, its correlations with presenting features of MM patients and its influence on the severity of the disease.

CD221 expression was evaluated on tumor cells from 56 consecutive patients with newly diagnosed MM, 10 extra-medullary sites and 19 HMCL. Thirty-seven of these 56 MM patients (median age 60 years) treated in our center according to ongoing IFM protocols⁷ (IFM99-02, 18 patients; IFM99-04, 9 patients; IFM 99-06, 10 patients) are included in the survival analysis. The 10 samples from extra-medullary sites were of malignant pleural effusions and peripheral blood from patients with plasma cell leukemias. The HMCL were either commercially available (L363, U266, OPM2, LP1, NCI H929, RPMI 8226), established by ourselves (XG1, XG2, XG6, Nan1, Nan2, Nan3, SBN, MDN, BCN) or generous gifts (KMS11, 12, 19, JIM3). Cells from tonsils, normal bone marrows, and reactive plasmacytoses were prepared as previously described.⁸

The phenotype of normal, reactive and malignant PC was analyzed in a four-color assay with anti-CD38, anti-CD45, and anti-CD138 monoclonal antibodies (mAb) as previously described by ourselves.⁸⁻⁹ The CD of interest, CD221, was evaluated using the 1H7 mAb conjugated to phycoerythrin (BD Biosciences) as previously described for CD20.⁹ Positivity of CD221 expression was defined as a

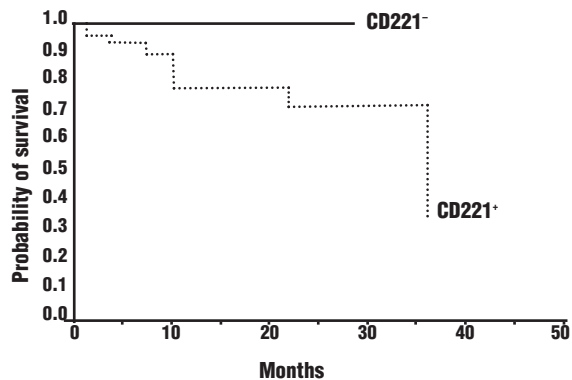


Figure 1. Overall survival according to CD221 phenotype. CD221 negative patients, n=10; CD221 positive patients, n=27; median survival: 35 months vs not reached, $p<0.05$.

mean fluorescence intensity ratio MFIR ≥ 1.2 . Fluorescent *in situ* hybridization (FISH) analysis of 13q and 14q32 abnormalities was performed on highly purified human myeloma cells as we previously described.¹⁰ Non-parametric tests were used for statistical analysis. Usual presenting characteristics including cytogenetics and CD221 expression were included in the survival analysis. Survival curves were plotted according to the Kaplan-Meier method, and were compared using the log-rank test. CD221 was never detected on either tonsil or reactive PC, but was detected in 6 of 13 PC samples (46%) of normal bone marrow, at low levels (MFIR < 2) ($p=0.05$). Forty-one of the 56 patients (73%) expressed CD221. Levels of expression in MM were significantly higher than those of normal bone marrow ($p<0.05$). Of note, CD221 was detected in 9 of 10 extra-medullary sites, and in 17 of 19 HMCL. A strong correlation was found with 14q32 abnormalities and CD221 expression. HMCL with either t(4,14) or t(14,16) expressed CD221 at higher levels than did the remaining HMCL, including HMCL with t(11,14), those with non-recurrent 14q32 abnormalities and those lacking any 14q32 translocation ($p=0.0049$). Information on both -13q and 14q32 genotype and CD221 phenotype was available for the 56 patients. A non-significant link was found between CD221 expression and 13q deletion. On the other hand, a significant, strong correlation was found with 14q32 abnormalities. As in HMCL, CD221 was detected at higher levels in patients with either a t(4,14) or t(14,16) ($p=0.0017$). CD221 was expressed in 27 out of the 37 (73%) patients available for survival analysis. CD221 expression was associated with a shorter survival (median 35 months vs not reached, $p<0.05$, Figure 1). The other single factor associated with a shorter survival was t(4,14) (survival rate 53.6% vs 81.4% at 2 years, $p<0.05$). This is the first study comparing the expression of CD221/IGF-1R on normal, reactive and malignant PC. We did not detect any CD221 on 5 reactive plasmacytoses. Although the number of cases is small, our data clearly suggest that these expansions of highly proliferating but short-lived PC progenitors and precursors do not use IGF-1 to survive and to grow. On the other hand, CD221 was detected (but at low levels) in 46% of normal bone marrow, but not in tonsil PC suggesting that CD221 could be specifically upregulated during the homing of PC in this special bone marrow microenvironment. In MM, we found that three-quarters of the patients expressed CD221 in agreement with a recent eval-