Decrease in the frequency of meningeal involvement in AIDS-related systemic lymphoma in patients receiving HAART

We evaluated the frequency of primary central nervous system lymphoma and leptomeningeal involvement in systemic non-Hodgkin's lymphoma (NHL) in HIV-infected patients. Those receiving highly active antiretroviral therapy (HAART) showed a decrease in leptomeningeal involvement in systemic NHL (0/30 vs. 12/87; p=0.023). Therefore HAART could prevent CNS involvement in systemic NHL.

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Non-Hodgkin's lymphomas (NHL) in HIV-infected patients often present with extranodal involvement. The central nervous system (CNS) infiltration is frequent and can appear as secondary spread of systemic NHL or as primary central nervous system lymphoma (PCL).[1-3]

Since the introduction of highly active antiretroviral therapy (HAART), a decline in the incidence of some neoplasms has been observed in HIV-infected patients. However, the effect of HAART on the incidence of lymphomas has been heterogeneous. While the incidence of PCL has diminished, the reduction in systemic NHL has been modest.[4-6] The prognosis of AIDS-related lymphomas (ARL) has improved since the introduction of HAART.[4-9] However, to our knowledge, there are no studies regarding the impact of HAART on the frequency of CNS involvement in systemic ARL. The aim of this study was to analyze whether the prevalence of CNS involvement in AIDS-related NHL has changed in patients receiving HAART.

We retrospectively studied a series of 131 patients diagnosed with ARL in a single institution between 1986 and 2006. This study was conducted according to the rules of good clinical practice of the Germans Trias i Pujol University Hospital. No patients were excluded from the analysis. The main clinical-biologic characteristics at the time of lymphoma diagnosis were recorded. Two types of CNS involvement were considered: leptomeningeal involvement in systemic NHL and primary CNS lymphoma. Leptomeningeal infiltration was diagnosed by morphologic microscopic examination of fresh cerebrospinal fluid (CSF) and PCL was diagnosed by brain biopsy or by detection of a cerebral mass suggestive of lymphoma with failure to anti-toxoplasma treatment and demonstration of Epstein-Barr virus DNA by PCR in CSF. The frequency of PCL and CNS involvement in systemic NHL was studied according to whether the patients were receiving HAART or not at the time of lymphoma diagnosis. HAART consisted of one or two protease inhibitors and two nucleoside reverse transcriptase inhibitors, and patients had been receiving this treatment for at least 6 months before lymphoma diagnosis.

Thirty-one out of 131 patients were receiving HAART at lymphoma diagnosis. The median (range) time from HIV detection until lymphoma diagnosis was 11.5 (1-19.6) years for patients who received HAART and 2.1 (0-18.9) years for those who did not. The median (range) CD4 lymphocyte count for patients on HAART was 192/μL (6-905) and for those without HAART 56/μL (1-803) (p=0.001). In addition, the median (range) RNA HIV load (measured in 48 patients) was 2,800 copies/mL (0-14,000,000) and 120,000 (280-2,700,000), respectively (p=0.0024). Fourteen patients had PCL and 12 secondary

Table 1. CNS involvement at lymphoma diagnosis according to HAART treatment in the 131 patients from the series.

	HAART before lymphoma n=31	*No HAART before lymphoma n=100*	*p*
CNS involvement (out of the 131 from the series)	1/31 (3.2%)	25/100 (25%)	0.008
PCL (out of the 131 from the series)	*1/31 (3.2%)	13/100 (13%)	0.108
Leptomeningeal spread secondary to systemic NHL (out of the 117 with systemic NHL)	0/30 (0%)	12/87 (14%)	0.023

**This patient had CD4 lymphocyte count of 6/μL and a HIV viral load of 690,000 copies/mL. HAART: highly active antiretroviral therapy; CNS: central nervous system; PCL: primary central nervous system lymphoma; NHL: non-Hodgkin's lymphoma.*

Table 2. Comparison of clinical-biolologic variables of the 117 patients with systemic NHL according to leptomeningeal involvement.

	Leptomeningeal involvement in systemic NHL (n=12)	*No CNS involvement (n=105)*	*p*
Age*	39 (12)	39 (10)	NS
Male sex	12 (100%)	80 (76%)	0.047
Risk factor			
IVDU	4 (33.3%)	53 (50%)	
Homosexual	6 (50%)	24 (23%)	
Heterosexual	2 (16.6%)	22 (21%)	NS
Transfusion	–	2 (2%)	
Unknown	–	4 (4%)	
AIDS clinical category			
A	7 (58.3%)	26 (25%)	0.029
B	1 (8.3%)	17 (16%)	
C	4 (33%)	62 (59%)	
Histologic type			
Burkitt	5 (42%)	67 (64%)	
Diffuse large B-cell	7 (58%)	18 (17%)	0.005
Other types#	0 (0%)	20 (19%)	
Performance status			
ECOG >2	3 (25%)	21 (20%)	NS
B symptoms	9 (75%)	69 (66%)	NS
Extranodal sites >1	10 (83%)	42 (40%)	0.005
Bone marrow involvement	4 (33%)	31 (30%)	NS
Serum LDH >270 U/L	12 (100%)	52 (50%)	0.003
CD4 lymphocyte<200/μL	N=9 5 (56%)	N=100 65 (71%)	NS

#Other types: 4 anaplastic lymphoma; 2 peripheral T-cell lymphoma; 2 plasmablastic lymphoma; 2 primary effusion lymphoma; 1 lymphoma MALT; 9 unclassifiable. A, B, C: AIDS clinical category according to the CDC definition, 1993 (10). NHL: non-Hodgkin's lymphoma; IPI: International Prognostic Index; LDH: lactate dehydrogenase (normal values up to 270 U/L); ECOG: Eastern Co-operative Oncology Group.

CNS involvement of systemic NHL. Data comparing the frequency of CNS involvement according to HAART are shown in Table 1. Table 2 shows the characteristics of the patients with systemic NHL regarding leptomeningeal involvement. A sharp decrease was observed in CNS involvement in our series among patients who were on HAART. This was statistically significant for meningeal involvement in systemic NHL. In addition, 5 meningeal relapses out of 35 responders among patients not receiving HAART were observed versus no relapses in 12 lymphoma responders on HAART (p=0.212). Of the 14 patients with PCL, only 1 was on HAART at lymphoma diagnosis. However, this patient had not responded to the antiretroviral therapy. After the introduction of HAART, a decline was observed in PCL.[5,6] Since PCL typically occurs in severely immunosuppressed patients with low CD4 counts, the increase in these lymphocytes produced by HAART is widely thought to be directly responsible for the fall in the incidence of PCL in the HAART era. In our series, patients without HAART had lower CD4 lymphocyte counts and a higher HIV load than those on HAART, supporting the hypothesis that these parameters could play a role in CNS involvement in ARL. Although the difference between the frequency of PCL in patients receiving HAART and those who did not was not statistically significant, our data support the hypothesis, because the only patient diagnosed with PCL while receiving HAART was a non-responder to antiretrovirals, and the mean (SD) of CD4 lymphocytes for patients with PCL was 47 (70)/μL. Furthermore, our study demonstrated, for the first time to our knowledge, of a significant decrease in leptomeningeal involvement in patients with systemic NHL on HAART (Table 1). However, the mechanism responsible for this remains unknown, since in our series these patients did not have a lower number of CD4 lymphocytes than those without leptomeningeal involvement (Table 2).

To summarize, these data confirm the decrease in the frequency of PCL in patients receiving HAART. Most importantly, this is the first report of a reduction in the prevalence of leptomeningeal infiltration at diagnosis of systemic NHL in patients receiving HAART, suggesting its possible role in the prevention of leptomeningeal involvement among systemic NHL. These findings support a change in the policy of universal CNS prophylaxis in these patients.

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