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ACUTE HEPATIC TOXICITY DURING CYCLIC CHEMOTHERAPY IN NON HODGKIN'S LYMPHOMA

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ABSTRACT

Background and Objective. Hepatic toxicity directly related to the drugs administered in cyclic chemotherapy (CT), although sometimes serious, does not limit the treatment of non-Hodgkin's lymphoma (NHL). Nevertheless, reports of reactivation of viral hepatitis in NHL patients with B virus (HBV) infection are becoming more frequent. The recent observation of two cases of severe liver toxicity directly correlated to CT and a case of fatal hepatic failure due to HBV replication prompted us to evaluate the hepatic toxicity of CT in 98 consecutive B-cell NHL patients treated with relatively homogeneous cyclic CT.

Methods. Acute hepatic toxicity was retrospectively evaluated in 98 consecutive B-cell NHL patients who received induction CT. HBV and HCV markers were checked at presentation. All patients were tested for ALT and bilirubin before every CT course, while tests for HBV-DNA and/or for HCV-RNA were performed with PCR only when hepatitis occurred.

Results. At presentation 22 patients (22.4%) were positive for HBsAg, and 11 (15.9%) were positive for anti-HCV. Acute hepatitis developed in 12 (12.2%) NHL patients: 8 (out of 22) in HBsAg-positive and anti-HCV-negative patients, 3 (out of 76) in HBsAg-negative patients, and 1 (out of 11) in anti-HCV-positive patients. Hepatitis was attributed to reactivation of chronic B hepatitis in 3 patients and to drug toxicity in 3 others; hepatitis was undefined in 6 cases.

Interpretation and Conclusions. Drug-related liver toxicity is not a rare occurrence in NHL patients. Reactivation of HBV replication is responsible for a relevant number of the hepatitis cases observed. We did not detect acute hepatitis due to the reactivation of HCV replication (in chronic C hepatitis carriers).

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Key words: lymphoma, hepatitis (B-C) reactivation, drug-related hepatotoxicity

Many cytotoxic drugs, even if they are metabolized by the liver, induce minimal or no hepatic damage.[1] Nevertheless, some drugs employed in the treatment of non-Hodgkin's lymphoma (NHL) can cause early liver toxicity characterized by a slight increase in ALT, moderate icteric hepatitis or, exceptionally, by hepatitis with massive necrosis.[2,3] An accurate evaluation of the incidence of toxicity directly due to drugs is difficult for many reasons. First, the prevalence of HBV and HCV infections in NHL patients is higher than in healthy individuals,[4-10] in particular in the immunocytoma subgroup.[11]

Second, cytotoxic or immunosuppressive therapy can induce reactivation of HBV[4,12,13] or HCV[14,16] replication, causing destruction of infected hepatocytes. This latter process may be due to partial restoration of the immune system following withdrawal of chemotherapy (CT). In fact many cases of fatal acute hepatitis due to reactivation of viral replication have been described in HBsAg-positive patients with NHL.[4,12,13,17-19] It must be noted, however, that most of these patients showed a hepatitis that evolved to complete regression.[4,12,17] By contrast, only one case of fulminant hepatitis in an anti-HCV-positive patient with NHL[20] and perhaps two other cases of fatal hepatic failure after reactivation of HCV and HBV replication have been reported.[21]

The recent observation of two cases of severe liver toxicity directly correlated to CT and a case of fatal hepatic failure due to HBV replication (among the patients followed in our unit) prompted us to evaluate the hepatic toxicity of CT in 98 consecutive B-cell NHL patients treated with relatively homogeneous cyclic CT.

Patients and Methods

Ninety-eight consecutive B-cell NHL patients (63 men and 35 women) treated with induction CT were enrolled from 1991 to 1995. Histologic diagnosis was formulated in accordance with the updated Kiel classification.[22] The demographic characteris-

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Table 1. Demographic characteristics, HBV and HCV markers, histologic lymphoma type (according to the updated Kiel classification), chemotherapeutic regimens in 98 B-cell NHL patients.

	Groups (a) I	II	III	Total
N° of patients (pt)	20	32	46	98
Age (y) median (range)	55 (38-70)	52 (20-70)	57 (23 -75)	54 (20-75)
Sex M n°	13	21	29	63
F n°	7	11	17	35
NHL hepatic involvement	2	5	4	11
Elevated serum ALT level*	1	2	3	6
Markers°				
HBsAg– Anti HCV–	4	15	18	37
HBsAg+ Anti HCV–	4	10	7	21
HBsAg– Anti HCV+	2	4	4	10
HBsAg+ Anti HCV+	0	1	0	1
Liver disease (at diagnosis)	1	5	3	9
Chemotherapeutic regimens^				
CNOP	11	0	0	11
CEOP	9	32	25	66
ProMACE-CytaBOM	0	0	21	21

Group I: centroblastic-centrocytic follicular. Group II: centrocytic (6 pts), centroblastic-centrocytic diffuse (26 pts). Group III: centroblastic (30 pts), immunoblastic (16 pts). *x1.5-2.4 normal serum ALT level (degree 0-1 WHO); °HCV determined in 69/98 patients; HBs Ag determined in 98/98 patients; ^number of courses of treatment: 4-10 (median 7 courses).

tics of these subjects are reported in Table 1. The patients were divided into 3 groups according to clinical prognosis: 20 centroblastic-centrocytic follicular lymphoma (Group I), 6 centrocytic (mantle cell) and 26 centroblastic-centrocytic diffuse lymphoma (Group II), 30 centroblastic and 16 immunoblastic lymphoma (Group III). The chemotherapeutic regimens included: CNOP[23] in 11 patients (11.2%), CEOP[24] in 66 patients (67.3%), and ProMACE-CytaBOM[25] in 21 patients (21.5%). The number of courses of cytotoxic CT ranged from 4 to 10 (median 7). At diagnosis, NHL liver involvement was demonstrated by cytology in 11 patients. Another 9 had histologically proven chronic liver disease: 4 alcoholic cirrhosis, 1 HBsAg positive cirrhosis, 2 anti-HCV positive cirrhosis, 2 anti-HCV positive chronic hepatitis (Table 1).

Table 2. Correlation between HBV and HCV markers and development of hepatitis in 98 B-cell NHL patients during cytotoxic therapy.

	HBs Ag+	HBs Ag–*	Anti-HCV+	Anti-HCV–
Acute hepatitis with massive necrosis	3/22 (13.6%)	1/76 (1.3%)	0/11 (0%)	0/58 (0%)
Icteric hepatitis	1/22 (4.5%)	1/76 (1.3%)	1/11 (9%)	0/58 (0%)
Anicteric hepatitis	4/22 (18.2%)	1/76 (1.3%)	0/11 (0%)	4/58 (6.9%)°
ALT level increase <2.5 times upper normal limit	4/22 (18.2%)	10/76 (13.1%)	2/11 (18%)	4/58 (6.9%)
	98 patients		69 patients	

*Of 76 HBs Ag-negative patients, 9 were HBs Ab positive, only one of whom developed anicteric hepatitis; °anti-HCV-negative patients were HBs Ag positive (column HBs Ag+).

All patients were tested for HBV markers at presentation, whereas anti-HCV antibodies were determined only in 69 patients (70.4%). ALT, AST, γ-GT, LDH and bilirubin were checked before every course of CT. Additional tests for HBV-DNA and/or HCV-RNA, δ virus, cytomegalovirus (CMV), and Epstein Barr virus (EBV) were performed only when severe hepatitis occurred.

Hepatitis B markers were tested by enzyme-linked immunoassays (Organon Teknika, M.B.S.), HBV-DNA by quantitative chemiluminescent assay (Digene), hepatitis C markers by enzyme-linked immunoassays (Ortho) and HCV-RNA by qualitative PCR (Roche). The presence of anti-EBV antibodies was detected by enzyme-linked immunoassays (Ortho), the δ antigen by enzyme-linked immunoassays (Organon Teknika), and the CMV antigen by direct immunofluorescence (Bioline).

Hepatic complications were classified into 4 categories: 1) acute hepatitis with diffuse necrosis; 2) icteric hepatitis with bilirubin greater than 1.6 mg/dL and serum ALT level at least three times the upper normal limit (UNL=50 IU/L); 3) anicteric hepatitis with bilirubin < 1.6 mg/dL and serum ALT level at least three times the UNL; 4) ALT increase (< 2.5 times UNL) with regression in about 30 days.

Statistical analysis was performed using Wilcoxon's test and univariate analysis.

Results

At presentation 22 out of the 98 patients (22.4%) were positive for HBsAg, and 11 out of the 69 tested (15.9%) were positive for anti-HCV; only one patient showed coinfection with the two viruses. A modest and transient increase in the serum ALT level was observed in 20 out of the 98 patients (20.4%). Another 12 (12.2%) developed acute hepatitis: of these, 8 (8/22, 36.3%) were HBsAg positive, 3 (3/76, 3.9%) HBsAg negative, and 1 (1/11, 9%) anti-HCV positive (Table 2). A higher incidence of hepatitis was observed in HBsAg-positive patients than in HBsAg-negative ones ($p < 0.005$), though the low number of events does not allow generalization of this finding.

Hepatitis could be attributed to exacerbation or reactivation of chronic B hepatitis in 3 out of 8 HBsAg-positive patients (37.5%). One subject showed a conversion from negative to positive HBV-DNA, which was quantified as 1039 pcg, whereas 2 other patients became positive for IgM anti-HBc. Hepatitis could be attributed directly to CT toxicity in 2 out of 8 HBsAg-positive patients (25%), since all the markers of viral infection (including HBV-DNA) were negative. The cause of hepatitis remained undefined in 6 subjects due to a lack of data on HBV markers during the acute phase. Three of these patients had been previously classified as HBsAg positive and 3 as HBsAg negative. The anicteric hepatitis that developed in one anti-HCV-positive patient (HBsAg, anti-HBs, anti-HBc negative) was attributable to direct CT toxicity since HCV-RNA as determined by PCR proved to be negative.

Hepatitis was temporary (from 4 weeks to 4 months) an all but 2 patients: one HBsAg-positive subject developed cirrhosis and ascites, with regression of the latter in 5 months; a second HBsAg-positive patient died of fulminant hepatic failure

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Table 3 . Characteristics of the 12 NHL patients who developed hepatitis during cytotoxic therapy (CT).

Patients						Liver disease	Etiology of hepatitis during CT	Evolution of acute hepatitis
#	Sex	Age	R (1)	UKC (a)	HBV-HVC Markers			
1	M	40	PR	cb	HBs Ag pos Anti-HCV neg	no	reactivation of HBV replication HBV-DNA = 1039 pcg	fatal hepatic failure
2	M	53	CR	ccf	HBs Ag pos Anti-HCV neg	no	reactivation of HBV replication shifting from HBc Ab neg to HBc IgM pos	icteric hepatitis, recovered in 3 months
3	M	35	CR	ib	HBs Ag pos Anti-HCV neg	no	reactivation of HBV replication shifting from HBc Ab neg to HBc IgM pos	icteric hepatitis evolved to cirrhosis (ascites and jaundice, recovered in 5 months)
4	M	42	CR	cb	HBs Ag pos Anti-HCV neg	no	direct toxicity from CT, HBV-DNA neg	icteric hepatitis evolved to cirrhosis (ascites and jaundice, recovered in 4 months)
5	M	43	CR	ccd	HBs Ag pos Anti-HCV neg	post-hepatitis cirrhosis (2)	direct toxicity from CT, HBV-DNA neg	anicteric hepatitis, recovered in 2 months
6	F	64	CR	cb	HBs Ag pos Anti-HCV neg	no	uncertain: HBV-DNA not determined	anicteric hepatitis, recovered in 2 months
7	F	54	PR	ccf	HBs Ag pos Anti-HCV neg	no	uncertain: HBV-DNA not determined	anicteric hepatitis, recovered in 2 months
8	F	66	CR	ib	HBs Ag pos Anti-HCV neg	no	uncertain: HBV-DNA not determined	anicteric hepatitis, recovered in 1 month
9	M	50	PR	cb	HBs Ag neg; HBc Ab pos Anti-HCV neg	alcoholic cirrhosis (2)	uncertain: HBV-DNA not determined	anicteric hepatitis and ascites, recovered in 2 months
10	M	54	PR	ib	HBs Ag neg; HBc Ab pos Anti-HCV neg	alcoholic cirrhosis (2)	uncertain: HBV-DNA not determined	icteric hepatitis, recovered in 2 months
11	M	53	CR	ccf	HBs Ag neg; HBc Ab pos Anti-HCV neg	no	uncertain: HBV-DNA not determined	anicteric hepatitis, recovered in 2 months
12	F	35	PR	ib	HBs Ag neg Anti-HCV pos	no	direct toxicity from CT, HCV-RNA PCR neg	anicteric hepatitis, recovered in 2 months

(1) R = remission; PR = partial remission; CR = complete remission. (2) no clinical evidence.
(a) Updated Kiel classification: ccf = centroblastic-centrocytic follicular lymphoma; ccd = centroblastic-centrocytic diffuse lymphoma; cb = centroblastic lymphoma; ib: immunoblastic lymphoma

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Table 4. Characteristics of HBsAg– or anti-HCV-positive patients, according to the presence or absence of acute hepatitis.

B-cell NHL	*Hepatitis*		*Total*
Hbs Ag + or Anti-HCV +	present	absent	
N° of patients	9	23	32
Age (y) median (range)	50 (35-65)	54 (37-70)	
Sex			
M n°	5	14	19
F n°	4	9	13
Histological type			
Centroblastic-centrocytic follicular	1	2	3
Centrocytic; centroblastic-centrocytic diffuse	1	17	18
Centroblastic; Immunoblastic	7	4	11
Hepatic involvement	1	4	5
Chemotherapeutic regimens			
CNOP	1	2	3
CEOP	4	18	22
ProMACE-CytaBOM	4	3	7

(Table 3). Three out of the 9 patients with chronic liver disease at presentation (2 with alcoholic cirrhosis, 1 with post-hepatitis B cirrhosis) developed acute hepatitis. None of the patients with hepatic involvement by NHL developed hepatitis.

In all patients hepatitis developed after 3 to 5 CT courses; however, complete remission of NHL was obtained in 7 out 12 cases (Table 3). At univariate analysis none of the possible risk factors considered (age, sex, histological type of lymphoma, presence of hepatic involvement, duration and type of CT) was significantly associated with the development of acute hepatitis (Table 4).

Discussion

Data on the incidence of hepatic toxicity in NHL patients treated with CT are still scanty and in most cases have been obtained through retrospective studies.[4,12,17,18] The present investigation, though retrospective and partly lacking in viral replication monitoring, might still provide further evidence on hepatic toxicity in NHL patients who are receiving cytotoxic therapy.

In our study the prevalence of HBsAg and anti-HCV positivity in NHL patients (22.4 and 15.9%, respectively) was significantly higher than that reported in northern Italians (respectively, 1.3% and 3.2%), but comparable to that observed in other studies on the subject.[4-7,11,12] Twelve out of 98 (12.2%) NHL patients developed hepatitis: 7 cases were mild, 4 serious but reversible, and 1 was fulminant hepatic failure. Hepatitis could be directly attributed to drug toxicity in 3 patients, to reactivation of HBV replication in 3 patients, and was undefined in 6 others (Table 3).

The three cases we observed suggest that direct drug hepatic toxicity is not unusual since it also occurs in HBsAg-positive and in anti-HCV-positive patients. These data are particularly important because NHL patients affected by chronic liver disease frequently undergo cytotoxic therapy. In fact, 3 out of the 9 patients with chronic liver disease at presentation developed acute hepatitis as a result of cytotoxic therapy.

Reactivation of HBV replication was undoubtedly responsible for a significant number of the hepatitis cases observed in our NHL patients (3 out of 8). Furthermore, this number could be underestimated since HBV markers were not monitored in 3 HBsAg-positive patients during cytotoxic therapy. By contrast, only one case of acute hepatitis unrelated to either exacerbation of viral HCV replication (HCV-RNA PCR negative) or to HBV superinfection was recorded among the eleven anti-HCV-positive NHL patients. These data are supported by a recent report of only one case of increased HCV replication in anti-HCV-positive NHL patients treated with conventional cytotoxic therapy.[20] Moreover, other data on the development of hepatitis due to reactivation of HCV replication have been reported in patients who undergo conditioning therapy for bone marrow[15] or heart transplantation.[26] It must be noted, however, that no risk factor for exacerbation or reactivation of HBV and/or HCV could be identified in our series (Table 4).

The mild and transient increase of serum ALT levels observed during cytotoxic therapy (20 out of 98 patients) was likely due to direct drug toxicity.

Several options have been proposed to reduce the risk of reactivation of HBV replication, but none has been considered useful. Treatment with less aggressive chemotherapeutic regimens is not viable because fatal reactivation of hepatitis has been described even in patients treated with a single immunosuppressive agent.[27,28] Continuous treatment with low-dose prednisone did not prevent reactivation of chronic HBV hepatitis and, what is more, it increased the risk of serious infections. α-interferon (INF) has not been employed in the prophylaxis of hepatitis because of a lack of data on the reactivation of HCV by chemotherapeutical regimens and the scarse response observed in HBsAg-positive patients.[12] It must be noted, however, that this last study evaluated a Chinese population, in whom HBV infection is mainly acquired at birth and is thus less responsive to INF treatment.

We suggest monitoring serum levels of ALT, AST and bilirubin before each course of therapy and delay CT in the case of first or second degree toxici-

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ty (according to WHO). INF could be considered in HBV or HCV hepatitis, as well as treatment with hyperimmune serum in selected HBV patients to avoid further liver damage due to chemotherapy toxicity.

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