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Efficacy of lamivudine to prevent hepatitis reactivation in hepatitis B virus–infected patients treated for non-Hodgkin lymphoma

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equivalent treatments. With only 90 participants, the study has insufficient power to permit any valid statement on the equivalence of the treatments, a weakness acknowledged by the authors in the final sentence of their manuscript.[2] Equivalency studies must be designed in accordance with strict methodologic criteria in order for their conclusions to have any statistical validity.[3] The unambiguous outcome of the Barritt and Jordan study and the totality of subsequent medical literature and clinical experience clearly indicate that additional placebo-controlled clinical trials in the treatment of VTED would be highly unethical.[4] The task at the present is to identify safer and more effective antithrombotic agents, not to revisit the past.

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To the editor:

Efficacy of lamivudine to prevent hepatitis reactivation in hepatitis B virus–infected patients treated for non-Hodgkin lymphoma

The association of hepatitis viruses with non-Hodgkin lymphomas (NHL) is not rare. Several authors have reported an exceeding prevalence of hepatitis C virus (HCV)[1-3] or of hepatitis B virus (HBV)[4,5] infection in patients affected by NHL. A sustained increase of alanine aminotransferase (ALT) associated with high levels of HBV viremia (HBV-DNA) 1 to 2 months after the suspension of chemotherapy has been described in patients suffering from NHL and infected by HBV.[7,8] Recently, a nucleotide analogue (lamivudine) was shown to be beneficial in HBV-infected patients with signs of active replication.[6] The aim of this study was to investigate the role of lamivudine to treat or to prevent hepatitis reactivation in HBV-infected subjects suffering from NHL and undergoing chemotherapy.

We screened 550 patients (271 males and 279 females) affected by NHL, ranging in age from 38 to 67 years (median 52 years), and 148 control subjects suffering from metabolic disorders, attending our institutions during the last 10 years. Of 550 NHL patients, 108 had signs of HBV contact (19%) and 21 were HBsAg-positive (3.5%), while 86 (15.6%) were HCV-Ab positive with detectable HCV-RNA in their serum (Table 1). HCV prevalence in NHL was higher than in the control group (15.6% vs 2.02% $P < .000$), while HBsAg-positive prevalence was not significantly different (3.5% vs 1.3%; ns). No age or sex distribution differences were found in the various groups (Table 1). NHL patients were treated according to different therapeutic protocols, which were chosen on the basis of the specific hystological type and clinical stage of the disease. Evaluation and follow-up of the patients included medical history, physical examination, complete blood count, ALT, and markers of viral hepatitis. Among the 21 HBV-positive NHL patients, 12 had hepatitis reactivation soon after chemotherapy. Of them, 9 were treated with lamivudine (Zeffix; Glaxo-Wellcome 100 mg/die), and 3 were not (prelamivudine era). All patients treated recovered from the viral reactivation and are still followed up, whereas the 3 patients who did not receive lamivudine died of acute liver failure. In 3 patients lamivudine was given prophylactically during and after chemotherapy, and the treatment was discontinued 2 months after the last chemotherapy course. These 3 patients did not show any sign of acute B hepatitis recurrence (Figure 1). These data confirm the efficacy of lamivudine, as it has been recently reported in the literature.[9-11] It is noteworthy that, at variance with "spontaneous" HBV reactivation in carriers of chronic hepatitis, which may relapse at lamivudine interruption, the halting of viral

Table 1. Epidemiological characteristics of NHL patients and control subjects

	NHL			Controls		
	Total	HBV	HCV	Total	HBV	HCV
Patients/subjects	550	21 (3.8%)	86 (15.6%)	148	2 (1.3%)	3 (2.02%)
Age (y)						
Median	52	45	58	56	51	63
(range)	(38-67)	(38-64)	(42-67)	(44-72)	(44-58)	(49-72)
Sex (m/f)	271/279	11/10	35/51	78/70	2/0	2/1
HBeAg/HBeAb	0/21	0/21	0/1	0/2	0/2	—
HBcAb	108	21	26	13	2	—
HBsAg	21	21	1	2	2	—
HBV-DNA+/HBV-DNA−*	—	0/21	0/1	0/2	0/2	—
HBV-DNA+/HBV-DNA−†	—	15/0*	1/0	—	—	—
HCV-Ab/HCV-RNA	86/86	1/1	86/86	3/3	0	3/3
ALT* mean (SD)	35.73 ± 21.3	22.27 ± 9.4	25.68 ± 12.4	33.4 ± 15.7	66 ± 16.9	62 ± 18.5
ALT† mean (SD)	31.67 ± 28.5	1051.28 ± 898.5‡	32.8 ± 28.7	—	—	—

*Before chemotherapy.
†1 to 2 months after chemotherapy.
‡Data on 15 patients, 6 patients not collectable.

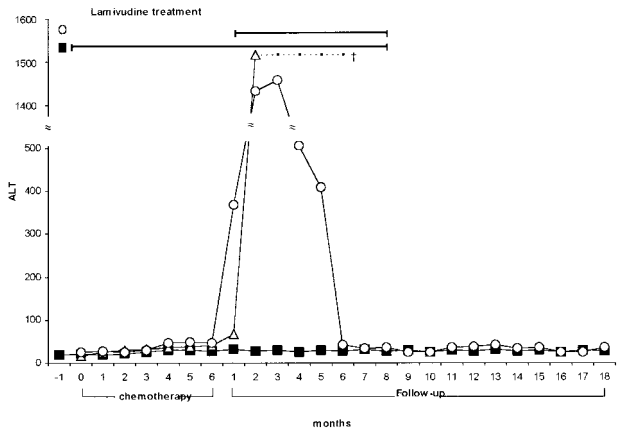

Figure 1. Lamivudine nontreated, treated, and pretreated NHL patients. ALT values of HBV-infected NHL patients nontreated (△) (n = 3), treated with lamivudine after chemotherapy (○) (n = 9), and pretreated with lamivudine (during and after chemotherapy) (■) (n = 3).

replication in NHL HBV–infected subjects persists even after lamivudine discontinuation. A possible explanation for such a different behavior is that viral replication in NHL patients is caused by the immunosuppressive activity of chemotherapy; the replication is followed by liver attack at postchemotherapy immunological recovery, leading to acute or even fulminant hepatitis. The use of lamivudine, by blocking B virus replication, interrupts the sequence of events; then, the drug is no more needed when the recovered immune surveillance re-establishes tolerance to a small viral load. In our series of NHL patients, while a high percentage of HBsAg-positive cases (12/21 = 57%) had signs of viral reactivation, no HCV-infected patient (n = 86) had ALT increase during or after chemotherapy. This seems to support the idea that the immune system might play a different role in the pathogenic mechanism(s) underlying HCV- and HBV-related chronicity.

In conclusion, our study, while confirming the high prevalence of HCV infection in NHL patients in specific geographic areas, points out that HCV reactivation after chemotherapy is not a clinical problem. By contrast, life expectancy in carriers of hepatitis B virus may be negatively influenced by the viral infection. Lamivudine has proven to be a useful drug to prevent or treat HBV reactivation in patients undergoing chemotherapy for NHL. This study may represent the basis for a prospective multicenter trial aimed to assess lamivudine efficacy in avoiding reactivation of HBV-related hepatitis.

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To the editor:

Language and the clonal myeloid diseases

Medicine has been fraught with linguistic ambiguities. Some terms are anachronisms, some lack precision, and some are inconsistent with current knowledge of the pathobiology of human disease. This terminology is disruptive to communication and understanding. Although the handful of experts in a field may be able to put such diagnostic designations into perspective, patients, students, physicians, nurses, demographers, and epidemiologists studying these entities are often uncertain or confused as to their place in the spectrum of relevant diseases or in the approaches to their therapy. Such terms should be amended where possible, but such recategorizations require the imprimatur of some organization or group. Although the list is long, 3 noteworthy candidates for change are discussed below.

Refractory anemia. This term has been obsolescent for decades and should be made obsolete. It derives from an early effort to distinguish among nonhemolytic anemias by whether they did or did not respond to iron or specific vitamin-replacement therapy. Moreover, most of the "refractory anemias" are accompanied by varying degrees of abnormalities in the concentration or morphology of white cells and platelets, leading to fruitless efforts to subcategorize the varied disease phenotypes. A mutation in a multipotential hematopoietic cell can produce a nearly limitless variety of manifestations as the multitude of phenotypes (and genotypes) of acute myelogenous leukemia indicate. No two are quite the same in phenotypic features. This variety of form occurs even within disease subsets with apparent similar cytogenetic abnormalities. The move toward genetic classification will be useful to motivate molecularly targeted therapists, but the best classification of leukemia for the patient will be by the curative drug to which it responds (ie, cladrabine-curable leukemia). Today, the anemias, bicytopenias, and multicytopenias in the array of refractory anemias are known to be neoplasms, that is, the clonal expression of a mutant multipotential hematopoietic cell. Thus, the