Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemo-immune therapy

The risk of developing hepatitis B virus (HBV) related liver disease in isolated anti-HBc carriers[1] undergoing chemo or chemo-immunotherapy for non-Hodgkin's lymphoma is not well known. The use of rituximab has been reported to cause even fatal HBV-related liver disease in this category of patients.[2-5]

In an attempt to solve this problem, we retrospectively analyzed 1,087 patients with non-Hodgkin's lymphoma seen from January 1989 through June 2006. Since then, in our Unit, all newly diagnosed patients undergo measurement of HBsAg, anti-HBs, anti-HBc, HBeAg, and antiHBe.

Patients were monitored by liver function tests during and after therapy as follows; on day 1 and day 14 of each cycle, every month for the first six months after completion of chemotherapy, then every 3-4 months for 24 months, and thereafter twice a year.

When a patient developed liver disease (defined as ≥ three-fold increase in alanine aminotransferase [AST] from baseline exceeding the upper limit of normal [>45 IU/L] or an absolute increase of ALT to more than 100 IU/L)[6] we investigated HBsAg. Liver disease attributable to HBV in potential occult carriers was defined as the re-emergence of HBsAg in HBsAg negative/ anti-HBc positive subjects (reverse seroconversion).[1]

Cheson's criteria were used to define the response to lymphoma treatment.[7]

Non-parametric data are expressed with median (range). For parametric groups, the χ^2 test was used to compare the two groups. The risk of HBV related liver disease was calculated using the Kaplan-Meier method.[8] The retrospective observational protocol study was approved by the Institutional Review Board.

Of 1,087 non-Hodgkin's lymphoma patients, 55 (5%) were overt HBV carriers, 394 (36%) were isolated anti-HBc positive, while 638 (58%) showed negative HBV markers or only anti-HBs antibodies. We focused on the 394 potential occult carriers: 200 males, 194 females, median age 62 years (range 34-80). The main lymphoma diagnosis was diffuse large B-cell lymphoma (n=185, 47%).

Of the 394 anti-HBc positive patients, 245 (62%) received chemotherapy and 74 (19%) had immunochemotherapy with anti-CD20 monoclonal antibody. Twenty-nine (7%) received other treatment (radiotherapy, interferon, antibiotics etc.) and 46 (12%) did not receive therapy (watch and wait) (Table 1).

Of the patients who received chemo±immuno therapy, 225 were treated with a single line of therapy, 59 with 2 lines of therapy and 64 with more than 2 lines of therapy.

Four of the 394 patients (1%) developed HBV-related liver disease: 2 out of 245 (0.8%) patients treated with chemotherapy only and 2 out of 74 (2.7%) treated with immuno-chemotherapy (p<0.05). No HBV-related liver disease occurred in patients who were simply monitored or in those treated with other therapies. The one year Kaplan-Meier[8] risk of HBV-related liver disease in patients treated with immuno-chemotherapy was 3%.

Three out of four events occurred as a consequence of the first line of therapy; one event occurred as a consequence of the third line of therapy.

Table 1. Results of the retrospective analyses of 394 isolated anti-HBc lymphoma patients.

Therapy	*Isolated antiHBc+ patients*	*Hepatitis B virus related liver disease*	
		N°	*%*
Chemotherapy	245	2	0.8
R-chemotherapy	74	2	2.7
Watch and wait	46	0	0
Other therapies (radiotherapy, interferon, antibiotics etc)	29	0	0

HBV-related liver disease occurred five months after discontinuation of cytotoxic therapy in 3 cases while in the other patient it occurred during immunochemotherapy, disrupting the chemotherapy schedule.

Two out of 4 patients were treated with lamivudine for hepatitis. The other 2 patients received only support treatment (pre-lamivudine era). Transaminase and bilirubin peaks were respectively 9 and 5 times the upper limit of normal in patients treated with Lamivudine, and 37 and 7 times the upper limit of normal in patients treated with support therapy.

All of the 4 patients obtained clinical remission of hepatitis with long-lasting persistence of HBsAg.

Two out of 4 patients obtained complete remission of the lymphoma, even though one of them relapsed and required further therapy. The other 2 patients died with progressive disease.

At present, with the increase in immunosuppressive therapy, the problem of HBV reactivation has become more common. A few cases of even lethal reverse seroconversion in isolated anti-core carriers have been reported after the use of rituximab.[2-5,9] However, there is clear evidence of the advantage of using rituximab.[10] The risk of rituximab induced HBV-related liver disease must be assessed.

In our center, complete assessment of HBV status has been routine clinical practice in all new lymphoma patients since 1989. Therefore, a retrospective analysis in a uniform population is feasible. One third of Lymphoma patients had isolated anti hepatitis B core positivity.

Our incidence of HBV-related liver disease (2.7%) was significantly greater in the anti-CD20 antibody group. Our results are limited by the fact that retrospective analyses can underestimate the events, particularly after one year post-therapy. Furthermore, none of these patients were on long-term maintenance therapy with rituximab. Larger, multicenter prospective observational trials are necessary to address this issue. A potential occult HBV carrier (i.e. isolated antiHbc) must be treated with the best clinical therapy available even including monoclonal antibodies. While a policy of prophylaxis remains controversial, close monitoring is mandatory.

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Acknowledgments: authors wish to thank Stanley L. Schrier for critical reading and suggestions.

Key words: chemotherapy, rituximab, HBV, potential occult carrier, reactivation.

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Citation: Targhetta C, Cabras MG, Mamusa AM, Mascia G, Angelucci E. Hepatitis B virus related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemo-immune therapy. Haematologica 2008 June; 93(6):951-952. doi: 10.3324/haematol.12557