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## Hepatitis B virus-associated B-cell non-Hodgkin lymphoma in non-endemic areas in Western Europe: clinical characteristics and prognosis

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## Abstract

The association between B-cell non-Hodgkin lymphoma (NHL) and hepatitis B virus (HBV) is well demonstrated by epidemiological studies. Most studies concerning this association have been conducted in endemic areas. Thus, little is known concerning the clinical characteristics of HBV-related lymphomas in non-endemic areas.

Here, we report the characteristics and outcomes of 39 patients with active HBV infection and B-cell NHL collected retrospectively in France and Italy. We also compared their characteristics with those of HCV-positive patients with NHL.

The gender ratio (M/F) was 3.3 and the median age at NHL diagnosis, 59 years. The pathological distribution was 24 (62%) diffuse large B-cell lymphomas (DLBCLs) and 15 (38%) other lymphomas subtypes: marginal zone lymphoma (n = 6), follicular lymphoma (n = 3), mantle cell lymphoma (n = 2), Burkitt's lymphoma (n = 1), and not otherwise specified low-grade B-NHL (n = 3). Treatment included antiviral therapy for 35 patients (90%). Twenty-two (92%) DLBCL patients received an R-CHOP or R-CHOP-like regimen, leading to complete remission for 18 (75%). At one year, 21 DLBCL patients (88%) were alive, and 13 other B-cell lymphoma patients (87%) were alive.

This European study underscores the predominance of DLBCL among patients with active HBV infection and their similar outcomes to non-HBV infected patients with DLBCL when treated with R-CHOP and antivirals.

## Introduction

Hepatitis B virus (HBV) is a hepatotropic virus that causes hepatitis and cirrhosis. According to the World Health Organization (WHO), 257 million people in the world have a chronic HBV infection, defined by a positive HbS antigen (HbSAg). Areas of high prevalence include Africa (6.1% according to the WHO), the Western Pacific, and Southeast Asia. The prevalence in Europe and North America is lower (1.6% according to the WHO). HBV is also an oncogenic virus and leads to an increased risk of developing hepatocellular carcinoma<sup>1</sup> and biliary cancer<sup>2</sup>. Several epidemiological studies have also shown an increased risk of lymphoid malignancies<sup>1,3–11</sup>. The risk is especially elevated for B-cell non-Hodgkin lymphoma (B-NHL) (odds ratio: 2.46)<sup>12</sup> (Supplementary Table 1).

The distribution of NHL subtypes in HBV-infected patients has only been studied in high-prevalence countries (Japan, China, Singapore, and Korea), where the association seems to predominate with diffuse large B-cell lymphoma (DLBCL), with an odds ratio around 2 reported in meta-analyses<sup>5,12–14</sup>.

In these regions, patients with both NHL and HBV appear to be younger and display more frequent advanced disease<sup>3,15–18</sup> than their HBV-negative counterparts. In northern regions, where the prevalence of HBV is low, there is little data on the characteristics of these lymphomas. Several studies have demonstrated the need for early detection, monitoring virological markers and providing antiviral treatment for patients with HBV infection receiving rituximab (R) immunotherapy to prevent HBV reactivation<sup>19</sup>, as described in guidelines<sup>20,21</sup>. However, the impact of anti-HBV therapy on the evolution of lymphoma in patients with active HBV infection needs to be evaluated. Our aim was to describe the characteristics and outcomes of patients with NHL and active hepatitis B in France and Italy, where the prevalence of HBV is low.

## Methods

### *Patient selection*

We retrospectively collected the data of patients with an active HBV infection diagnosed with NHL between June 2002 and April 2017 in three hematology units in the Paris area in France (St Louis Hospitals, Paris, and the Versailles Medical Center, Le Chesnay) and Italy (Pavia). The inclusion criteria consisted of a diagnosis of B-NHL, defined by histological analyses, and a diagnosis of active HBV infection. Active HBV infection was defined by the positive detection of either HBs antigen (HBsAg) and/or HBV DNA by polymerase chain reaction (PCR) ( $\geq 20$  UI/mL) at the diagnosis of B-NHL. Patients had all been tested for hepatitis C and HIV and were excluded from the present study in case of co-infection.

We finally compared the characteristics and outcomes of HBV-positive patients with B-NHL to those of HCV-positive patients with B-NHL enrolled in the ANRS HC-13 Lympho-C Study<sup>22</sup>.

### *Data collection and assessment of disease activity*

The following demographic data were collected from medical reports for each patient: age at lymphoma diagnosis, gender, place of birth, which was categorized by large regions (Europe, West Africa, North Africa, and China or Southeast Asia). Lymphomas were classified according to the WHO 2008 classification and staging was determined according to the Ann Arbor classification following clinical examination, CT-scan, and/or PET-scan and bone marrow evaluation, when available. Staging included a physical examination using the Eastern Cooperative Oncology Group performance status (EGOG/PS). Extra-nodal involvement was defined as at least one extra-nodal site. Liver and spleen were considered to be involved when nodular lesions were detected or when marked organomegaly significantly regressed after treatment; the spleen was not considered to be an extra-nodal site, bone-marrow infiltration was considered as extra-nodal involvement, and digestive involvement included digestive tract and/or pancreatic involvement. Routine laboratory test results were collected, including the presence of a monoclonal component and lactate dehydrogenase (LDH) levels. Virological hepatitis B profiles were collected at the diagnosis of lymphoma, assessment, HBsAg and, when available, anti-HBc, anti-HBs, and anti-HBe antibodies, HBe antigen, and HBV DNA viral load determined by PCR.

### *Treatment and outcomes*

Front-line treatment for lymphoma, living status at last follow-up, and, if applicable, date of relapse and date and causes of death, as well as antiviral treatment and virological responses, were recorded. The hematological response was evaluated at the end of front-line treatment. Response and progression were evaluated in accordance with the Revised Response Criteria for Malignant Lymphoma<sup>23</sup>. Overall survival (OS) was measured from lymphoma diagnosis to death by any cause.

### *Statistical analysis*

Descriptive statistics include the mean and range for continuous variables and frequency (%) for categorical variables. In univariate analysis,  $\chi^2$  and Fisher's exact tests were used, as appropriate, to compare categorical variables. Overall survival (OS) was measured from lymphoma diagnosis to death by any cause. The probability of OS was defined using the Kaplan-Meier method and differences were compared with the log-rank test. Follow-up was defined from B-NHL diagnosis to the last follow-up. The differences were considered to be significant for  $p < 0.05$ .

The study was performed after approval by the Ethics Committee (Comité de Protection des Personnes CPP) and conducted according to the principles expressed in the Helsinki Declaration.

## **Results**

### *Patient characteristics (Table 1)*

Among 43 patients with NHL and chronic HBV infection, 39 had been diagnosed with B-NHL and four with T-cell lymphoma were excluded. Only these 39 patients were included in the analysis. Among these 39 patients with B-NHL, most were men (27/39), and the median age was 59 years, ranging from 29 to 88 years. Twenty-two patients (56%) were born in Europe (12 from Italy, eight from France, and two from other countries); whereas 44% were born in regions endemic for HBV (six in North-Africa, seven in West Africa, and four in China or Southeast Asia).

### *Histological and clinical features*

The histological subtype was distributed as follows: DLCL (n = 24), follicular lymphoma (n = 4), splenic marginal zone lymphoma (SMZL) (n = 3), mucosa-associated lymphoid tissue lymphoma (MALT) (n = 3), mantle-cell lymphoma (n = 2), not otherwise specified low-grade B-NHL (LGNHL) (n = 3), and Burkitt's lymphoma (n = 1). None of the primary DLCLs had histological characteristics suggestive of a low-grade component in lymph node nor in bone marrow. One patient underwent histological transformation to DLCL five years after an initial diagnosis of follicular lymphoma. Overall, 27 patients (69%) had at least one extra-nodal involvement, including 10 of the bone marrow among 19 available bone-marrow biopsy results; seven of the liver, and four of the gastrointestinal tract. Twenty-five patients (64%) had Ann Arbor stage III/IV disease. Five patients (13%) had a monoclonal component.

### *Lymphoma treatments and responses (Table 2)*

All 24 DLCL patients received front-line immunochemotherapy with a standard anthracycline regimen (Rituximab-CHOP) or an R-CHOP-like regimen, such as R-ACVBP<sup>24</sup>. Treatment of one of these patients included consolidation with radiotherapy. Eighteen patients (75%) achieved complete remission (CR) at the end of front-line treatment, two (8%) achieved partial remission (PR), and none had initial refractory or progressive disease (PD). Data were missing for four patients. Among the two patients in PR at the end of treatment, who had been treated with R-CHOP; one died of lymphoma progression after two other lines of treatment and the other achieved CR after second-line treatment with R-bendamustine. Treatment of the patients with other lymphomas was more heterogeneous: R-chemotherapy (n = 10), or other strategies (n = 5) (Table 2).

### *HBV-related events and antiviral treatment*

The diagnoses of HBV infection and NHL were concomitant for all patients. Twenty five patients (65%) were positive for HbsAg and had a detectable viral load; 6 patients had only a positive HbsAg and 8 patients had only a detectable viral load (Table 1). No patient had a clinical history of cirrhosis before the diagnosis of NHL. A Metavir fibro-scan (n = 7) and/or liver biopsy was performed for only nine patients. Among them, one had F3 stage cirrhosis and the others had F0 or F1 stage disease. Thirty-five patients (90%) received antiviral

treatment following the diagnosis of NHL. Antiviral treatments included tenofovir (n = 8, 23%), lamivudine (16, 46%), and entecavir (11, 31%). Among the 4 patients without data on antiviral treatment, all had at least a positive HbsAg. Two patients had a DLBCL, one achieved CR then died of CHC, the other had PD; the two others (one with SZML, one with MALT NHL) achieved RC. No chemotherapy was reduced or interrupted because of undesirable effects. Data were missing for four patients. At last news, data on the HBV viral load was available for 25 patients, 19 (76%) have negated their viral load; all these patients had previously received an antiviral treatment. No patients developed cirrhosis during follow-up, but two were diagnosed with a hepatocellular carcinoma (two and five years after the diagnosis of lymphoma); both had received immunochemotherapy for DLBCL and died of carcinoma progression while they were in CR for lymphoma.

### *Outcomes*

With a median follow-up of 39 months (range 1 to 184 months), thirty-one patients were alive at last follow-up, 25 patients (64%) were still in CR and 3 (8%) in PD. Eight patients (21%) died during follow-up, 7 had been diagnosed with DLBCL and had been treated with R-CHOP. Among them, four died from lymphoma progression, two from hepatocellular carcinoma progression (see above), and one from implantable chamber catheter infection during chemotherapy. Another patient with LG-NHL died of lymphoma progression. All had a positive viral load at diagnosis and all received antiviral treatment during lymphoma treatment. Overall, median survival was 24 months for DLBCL patients and 68 months for patients with other lymphomas (Figure 1). Thirty-four patients (87%) were alive 1 year following NHL diagnosis.

### *Comparison of lymphoma features with HCV associated lymphomas*

We compared the characteristics and outcomes of the 39 patients with B-cell NHL and active HBV infection with the 116 patients with B-cell NHL and active HCV infection enrolled in the ARNS HC-13 lympho-C study. HBV patients were more frequently male than HCV-positive NHL patients (69% versus 50%,  $p = 0.04$ ). There was a significant difference in the histological distribution, the MZL subtype being more frequent in patients with active HCV infection (39%) than in those with active HBV (8%) The presence of a monoclonal component was also more frequent in patients with active HCV infection than among HBV-positive patients (42% versus 13% respectively,  $p < 0.05$ ).

Among the DLBCL patients in these two populations (24 DLBCLs with active HBV and 45 DLBCLs with active HCV), a monoclonal component was less frequent in HBV-positive than HCV-positive DLBCL patients (8% versus 32%,  $p = 0.03$ ) (supplementary Table 2) and none of the DLBCL had transformed from MZL among HBV-positive patients, whereas the DLBCL 16 of the 45 HCV patients had transformed from MZL. The frequency of extra-nodal involvement was high in both populations with hepatitis (63% for HBV-infected DLBCL and 73% for HCV-infected DLBCL) and appeared to predominate in the liver (27% in HBV-infected DLBCL patients and 30% in HCV-infected DLBCL patients).

## Discussion

This clinical study analyzing the characteristics and outcomes of 39 patients with active HBV infection and B-cell NHL collected retrospectively in France and Italy is one of few to be conducted in low-incidence endemic areas<sup>24–26</sup>. Although it is a European study, many patients were born in HBV-endemic areas (44%). The predominant histological subtype was DLBCL, constituting almost two thirds (62%) of NHL diagnoses in patients with an active HBV infection. These patients showed a high frequency of advanced lymphoma stages (64% Ann Arbor III-IV) and frequent extra-nodal involvement, especially in the liver (26%). Almost all patients received antivirals and immune-chemotherapy, allowing most to achieve a complete response (67%), without liver toxicity.

The association between HBV infection and NHL has been demonstrated for HBsAg-positive patients<sup>13</sup>, although patients with occult HBV infection have been shown to also be at higher risk of NHL<sup>27</sup>. Two meta-analyses confirmed this association, regardless of the region and endemicity of HBV<sup>10,14</sup>. However, only a few studies have analyzed the characteristics of HBV-associated NHL in low-endemicity regions<sup>7,28</sup>. Unlike studies performed in high-endemicity regions, in which patients with HBV-associated NHL were shown to be younger than those with non-HBV-related NHL, patients with HBV-NHL in our study had a median age of 59 years, which is similar to that of non-HBV-NHL patients<sup>15–17,29</sup>. The clear male predominance among the cases presented herein can be explained by the large proportion of immigrants (44%) in our series. The histological distribution we found is in accordance with that of previous studies, revealing a predominance of DLBCL among HBV-associated NHL, a subtype for which the association appears to be the highest (OR 1.2 to 7.22, OR 2.06 in meta-analyses (Table 1)). The frequent advanced Ann Arbor stages and extra-nodal involvement in our series is also in accordance with other studies<sup>15,16,29</sup>. *Wang et al.* also reported that liver dysfunction in HBsAg-positive patients is frequent and may constitute a poor prognostic factor<sup>15</sup>. We did not observe this in our study, probably due to the generalized use of antiviral treatment.

The immunochemotherapy regimen led to frequent hematological responses in DLBCL patients (75% of patients in CR in our study). In endemic regions, a previous study reported a lower CR rate (33%) with a one-year OS of 76% for patients with DLBCL and positive HbsAg treated with R-CHOP or CHOP or CHOP like<sup>29</sup>, while another study where patients were treated with R-CHOP, the CR was much higher (58%) and a one-year OS of 79%<sup>30</sup>. These different outcomes could be due to less frequent use of rituximab in NHL patients positive for HBsAg<sup>17,29,31</sup> in endemic regions and/or less frequent use of antiviral treatments linked to their lower availability in developing countries. Several studies have highlighted the benefits of rituximab<sup>17,31</sup> and antiviral treatment<sup>32–34</sup> in HBV-NHL patients. Of note, we observed no case of hematological response after antiviral treatment alone in our series nor has it been reported in the literature, in contrast to what has been largely reported in HCV-related NHL.



Indeed, although there is little data concerning HBV-related NHL in northern countries, the association between HCV infection and B-NHL has been largely explored. These NHLs are characterized by a predominance of MZL and DLBCL, having frequently transformed from low-grade NHL<sup>22,34</sup>. MZLs are frequently associated with the presence of a monoclonal component<sup>36</sup>. Immunological and pathological data, as well as the hematological responses obtained after antiviral treatment, are consistent with a stepwise model of lymphomagenesis induced by chronic antigenic stimulation. HBV-related NHL patients are more often men and have a lower frequency of the MZL subtype than those with HCV-related B-NHL (8% *versus* 39%) and they have no DLBCL with a low-grade component<sup>37</sup>. Accordingly, the frequency of a monoclonal component is low among HBV-related NHL patients suggesting that the stepwise model of lymphomagenesis induced by chronic antigenic stimulation proposed for HCV-related NHL is not valid for HBV-related NHL. In contrast, extra-nodal involvement is common in both HBV-related and HCV-related NHL, mainly involving the liver and digestive tract. These data suggest that presentation of the lymphoma may be associated with regional lymphomagenesis in the hepatic area, possibly induced by HCV or HBV-induced inflammation or direct infection of B-cells by the virus<sup>36</sup>. Our group and others previously reported *in situ* detection of HCV proteins in lymphoma tissues by immunostaining. This suggests that the transformation of B cells may be associated with their infection by HCV, which may participate in the maintenance and growth of tumour cells<sup>22,35</sup>. Consistent with this hypothesis, one study demonstrated the presence of HBV antigen and DNA in DLBCL tissue, suggesting a transforming effect of HBV in B lymphocytes<sup>37</sup>. Finally, *Ren et al.*<sup>16</sup> sequenced tumors and peripheral blood samples from HBsAg-positive DLBCL. They described an enhanced rate of mutagenesis and a distinct set of mutation targets in HBsAg positive DLBCL, supporting that an antigen-independent mechanism, rather than chronic antigenic stimulation, is favored in HBV-related lymphomagenesis by analysis of immunoglobulin heavy chain gene sequences. We retrospectively collected all HBV-associated NHL cases in Europe, an area of low endemicity for HBV infection. These patients had predominantly advanced-stage DLBCL, with frequent liver involvement, and frequent long-term hematological responses when they received a combination of immuno-chemotherapy and antiviral treatment. Additional studies are needed to explore the lymphomagenesis of this association.

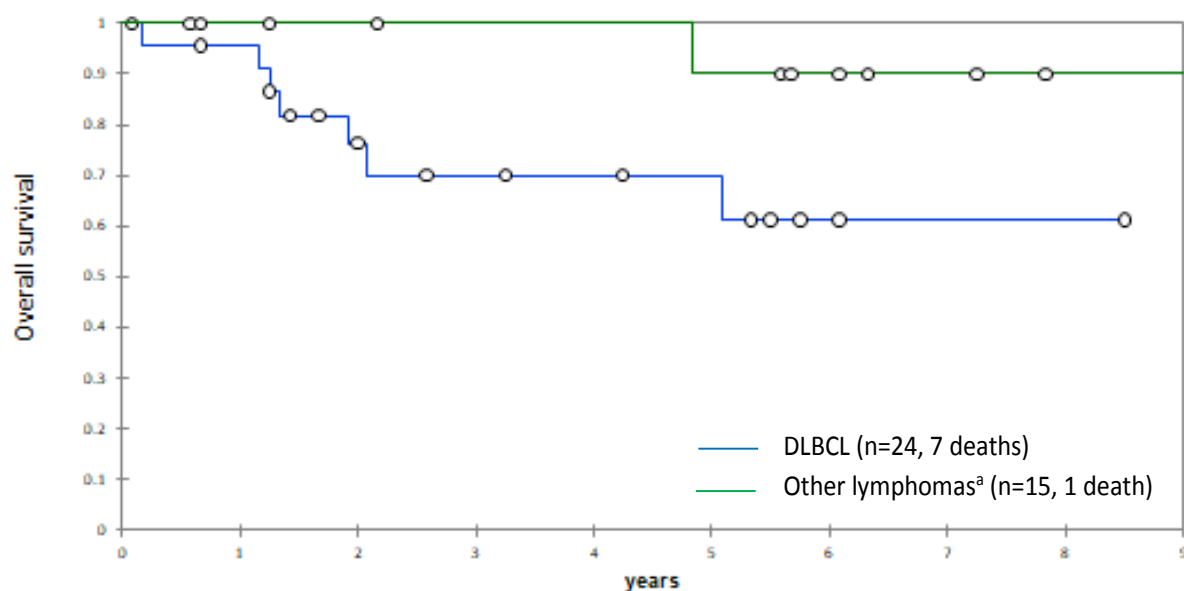
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**Figure 1. Overall survival of the 39 patients with B-cell non Hodgkin lymphoma and active HBV infection according to lymphoma subtypes**



Numbers of patients at risk

DLBCL	24	21	14	11	10	9	5	3	1	0
Other lymphomas	15	13	12	12	12	11	8	5	4	4

#### Figure legends

DLBCL: Diffuse large B cell lymphoma

<sup>a</sup>: splenic marginal zone lymphoma (n=3), mucosa associated lymphoid tissue lymphoma (3), follicular lymphoma (3), mantle cell lymphoma (2), Burkitt lymphoma (1), low grade not otherwise specified (3)

**Table 1. Demographic, clinical, immunological, and virological features of 39 patients with B-cell non Hodgkin lymphoma and active HBV infection**

	<b>Total n = 39 (%)</b>	<b>DLBCL n = 24 (%)</b>	<b>Others<sup>a</sup> n = 15 (%)</b>
<b>Gender</b>			
Male	27 (69)	16 (67)	11 (73)
Female	12 (31)	8 (33)	4 (27)
<b>Region of birth</b>			
Europe	22 (57)	15 (63)	7 (47)
North Africa	7 (18)	3 (12)	4 (26)
West Africa	6 (15)	2 (8)	4 (26)
China or Southeast Asia	4 (10)	4 (17)	0 (0)
<b>Age years, median [range]</b>	59 [29-88]	60 [29-88]	58 [32-76]
<b>Ag HBs<sup>b</sup></b>			
Positive	31 (89)	22 (96)	11 (79)
Negative <sup>c</sup>	4 (11)	1 (4)	3 (21)
<b>Viral load (&gt; 20 UI/mL)<sup>b</sup></b>			
Positive	33 (89)	22 (96)	11 (79)
Negative <sup>d</sup>	4 (11)	1 (4)	3 (21)
<b>Ann Arbor stage</b>			
I-II	14 (36)	8 (33)	6 (40)
III-IV	25 (64)	16 (67)	9 (60)
<b>Performance status<sup>d</sup></b>			
0-1	30 (79)	18 (75)	12 (86)
2-4	8 (21)	6 (25)	2 (14)
<b>Lymphoma involvement</b>			
Extranodal	27 (69)	15 (63)	12 (80)
Bone marrow	10	4	6
Liver	7	4	3
Digestive tract	4	2	2
Bone	4	2	2
Others	7	5	2
Lymph node only	12 (31)	9 (37)	3 (20)
<b>LDH<sup>d</sup></b>			
Within normal range	18 (49)	9 (39)	9 (64)
Elevated	19 (51)	14 (61)	5 (36)
<b>Monoclonal component<sup>e</sup></b>			
Yes	5 (13)	2 (8)	3 (20)
No	34 (87)	22 (92)	12 (80)

Abbreviations: DLBCL: Diffuse Large B-cell Lymphoma ; LDH : Lactate Deshydrogenase

<sup>a</sup> splenic marginal zone lymphoma (SMZL) (n=3), mucosa associated lymphoid tissue lymphoma (MALT) (3), follicular lymphoma (3), mantle cell lymphoma (2), Burkitt lymphoma (1), low grade not otherwise specified (LGNHL) (3)

<sup>b</sup> missing data (4 for AgHbS, 2 for viral load, one for PS, 2 for LDH)

<sup>c</sup> with positive viral load, positive anti-HBc antibodies and positive anti-HBs antibodies for all these 4 cases

<sup>d</sup> with positive HBs Ag for all these 4 cases

<sup>e</sup> IgG (n = 3), IgM (1), unspecified (1), in patients with DLBCL (2), SMZL (1), MALT (1) and LGNHL (1)

**Table 2. Therapeutic strategies and their hematological responses in patients with B-cell non Hodgkin lymphoma and active HBV infection**

	DLBCL		Others	
	N = 24	CR = 18	N = 15	CR = 11
Hematological treatment				
R-CHOP	22	16	6	5
R-others	2 <sup>a</sup>	2	4 <sup>b</sup>	2
R only	0	0	1	1
Others <sup>c</sup>	0	0	4	3
Antivirals	22	-	13	-
Lamivudine	11	-	5	-
Tenofovir	6	-	2	-
Entecavir	5	-	6	-

CR: Complete remission, HBV: hepatitis B virus

<sup>a</sup>: R-ACVBP in both cases;

<sup>b</sup>: R-chlorambucil, R-bendamustine, R-DHA and autologous stem cell transplantation, R-CVP in one case each

<sup>c</sup>: corticosteroids only, eradication of Helicobacter pylori, wait and watch for two