Efficacy of prophylactic antiviral therapy and outcomes in HBsAg-negative, anti-HBc-positive patients receiving chemotherapy: a real-life experience

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Objective The aim of this study is to evaluate the outcomes of hepatitis B surface antigen (HBsAg)-negative, anti-HBc-positive patients who received immunosuppressive therapies.

Patients and methods We retrospectively evaluated the medical records of HBsAg-negative, anti-HBc-positive patients with hematological diseases or solid tumors who underwent immunosuppressive therapies and were referred because of positive baseline hepatitis B virus (HBV) serology or HBV reactivation. The referral date was according to the judgment of the treating physician at the time of identification of any signs of HBV infection.

Results We included 55 HBsAg-negative, anti-HBc-positive patients. Of these, 31 received antiviral prophylaxis (group 1), whereas 24 patients did not receive any anti-HBV agent (group 2). The majority of patients [49/55 (89%)] had hematological malignancies and most of them 39/55 (71%) received rituximab-containing regimens. Lamivudine was used as antiviral prophylaxis in 13/31 (42%) patients of group 1. One patient in this group experienced HBV reactivation and was treated successfully with tenofovir add-on therapy. All patients in the second group experienced HBV reactivation and most of them [19/24 (79%)] were treated with tenofovir or entecavir as rescue therapy. Two of these patients (one of the tenofovir/entecavir subgroup and one of the lamivudine subgroup) eventually died because of hepatic failure despite rescue treatment.

Conclusion Patients with serological markers of previous HBV infection are still at risk for HBV reactivation. Screening of both anti-HBs and anti-HBc is mandatory before chemotherapy. Pre-emptive antiviral prophylaxis, including lamivudine, is highly effective in all subgroups of such patients, whereas deferring treatment upon HBV reactivation is not enough to rescue all cases.
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Introduction

About 350 million individuals worldwide are chronically infected with the hepatitis B virus (HBV) defined by a positive hepatitis B surface antigen (HBsAg) in the serum [1]. It is well known that all patients with chronic HBV infection are at risk of reactivation if they present concomitant hematological, oncological, gastrointestinal, rheumatological, or dermatological diseases that require immunosuppressant or cytotoxic chemotherapy, especially with anti-CD20 antibodies or high-dose corticosteroids [2,3]. Thus, current guidelines for the management of HBsAg-positive patients strongly recommend routine antiviral prophylaxis before immunosuppressive or chemotherapy [4–6]. However, the management of HBsAg-negative, anti-HBc-positive patients who are scheduled to start immunosuppressive or chemotherapy has not been completely elucidated.

It is widely accepted that loss of HBsAg does not necessarily lead to a complete clearance of the virus as HBV covalently closed circular DNA can persist in the liver and HBV DNA may still be detected in serum and peripheral blood mononuclear cells several decades after an apparent recovery from HBV infection [7,8]. This occult hepatitis B virus infection (OBI) is controlled by the immune system mainly through HBV-specific cytotoxic T cells, but B cells also play an important role through antigen presentation [7–9]. HBV reactivation in OBI patients can occur during or after immunosuppressive therapy by suppression of immune control, but even in untreated patients with hematological malignancies such as lymphoma or chronic lymphocytic leukemia (CLL) because of a 'per-se' immune-compromised state [9–11]. In particular, the use of rituximab, a chimeric mouse human monoclonal antibody against CD20$^+$, and similar agents,

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has been associated with HBV reactivation even in HBsAg-negative, anti-HBc-positive patients [12–14].

The role of prophylactic antiviral therapy in HBsAg-negative, anti-HBc-positive patients has been assessed in some studies, but data and recommendations remain weak [15–17]. Recently, published guidelines from the American Gastroenterological Association recommend antiviral prophylaxis in HBsAg-negative, anti-HBc-positive patients treated with B-cell-depleting agents, tumor necrosis factor-α inhibitors, other cytokine or integrin inhibitors, tyrosine kinase inhibitors, and moderate or high doses of corticosteroids daily for 4 weeks or more, but the grade of evidence is rather weak [18].

In this retrospective study, we aimed to evaluate HBsAg-negative, anti-HBc-positive patients with hematological diseases or solid tumors who received chemotherapy and were referred either because of HBV reactivation or to receive prophylactic antiviral therapy, emphasizing the significance of antiviral prophylaxis or rescue therapy with lamivudine (LAM) or new-generation oral antivirals [entecavir (ETV) or tenofovir (TDF)].

Patients and methods

We retrospectively evaluated the medical records of patients with lymphoma, CLL, other hematological diseases requiring immunosuppression, or solid tumors who underwent conventional chemotherapy, and corticosteroids, or rituximab-based therapies between January 2009 and April 2015 and have been referred by the treating hematologist–oncologist to our Hepatology Unit. The referral date was according to the judgment of the treating physician (hematologist–oncologist) at the time of identification of any signs of HBV infection. Specifically, the reason for referral was either positive baseline HBV serology (anti-HBc-positive, HBsAg-positive, or negative) or HBV reactivation. As there are no clear diagnostic criteria in this population for HBV reactivation, we defined as HBV reactivation the reappearance of HBsAg or HBeAg (reverse seroconversion) and/or elevation of the alanine aminotransferase to more than three times of the upper limit of normal with an associated absolute quantitative determination of HBV DNA greater than or equal to 2×10^4 IU/ml during chemotherapy/immunosuppression or until 12 months after discontinuation.

Of 146 patients with signs of HBV infection who were referred and evaluated in our Hepatology Unit, we excluded those with positive HBsAg at baseline and those with reactivation who had no available baseline HBV serology. Moreover, patients with a history of HBV vaccination, concomitant infection with hepatitis C, D, or HIV, concomitant chronic liver disease because of autoimmune or Wilson's disease, a history of significant alcohol consumption during the last year (>30 g daily), hematopoietic stem-cell transplantation, liver transplantation, and treatment with any antiviral agent other than interferon-α or any type of immunosuppression during the last 12 months were also excluded.

The database that we analyzed included patients' demographic and epidemiological characteristics, medical history data, clinical and laboratory data, and treatment history. The study has been carried out according to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by each hospital ethics committee.

Quantitative determination of HBV DNA was performed using a quantitative real-time PCR kit (COBAS Taqman HBV Test; Roche Diagnostics, Meylan, France).

Statistical analysis

All statistical analyses were carried out using SPSS for Windows 21.0 (SPSS Inc., Chicago, Illinois, USA). Pearson χ^2-analysis was used to compare categorical variables, whereas the Mann–Whitney rank-sum test was used to compare continuous variables. A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Patient population

We included 55 patients with malignancy who had a history of HBsAg-negative, anti-HBc-positive (anti-HBs positive or negative) serology before (or at) diagnosis and before chemotherapy initiation. Among these patients, 16 (29%) have been referred with HBV reactivation during chemotherapy courses. The other 39 patients were referred by the treating physician before starting chemotherapy to decide whether prophylactic antivirals should be started or not according to the hepatologist's judgment. The median follow-up of all referred patients has been 8 months (range 1–36 months).

At inclusion in the study, 31 patients were receiving antiviral prophylaxis (group 1), whereas 24 patients were not receiving any anti-HBV agent (group 2). Their median age was 70 years (range 26–89 years) and most of them were men (36/55 or 65.5%). The majority of the patients (49/55 or 89%) had hematological malignancies (17 patients with CLL and 32 patients with lymphoma), whereas six patients had solid tumors or other hematological diseases requiring immunosuppression. In total, 39/55 (71%) of the patients received rituximab as part of the immunosuppressive regimen. In particular, rituximab was used by 18 of 31 patients (58%) in group 1 and 21 of 24 patients (87.5%) in group 2. Twenty-six patients were anti-HBs negative and 29 were anti-HBs positive. Anti-HBs positivity was detected in 18 of 31 (58%) patients of group 1 and in 11 of 24 (46%) patients of group 2. A high genetic barrier antiviral agent (ETV or TDF) was used by 18 of 31 (58%) patients of group 1 as antiviral prophylaxis and 19 of 24 (79%) patients of group 2 as rescue therapy for HBV reactivation (Table 1).

Group 1

LAM was used as antiviral prophylaxis in 13 of the 31 (42%) patients in this group. Most of these patients [11/13 (84.5%)] were anti-HBs negative and mainly had hematological malignancies [10/13 (77%)]. Only a minority of them [5/13 (38.5%)] were treated with rituximab-based regimens. One (7.7%) of the 13 patients under LAM prophylaxis who had lymphoma and was receiving a rituximab-containing regimen experienced HBV reactivation. He was anti-HBs negative before chemotherapy. He seroconverted to both HBsAg and HBeAg seropositivity, developing serum HBV DNA levels of 18 000 IU/ml at

Table 1. Baseline demographic and clinical characteristics

	Group 1 ($N=31$) [n/N (%)]	Group 2 ($N=24$) [n/N (%)]	All patients ($N=55$) [n/N (%)]
Age [median (range)] (years)	68 (26–85)	74 (54–89)	70 (26–89)
Sex: male	20 (64.5)	16 (67)	36 (65.5)
Anti-HBc(+)/anti-HBs(−)	13/31 (42)	13/24 (54)	26/55 (47)
Anti-HBc(+)/anti-HBs(+)	18/31 (58)	11/24 (46)	29/55 (53)
Underlying disease			
Hematological malignancies	27/31 (87)	22/24 (92)	49/55 (89)
CLL	5/27 (18.5)	12/22 (54.5)	17/49 (35)
Solid tumors or other hematological diseases	4/31 (13)	2/24 (8)	6/55 (11)
R-based	18/31 (58)	21/24 (87.5)	39/55 (71)
ETV/TDF	18/31 (58)	19/24 (79)[a]	37/55 (67)
LAM	13/31 (42)	5/24 (21)[a]	18/55 (33)

CLL, chronic lymphocytic leukemia; ETV, entecavir; HBV, hepatitis B virus; LAM, lamivudine; TDF, tenofovir.
[a]As rescue antiviral treatment for HBV reactivation.

15 months after chemotherapy initiation. He was treated successfully with TDF add-on rescue therapy, resulting in undetectable serum HBV DNA and normalization of liver enzymes.

ETV or TDF was used as antiviral prophylaxis by 18 of 31 (58%) patients in this group. Most of them [16/18 (89%)] were anti-HBs positive and mainly had hematological malignancies [17/18 (94.5%)]. The majority [13/18 (72%)] were treated with rituximab-based regimens. None of these patients experienced HBV reactivation.

Group 2

All 24 patients experienced HBV reactivation, with reversion to HBsAg and HBeAg seropositivity in 15 (62.5%) of them. Approximately half of them (13/24 or 54%) were anti-HBs negative at the onset of chemotherapy and mainly had hematological malignancies [22/24 (92%)]. The majority of these patients [21/24 (87.5%)] received a rituximab-containing regimen. The median HBV DNA level at the time of diagnosis of HBV reactivation was 6.7×10^5 IU/ml (range 38×10^3–4×10^7 IU/l) and the median alanine aminotransferase level was 172 IU/l (range 53–998 IU/l). The median time from the onset of chemotherapy until HBV reactivation was 6.5 months (range 3–24 months).

Nineteen patients (79%) were treated with a high genetic barrier nucleos(t)ide analogue (ETV or TDF) as rescue therapy. One patient died because of hepatic failure despite antiviral treatment. This female patient had CLL and was treated with a rituximab-containing regimen. She was anti-HBs positive before chemotherapy. She developed seroconversion to HBsAg and HBeAg positivity with serum HBV DNA levels of 1.53×10^5 IU/ml at 10 months after chemotherapy initiation. The other 18 patients achieved normalization of liver enzymes with stabilization of liver function without liver-related complications or deaths.

Five patients (21%) were treated with LAM as rescue therapy. One patient died from hepatic failure because of the emergence of a LAM-resistance HBV mutant strain (M204V/L180M) at 4 months after LAM onset despite TDF add-on rescue therapy. This patient had lymphoma and was treated with a rituximab-containing regimen. He was anti-HBs negative before chemotherapy. He developed seroconversion to both HBsAg and HBeAg positivity with HBV DNA levels of 4×10^7 IU/ml at 3 months after chemotherapy initiation. The other four patients achieved normalization of liver enzymes with stabilization of liver function without liver-related complications or deaths (Table 2).

Discussion

Our study reported the real-life experience from a liver clinic in patients with serologic evidence of previous HBV infection and hematological or other malignancies.

It is known that traces of serum HBV DNA are often detectable for many years after clinical recovery from acute hepatitis B despite the presence of anti-HBs, leading to a condition generally known as seropositive OBI [19,20]. It seems that HBV persists in the liver despite the clearance of HBsAg and the development of anti-HBs as the result of a delicate balance between viral replication and an efficient immune control mainly because of HBV-specific T cell response [8,21]. This balance is easily influenced either by changes in host factors or by external agents such as immunomodulatory medications.

In terms of host factors, there is considerable evidence indicating that diseases with a pathophysiology on the basis of lymphocyte dysfunction, such as hematologic malignancies, are strongly implicated in the induction and maintenance of the occult status of HBV infection [20,21]. In this context, lymphoproliferative diseases such as CLL are of high interest. Specifically, in CLL, both cellular and humoral immunity are impaired with qualitative and quantitative defects in B cells, T cells, natural killer cells, neutrophils, and the monocyte/macrophage lineage [22]. These abnormalities may induce a state of a relative 'immunoparalysis' in the anti-HBV immune response but may also contribute actively toward the induction of HBV reactivation [23].

It is well known that immunosuppressive and antineoplasmatic therapies, especially rituximab-based therapies, induce severe and durable B-cell depletion favoring HBV replication [3]. We included 24 HBsAg-negative, anti-HBc-positive patients (13 anti-HBs negative and 11 anti-HBs positive) who did not receive antiviral prophylaxis despite the fact that the vast majority of them received rituximab-based therapies [22/24 (91.5%)]. This finding can be justified by the fact that our cohort has included patients from 2009 when the strategy of prophylactic antiviral therapy in these patients was not well documented even by expert guidelines [24]. In our study, all these patients developed HBV reactivation, whereas

Table 2. Characteristics, clinical course, and outcomes of groups of patients

	Group 1 ($N=31$) [n/N (%)]		
	LAM ($N=13$)	ETV/TDF ($N=18$)	Group 2 ($N=24$) [n/N (%)]
R-based	5/13 (38.5)	13/18 (72)	21/24 (87.5)
Anti-HBc(+)/anti-HBs(−)	11/13 (84.5)	2/18 (11)	13/24 (54)
Anti-HBc(+)/anti-HBs(+)	2/13 (15.5)	16/18 (89)	11/24 (46)
Underlying disease			
Hematological malignancies	10/13 (77)	17/18 (94.5)	22/24 (92)
CLL	2/10 (20)	3/17 (17.5)	12/24 (50)
Solid tumors or other hematological diseases	3/13 (23)	1/18 (5.5)	2/24 (8)
Reactivation	1/13 (8)	0/18 (0)	24/24 (100)
Reactivation HBV DNA [median (range)] (IU/l)	18 000	–	6.7×10^5 (38×10^3–4×10^7)
Reactivation ALT [median (range)] (IU/l)	260 (–)	–	172 (53–998)
HBsAg/HBeAg seroconversion	1/1 (100)	–	15/24 (62.5)
Liver function improvement	13/13 (100)	18/18 (100)	19/24 (79)
ETV/TDF[a]	–	–	19/24 (79)
ETV/TDF failure[a]	–	–	1/19 (5)
LAM[a]	–	–	5/24 (21)
LAM failure[a]	–	–	1/5 (20)
Liver-related deaths	0/13 (0)	0/18 (0)	2/24 (8.5)
Nonliver-related deaths	0/13 (0)	5/18 (28)	3/24 (12.5)

ALT, alanine aminotransferase; CLL, chronic lymphocytic leukemia; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine; TDF, tenofovir.
[a]As a rescue antiviral treatment for HBV reactivation in the patients in group 2.

reverse seroconversion occurred in 15 of 24 (62.5%) patients (12 patients with HBsAg and HBeAg reverse seroconversion and three patients only with HBeAg seroconversion). HBV reactivation rates among HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive treatment vary in the literature, ranging from 3.8 to 27.7% perhaps because of the significant heterogeneity among studies [25–28]. Our cohort included patients treated for their underlying hemato-oncological malignancies. In most cases, a hepatology consultation was scheduled because of HBV serological pattern evaluation and/or aminotransferases elevation up to the levels of acute hepatitis. Thus, the reference of these patients was likely because of HBV reactivation, whereas patients with no reactivation have not been recorded because of non-reference. This selective population from 'real' daily practice is a significant limitation of our study. Therefore, no estimation of HBV reactivation rates can be made. However, in the context of hematological malignancies, especially if B-cell-depleting agents are used (rituximab), consideration of antiviral prophylaxis seems to be emerging even in HBsAg-negative, anti-HBc-positive patients [15–18,29–31]. Thus, our study underlines the importance of the recently published American Gastroenterological Association guidelines, which strongly recommend antiviral prophylaxis even in HBsAg-negative patients [18].

We recorded two fatal cases, both of them among patients who did not receive pre-emptive antiviral prophylaxis and were treated only after the development of HBV exacerbation. One patient died despite ETV/TDF treatment and another died despite initial LAM therapy and TDF add-on rescue therapy upon LAM resistance. LAM is associated with a high rate of drug resistance when used for longer than 1 year, whereas the LAM-resistance rate may be even higher in patients on immunosuppressive treatment [32]. Fatal outcomes have been reported previously because of LAM-resistant mutant strains in naive patients with undetectable HBV DNA treated with rituximab-based regimens [33]. There are a few studies comparing the efficacy of low and high genetic barrier agents in the prophylaxis of HBV reactivation and even fewer in patients with resolved hepatitis [34,35]. In HBsAg-positive patients, prophylaxis of HBV reactivation with a high genetic barrier agent (ETV or TDF) seems to have higher efficacy compared with low genetic barrier agents such as LAM [36,37]. In our study, prophylaxis with LAM was effective in all except one of 13 patients, although five (38.5%) of them received rituximab-based regimens. There was, however, one (7.7%) patient who experienced HBV reactivation despite prophylaxis with LAM, but he responded well to rescue therapy with TDF. Prophylaxis with ETV or TDF was effective in all 18 patients in our study, with 18 (66.5%) of them receiving rituximab-based regimens. Thus, in accordance with previous reports in patients with resolved hepatitis, we confirm the high efficacy of antiviral prophylaxis in HBV reactivation [15,31,38].

Conclusion

Patients with serological markers of previous HBV infection are still at risk for HBV reactivation, especially when they receive chemotherapy including specific monoclonal agents. Therefore, screening of both anti-HBs and anti-HBc before chemotherapy initiation is mandatory. Antiviral prophylaxis with ETV or TDF was highly effective in all subgroups of patients. LAM also seem to offer acceptable efficacy in the prophylaxis of HBV reactivation in HBsAg-negative, anti-HBc-positive patients under immunosuppression/chemotherapy and may play an important role especially because of its low cost and wide global availability. Prophylaxis with any agent is preferable to deferred anti-HBV therapy upon HBV reactivation, even if a high genetic barrier agent is used for the treatment of reactivation.

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Conflicts of interest

There are no conflicts of interest.

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