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Hepatitis B Virus Reactivation in Patients with Previously Resolved Hepatitis B Treated with Rituximab-Containing Chemotherapy for B-Cell Lymphoma

ORIGINAL INVESTIGATION

Erol Çakmak

ABSTRACT

Objective: This study aimed to determine the frequency of HBV reactivation and the potential predictive factors in resolved hepatitis B virus (HBV) patients [hepatitis B surface antigen (HBsAg)-negative and antibody to hepatitis B core antigen (anti-HBc)-positive patients] who received rituximab-containing chemotherapy for B-cell lymphoma.

Materials and Methods: A retrospective examination was performed for HBV-related markers in 106 patients before and after receiving rituximab-containing chemotherapy for CD20-positive B-cell lymphoma.

Results: Of the 106 patients with CD20-positive B-cell lymphoma who received rituximab-containing chemotherapy, 98 were HBsAg negative and 8 were HBsAg positive; among the 98 patients, 64 (65.7%) were anti-HBc negative and 34 (34.7%) were anti-HBc positive. Of the 34 CD20-positive B-cell lymphoma patients with resolved HBV infection who received rituximab-containing chemotherapy, 26 (76.5%) were anti-HBsAg antibody (anti-HBs) positive and 8 (23.5%) were anti-HBs negative. Of these 8 anti-HBs-negative patients, HBV reactivation occurred in 4 (50%) patients; no HBV reactivation was observed in any of the 26 anti-HBs-positive patients. Compared with the anti-HBs-positive patients, the rate of HBV reactivation in B-cell lymphoma patients who were anti-HBs negative and had resolved HBV infection revealed a highly significant relationship ($p<0.001$).

Conclusion: HBV reactivation occurred in 50% of the CD20-positive B-cell lymphoma anti-HBs-negative patients with resolved HBV infection who had received rituximab-containing chemotherapy and in none of the anti-HBs-positive patients. This indicates that anti-HBs negativity in the patients with resolved HBV infection is an important risk factor, and the antiviral prophylaxis should certainly be administered to such patients.

Keywords: Hepatitis B virus, HBV reactivation, rituximab, B-cell lymphoma

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Department of Gastroenterology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

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Correspondence Erol Çakmak Department of Gastroenterology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey Phone: +90 346 444 44 58 e.mail: drecakmak@hotmail.com

INTRODUCTION

Hepatitis B virus (HBV) is the most common viral agent worldwide that affects the liver. It is estimated that 350–400 million people globally suffer from chronic HBV infection (1). The incidence of chronic HBV infection varies between 0.2% and 20%, with differences observed according to the geographical region; however, presumably, 1 in every 3 persons of the global population is exposed to HBV (1, 2). In Turkey, the prevalence of chronic HBV infection ranges from 2% to 8%, and it is classified as an intermediate endemic country (3, 4). Epidemiological studies in Turkey have reported the rate of HBV exposure to be 30.6%, which is similar to that of the general global population (4). Therefore, the majority of people are unaware that they have been exposed to or are suffering from HBV infection. The majority of these individuals is not medically followed-up or treated for HBV infection.

When immunosuppressive treatment or cancer chemotherapy is administered to the patients exposed to HBV infection, the reactivation of HBV is frequently increase dramatically (5). The emergence of HBV reactivation in these patients causes a delay or early termination of the immunosuppressive or chemotherapy treatment being applied. Furthermore, HBV reactivation can render the course of the existing disease dangerous, and different clinical manifestations may be seen varying from elevated asymptomatic aminotransferase to life-threatening fulminant hepatic failure (6). In patients with non-Hodgkin's lymphoma, hepatitis B surface antigen (HBsAg) positivity and exposure to HBV infection are more widespread than in the general population; therefore, HBV reactivation is seen more often in these patients (7, 8). In this study, as a result of the use of chemotherapy in HBsAg-positive cancer patients, the incidence of HBV reactivation varies between 26% and 53% (5, 9). The HBV reactivation rate has been reported to be 24.4%–85% in patients with HBsAg-positive lymphoma and 4.1%–41.5% in lymphoma patients with resolved HBV infection [HBsAg negative/hepatitis B core antigen (anti-HBc) positive] (10, 11). In

recent years, with the use of treatments containing rituximab in B-cell lymphoma patients with HsAg positivity and resolved HBV infection, a serious increase in the rate of HBV reactivation has been observed (12).

Rituximab is a chimeric monoclonal antibody against CD20, which is particularly expressed on the surface of B lymphocytes. Rituximab is widely used as a CD20 marker in the treatment of hematological cancers and B lymphocytes (13). Rituximab along with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is a proven standard chemotherapy treatment, which regulates the clinical course and reduces the relapse rate in patients with CD20-positive B-cell lymphoma (14). In HBV infection, B and T lymphocytes play a significant role in viral clearance and inflammation (15). In particular, B-cells produce neutralizing antibodies, prevent viral spread, and eliminate viruses that are present in circulation. When rituximab is administered, the suppression effects of both B and T lymphocytes on HBV are hindered and the HBV infection is reactivated (16).

A previous study reported that while the HBV reactivation rate in patients with resolved HBV infection was 0% in those who received cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) treatment, it was 24% in patients administered R-CHOP treatment (17). Another study related to HBV reactivation has reported HBV reactivation rates of 40%–80% in HBsAg-positive patients who received rituximab-containing chemotherapy and 1.5%–27% in patients with resolved HBV infection (18). There is a need to define the HBV reactivation risk during and following rituximab treatment in the epidemiological studies of the Turkish population, which has a high rate of resolved HBV infection.

This retrospective study aimed to identify the frequency of HBV reactivation and the predictive factors in patients with resolved HBV infection who were treated with a chemotherapy regime containing rituximab for B-cell lymphoma.

MATERIALS and METHODS

A retrospective analysis was performed on 106 patients who were diagnosed with CD20-positive B-cell non-Hodgkin's lymphoma according to the World Health Organization classification for pathological diagnosis, between January 2010 and April 2017; these patients were administered rituximab-containing chemotherapy, and they completed the follow-up (19). The study was approved by the Ethics Committee of Cumhuriyet University. Of these patients, 8 were HBsAg positive. A total of 98 patients who received rituximab-containing chemotherapy and who were HBsAg negative before the chemotherapy were included in the study. Of these 98 patients, 64 were hepatitis B core antigen (anti-HBc) negative and 34 were anti-HBc positive. Of the 34 patients with resolved HBV infection, 26 were anti-HBsAg antibody (anti-HBs) positive and 8 were anti-HBs negative.

The demographic characteristics; the pretreatment Eastern Cooperative Oncology Group (ECOG) score; Ann Arbor staging; histology; number of rituximab cycles; serum anti-HBc, anti-HBs, and HBV DNA levels; and serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), lactate dehydrogenase (LDH), and albumin levels and changes were recorded for each of the 98 HBsAg-negative patients. Patients were excluded if they had hepatitis A, hepatitis C, hepatitis D, human immunodeficiency virus infection, autoimmune hepatitis, or secondary malignancy. HBV DNA was tested using a polymerase chain reaction assay (COBAS AmpliPrep/COBAS TaqMan system; Roche Molecular Systems Inc., Branchburg, New Jersey, United States). The lower limit for HBV DNA was determined as 20 IU/mL.

Definitions of Hepatitis and HBV reactivation

In the absence of the clinical and laboratory features of acute hepatitis A or hepatitis C infection or other systemic infections, hepatitis was defined as serum ALT level thrice the upper limit of normal (ULN, 40 IU/L at our hospital) or an increase of >100 IU/L in the absolute ALT level. Hepatitis was attributed to HBV reactivation when there was an evidence of HBsAg seroversion (the reappearance HBsAg) or was defined as a 10-fold increase in HBV DNA levels compared with the baseline levels or an absolute increase in the HBV DNA levels $>10^5$ copies/mL (20, 21).

Statistical analysis

All statistical analyses were performed using Statistical Packages for the Social Sciences (SPSS) version 22.0 software (IBM Corp.; Armonk, NY, USA). Kolmogorov–Smirnov independent samples t-test was used when the parametric test assumptions were met, and Mann–Whitney U-test was used when they were not met. For comparing the data obtained, X^2 and Fisher's exact tests were applied to 2×2 sequences, and only X^2 test was applied to multiple sequences. In all analyses, a value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study included 106 patients with CD20-positive B-cell lymphoma who received rituximab-containing chemotherapy (Figure 1). Of these patients, 98 were HBsAg negative and 8 were HBsAg positive. Of the 98 HBsAg-negative patients, 64 (65.3%) were anti-HBc negative and 34 (34.7%) were anti-HBc positive. Of the 34 patients with resolved HBV infection, 26 (76.5%) were anti-HBs positive and 8 (23.5%) were anti-HBs negative. In the patients with CD20-positive B-cell lymphoma who received rituximab-containing chemotherapy, the resolved HBV infection was observed in 34% patients and HBV reactivation in 4.1%.

The basic characteristics of the 98 HBsAg-negative patients with CD20-positive B-cell lymphoma who received rituximab-containing chemotherapy are summarized in Table 1. While no HBV reactivation occurred in 94 (95.9%) patients, HBV reactivation was determined in 4 (4.1%) patients. No significant effect of age, gender, ECOG status, Ann Arbor stage, the presence of B symptoms, or an increase in serum LDH levels on HBV reactivation was observed.

The histological subtypes of the patients with CD20-positive B-cell lymphoma are summarized in Table 2. When examined for HBV reactivation, the most common subtype observed was diffuse large B-cell lymphoma in 69 (70.4%) patients. Of the 4 patients with HBV reactivation, 3 (75%) exhibited this subtype and 1 (25%) exhibited marginal zone B-cell lymphoma.

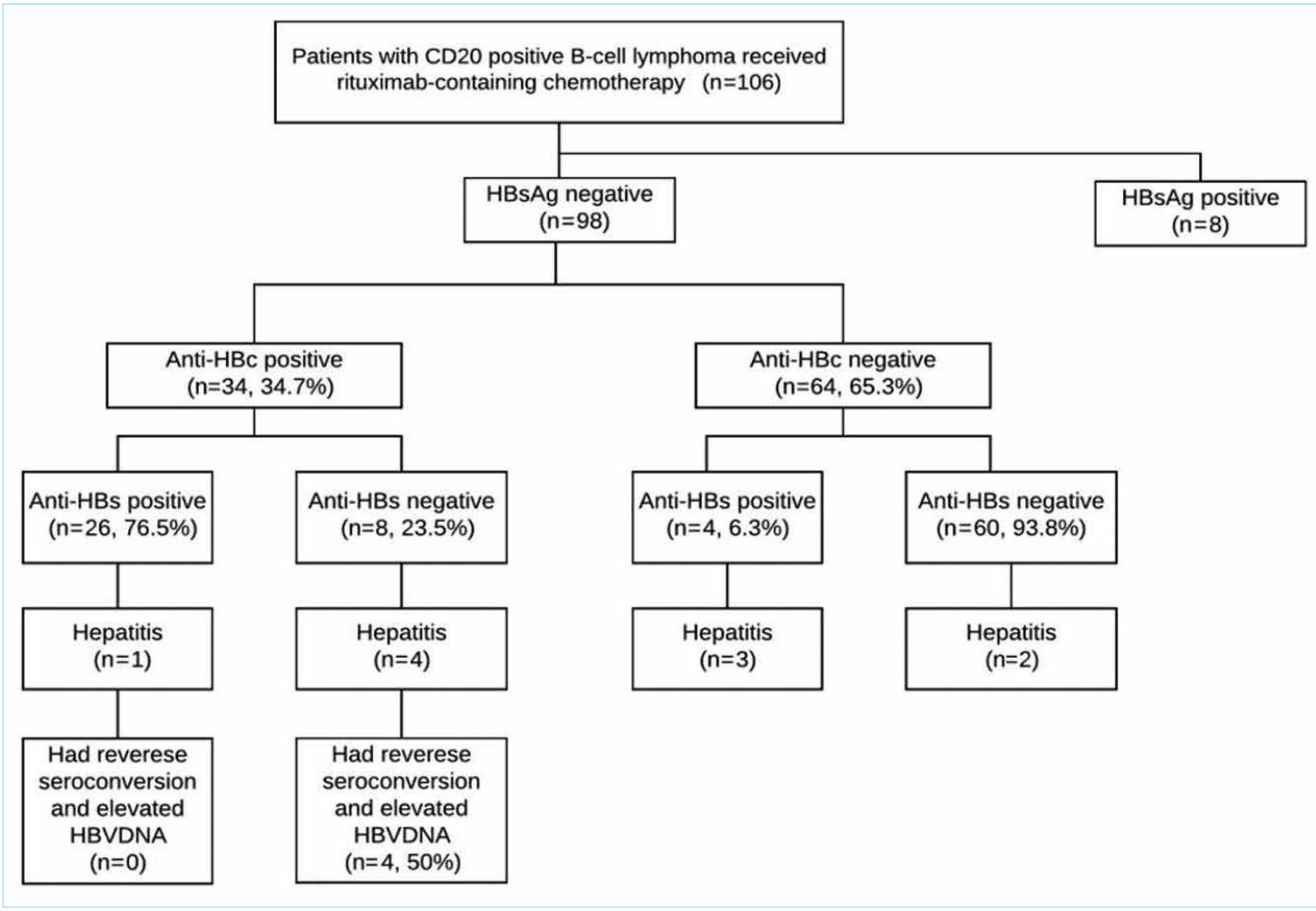

Figure 1. The hepatitis B virus status and the course of hepatitis in 106 patients receiving rituximab-containing chemotherapy for CD20-positive B-cell lymphoma

When the 34 patients with CD20-positive B-cell lymphoma and resolved HBV infection were evaluated, 26 (76.4%) were found to be anti-HBs positive and 8 (23.6%) were anti-HBs negative. HBV reactivation developed in 4 (11.7%) of the 34 patients with CD20-positive B-cell lymphoma and resolved HBV infection. No statistically significant difference was observed regarding the age, gender, ECOG status, Ann Arbor stage, presence of B symptoms, serum ALT, serum TB, and increased serum LDH in the patients with CD20-positive B-cell lymphoma and resolved HBV infection ($p>0.05$). HBV reactivation developed in 4 (50%) of the 8 anti-HBs-negative patients with resolved HBV infection and in none of the 26 anti-HBs-positive patients. The rate of HBV reactivation was determined to be considerably higher in the anti-HBs-negative patients with resolved HBV infection than in the anti-HBs-positive patients ($p<0.001$; Table 3).

The details of the 4 CD20-positive B-cell lymphoma patients with HBV reactivation are summarized in Table 4. All of these patients were male and anti-HBs negative with advanced Ann Arbor stage. Baseline HBV DNA was not observed in any patient. The baseline ALT levels of all the patients were normal. The likelihood of HBV reactivation emergence was higher after mean 6 R-CHOP cycles (range, 4–8 cycles) at a median of 50 days (range, 10–251 days). After determining the serum HBV DNA in the patients, antiviral treatment was immediately commenced. All the patients were treated with entecavir (0.5 mg/day), and no problems were encountered. Liver function improved with the treatment in all the patients, and serum HBV DNA could not be determined. Mortality associated with HBV reactivation was not observed in any patient.

DISCUSSION

The results of this study indicated resolved HBV infection in 34% and HBV reactivation in 4.1% of the patients with CD20-positive B-cell lymphoma who received rituximab-containing chemotherapy. HBsAg positivity and resolved HBV infection were found to be higher in patients with B-cell lymphoma than in the general population. In the general population of Turkey, which has an intermediate endemic profile regarding HBV infection, HBsAg positivity has been reported to be 4% and resolved HBV infection has been reported to be 30.6% (3). In previous studies, the prevalence of B-cell non-Hodgkin's lymphoma was reported to be 8.5% in the HBsAg-positive patients and 2.8% in the control group (22, 23). The rate of resolved HBV infection in B-cell lymphoma patients was observed to be 30.1%-33.3%. Studies have also reported the rate of HBV reactivation in B-cell lymphoma patients to be 3.6%-8.3% (24, 25). In the present study, the rate of resolved HBV infection was determined to be 34% and that of HBV reactiva-

Table 1. Baseline characteristics of CD20-positive B-cell lymphoma patients receiving R-CHOP containing chemotherapy

Characteristics	All Patients (n=98)	HBV Reactivation (n=4)	HBV No Reactivation (n=94)	p
Sex				
Male	59	4	55	
Female	39	0	39	0.097
Age				
Mean	58	65	58	
Range	18-83	59-71	18-83	0.348
ECOG				
0/1	84	4	80	
2	14	0	14	0.261
Ann Arbor stage				
I-II	39	1	38	
III-IV	59	3	56	0.660
B symptoms				
Presence	45	3	42	
Absence	53	1	52	0.233
Serum LDH				
Normal	46	2	45	
Increased	51	2	49	0.934
ALT, U/L				
Median	24	30	17	0.102
Range	5-35	10–39	5–35	
AST, U/L				
Median	28	33	24	0.069
Range	12-74	22-50	12–74	
Bilirubin, mg/dL				
Median	0.7	0.6	0.7	0.851
Range	0.2-1	0.4-0.8	0.2–1	
Anti-HBs				
Positive	30	0	30	0.175
Negative	68	4	64	
Anti-HBe				
Positive	32	3	29	0.065
Negative	66	1	65	

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; HBV: hepatitis B virus; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase
Significant difference with p value<0.05

tion was determined to be 4.1% in patients with B-cell lymphoma, which was similar to the findings of the previous studies and higher than the rates in the general population.

Table 2. The histological subtypes in CD20-positive B-cell lymphoma patients with hepatitis B virus reactivation

Histological subtype	HBV reactivation Total no. of patients (%)	HBV reactivation (per histological subtype %)
Total	98 (100%)	4 (4.1%)
Diffuse Large B-cell lymphoma)	69 (70.4%)	3 (75%
Mantle cell lymphoma	9 (9.2%)	0
Follicular lymphoma	8 (8.2%)	0
Marginal zone B-cell lymphoma)	7 (7.1%)	1 (25%
Burkitt lymphoma	3 (3.1%)	0
Lymphoplasmacytic lymphoma	2 (2%)	0

HBV: hepatitis B virus

Table 3. HBV reactivation rate in patients with resolved HBV undergoing R-CHOP containing therapy

		HBV reactivation		
		Yes	No	p
Patients with resolved HBV undergoing rituximab-containing therapy (n=34)	Anti-HBs positive	0	26	0.001
	negative	4	4	

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; HBV: hepatitis B virus; Anti-HBs: hepatitis B surface antibody. Significant difference with p value<0.05

The use of rituximab in the treatment of B-cell lymphoma is known to cause an increase in the risk of opportunistic viral or fungal infection. Through B and T cells, rituximab eliminates various humoral and cellular immunosuppressive effects. In association with this, there is an increase in the serious viral infections such as those caused by HBV, herpes simplex virus, cytomegalovirus, and parvo virus (26). It is known that in individuals exposed to HBV infection, HBsAg becomes negative but anti-HBc and/or anti-HBs remain seropositive. Years later, even if these individuals are anti-HBs positive, the virus persists in the liver. In patients with resolved HBV infection, as there is a remaining HBV covalently closed circular deoxyribonucleic acid in the hepatocytes, which provides a permanent template for HBV replication, HBV reactivation occurs during or after immunosuppressive treatment (27).

As the cellular and humoral suppression of B and T cells is eliminated particularly during or after a chemotherapy treatment that contains rituximab, HBV rapidly replicates and infects hepatocytes. When there is HBV reactivation, clinical signs and symptoms manifest, ranging from asymptomatic to fulminant hepatitis with a fatal course. Moreover, it is extremely difficult to predict the course of the disease on an individual level in HBV reactivation (28). Therefore, in all individuals who receive immunosuppressive treatment exposure to HBV must be questioned and the necessary screening tests must be applied. Specifically in regions with

Table 4. The details and disease course of the 4 CD20-positive B-cell lymphoma patients with resolved HBV and HBV reactivation

Baseline					At Diagnosis of HBV Reactivation								
Patient No.	Age (Years)	Sex	Ann Arbor stage	Anti-HBs	HBV DNA (copies/μL)	ALT (U/L)	No. of Cycles of R-CHOP received Before Reactivation	No. Of Days Between Last R-CHOP and Reactivation	HBV DNA (IU/mL)	Peak ALT (U/L)	Peak Total Bilirubin (mg/dL)	Treatment With antiviral therapy	Outcome
1	63	M	IV	Negative	Not detected	25	6	75	2.22x108	329	2.62	Entecavir	Died of Lymphoma
2	70	M	IV	Negative	Not detected	27	6	251	2.40x106	1134	13.71	Entecavir	Alive and well
3	72	M	IV	Negative	Not detected	18	4	10	1.70x108	179	3.83	Entecavir	Died of Sepsis
4	60	M	III	Negative	Not detected	10	8	26	3.02x105	1862	6.24	Entecavir	Alive and well

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; HBV: hepatitis B virus; M: male; Anti-HBs: hepatitis B surface antibody; ALT: alanine transaminase

endemic HBV infection exposure, HBV reactivation is a source of significant concern with respect to morbidity and mortality in the lymphoma patients receiving rituximab-containing chemotherapy.

In previous studies, HBV reactivation has been found to be much higher in the HBsAg-positive and resolved HBV infection patients receiving rituximab-containing chemotherapy than in the lymphoma patients treated with rituximab-free chemotherapy (17, 29). Furthermore, the rates of HBV reactivation have revealed differences between HBsAg-positive and resolved HBV infection patients receiving rituximab-containing chemotherapy. HBsAg-positive patients are at the highest risk with respect to HBV reactivation. Considerably higher rates of 59%–80% HBV reactivation are associated with rituximab-containing chemotherapy in HBsAg-positive patients (30, 31). In lymphoma patients with resolved HBV infection who receive rituximab-containing chemotherapy treatment, the HBV reactivation risk has been reported to be lower than that in HBsAg-positive patients at 2.3%–28.9% (32-34).

Consistent with the findings of other studies, HBV reactivation developed in the present study in 4 of 34 (11.7%) patients with B-cell lymphoma and resolved HBV infection who received rituximab-containing chemotherapy. Lymphoma patients with resolved HBV infection may be overlooked considering the antiviral prophylaxis before starting rituximab-containing chemotherapy. Consequently, severe morbidity and even mortality may occur in association with HBV reactivation.

In the present study, no statistically significant difference was determined in the age, gender, ECOG status, Ann Arbor stage, presence of B symptoms, serum ALT, serum TB, and serum LDH with respect to HBV reactivation in patients with B-cell lymphoma and resolved HBV infection who received rituximab-containing chemotherapy; however, the HBV reactivation rate was 50% in B-cell lymphoma patients who were anti-HBs negative and 0% in those who were anti-HBs positive, and the difference was determined to be statistically significant ($p<0.001$). Similarly, previous studies have found the HBV reactivation rate to be higher in anti-Hbs-negative lymphoma patients with resolved HBV infection who received rituximab-containing chemotherapy (33-35). In anti-HBs-negative patients with resolved HBV who receive rituximab-containing chemotherapy for B-cell lymphoma, the HBV reactivation rate has been found to be significantly increased.

In an extensive meta-analysis of lymphoma patients with resolved HBV infection who received rituximab-containing chemotherapy, the reactivation risk was 24% in anti-HBs-negative patients and 5.6% in anti-HBs-positive patients (34). In another study of lymphoma patients with resolved HBV infection who received rituximab-containing chemotherapy, the 2-year cumulative reactivation risk was 68.3% in anti-HBs-negative patients and 34% in those who were anti-Hbs positive (25). In the present study, the HBV reactivation risk was determined to be 50% in anti-HBs-negative patients and 0% in those who were anti-HBs positive. Thus, in the present study, the HBV reactivation risk was much higher in anti-HBs-negative patients.

These differences between studies can be attributed to lymphoma subtypes, non-homogenous groups, and geographical differences. After stratification of the reactivation risk with these results, anti-HBs test must be added for patients who are going to receive immunosuppression treatment, and in cases of anti-Hbs-negative B-cell lymphoma with resolved HBV, antiviral prophylaxis must be

administered as there is an increased risk of HBV reactivation. In some studies of patients receiving rituximab treatment, it has been reported that although the rates of HBV reactivation are lower in anti-HBs-positive patients than in anti-HBs-negative patients, there is still a risk of HBV reactivation and the benefits of antiviral prophylaxis who are going to receive rituximab treatment (36). However, there is no consensus as yet on the subject of antiviral prophylaxis for patients with resolved HBV infection who are going to receive immunosuppressive treatment. Some guidelines recommend antiviral prophylaxis for patients with resolved HBV infection who are going to receive rituximab treatment regardless of the anti-HBs status. In contrast, some experts have recommended that if HBV DNA is negative in patients with anti-HBs positivity and resolved HBV infection before receiving rituximab treatment, there should be regular monthly serum HBV DNA follow-up (36-38).

It was concluded from the present study that as HBV reactivation developed in 50% of the anti-HBs-negative patients with resolved HBV infection who received rituximab treatment, antiviral prophylaxis should be administered to anti-HBs-negative patients without testing the serum HBV DNA. Furthermore, as HBV reactivation did not develop in any of the anti-HBs-positive patients with resolved HBV infection who received rituximab treatment, monthly follow-up can be recommended for HBV DNA-negative patients with anti-HBs positivity, and antiviral prophylaxis should be given when necessary. It is known that HBsAg and anti-HBc screening must be applied before chemotherapy and immunosuppressive treatment (38, 39); however, as seen in the present study, as HBv reactivation developed at a considerably higher rate in anti-HBs-negative patients, anti-HBs screening should also be applied together with HBsAg, anti-HBc, and HBV DNA testing.

In studies reporting lamivudine as the first oral antiviral agent for treatment of HBV reactivation, a reduction of 79% or more has been observed in the risk of HBV reactivation and HBV-related hepatitis. Although lamivudine is economic, safe, and well tolerated, tyrosine-methionine-aspartate-aspartate (YMDD) mutation can occur with its long-term use (>6 months) (40, 41). In a randomized clinical study, the HBV reactivation rate was 6.6% with entecavir and 30% with lamivudine in HBsAg-positive patients receiving rituximab-containing chemotherapy for diffuse large B-cell lymphoma. Furthermore, the incidences of HBV-related hepatitis, chemotherapy disruption, and treatment-related adverse events were lower in the entecavir group (42). Therefore, in chronic HBV infection, rather than lamivudine, drugs with high genetic barriers to resistance such as entecavir or tenofovir, should be selected. When long-term antiviral prophylaxis is necessary against HBV reactivation, entecavir or tenofovir should be preferred (39).

There is no consensus as to how long the antiviral prophylaxis should be continued after the termination of immunosuppressive treatment. Some researchers have recommended continuing for 6 months after chemotherapy (38-40); however, in a study of lymphoma patients receiving rituximab-containing chemotherapy, it was reported that hepatitis B flare-ups and severe hepatitis developed because of HBV reactivation in periods longer than 6 months after terminating chemotherapy (43, 44). Therefore, most researchers have recommended that antiviral prophylaxis should be continued for at least 12 months after terminating the use of B-cell-depleting agents such as rituximab (45). In the present study, entecavir was used in all the patients with HBV reactivation. The patients tolerated entecavir well, and no viral resistance or side-effects were encountered. Furthermore, when the patients in the present study with HBV reactivation were examined, it was seen that in 1 patient, the HBV reactivation developed 251 days after the final dose of rituximab-containing chemotherapy; therefore, antiviral prophylaxis should be continued for at least 12 months after completing chemotherapy.

There were some limitations to this study, i.e., only Turkish patients were included, and the sample size was small.

CONCLUSION

In summary, in patients with resolved HBV infection receiving rituximab-containing chemotherapy for B-cell lymphoma, anti-HBs negativity is an extremely significant risk factor for HBV reactivation. This factor in B-cell lymphoma patients, especially before rituximab treatment, indicates that anti-HBs status should be added to the screening protocol and antiviral prophylaxis must be administered to anti-HBs-negative patients. In future, there is a need for more extensive studies to evaluate the HBV reactivation risk in anti-HBs-negative lymphoma patients and to investigate the effect of serum anti-HBs titers and HBV vaccination on reactivation risk.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cumhuriyet University Faculty of Medicine.

Informed Consent: Informed consent is not necessary due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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