Evaluation of hepatitis B markers and reactivation of hepatitis B infection in non-hodgkin lymphoma patients treated with rituximab: A single-center study

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Purpose: To assess the frequency of hepatitis B infection reactivation and to evaluate the alterations in hepatitis B virus (HBV) infection markers in non-Hodgkin lymphoma (NHL) patients treated with rituximab-based chemotherapy (R-CT).

Methods: Retrospective analysis was performed using data derived from the medical records of 180 NHL patients (89 women, 91 men) who received R-CT in the hematology department of a tertiary care. The baseline descriptives, clinical data, and laboratory data, including NHL subtypes, chemotherapy cycles and regimens, HBV infection markers, HBV reactivation indicators, antiviral prophylaxis, and prognostic outcomes were noted.

Results: The average age was of 180 61.19 ±14.02 (range: 21-94) and the most common diagnoses were diffuse large B-cell lymphoma (n=108, 60%), marginal zone lymphoma (n=25, 13.9%), chronic lymphocytic lymphoma (n=18, 10%), lymphoplasmocytic lymphoma (n=4, 2.2%), and mantle cell lymphoma (n=4, 2.2%), respectively. Positivity rates for HBsAg, anti-HBs, and anti-HBc IgG were 8 (4.4%), 59 (32.8%), and 53 (29.4%), respectively. Isolated positivity for HBc IgG was detected in 14 (7.8%) patients. Antiviral prophylaxis was administered in 30 cases (16.7%) and entecavir (n=21), lamivudin (n=8) and tenofovir (n=1) were given. In case of viral reactivation (n=4, 2.2%), entecavir treatment was successful and no mortality associated with fulminant hepatitis or hepatic failure were reported.

Conclusion: We conclude that NHL patients receiving R-CT must be closely monitored for reactivation of HBV infection. Antiviral prophylaxis must be initiated without delay in selected cases and careful follow-up of these patients is crucial to minimize morbidity and mortality.

Key Words: *Hepatitis B; Reactivation; Non-hodgkin lymphoma; Rituximab; Prophylaxis*

INTRODUCTION

Hepatitis B virus (HBV) infection still constitutes a severe health problem and a moderate endemic disease in some areas of the world. A remarkable percentage proportion of hepatitis B surface antigen (HBsAg) negative/anti-hepatitis B core antigen (anti-HBc) positive patients with non-Hodgkin lymphoma (NHL) that undergo rituximab-based chemotherapy (R-CT) may suffer hepatitis B virus (HBV) reactivation [1].

In Turkey, the estimated overall population prevalence is 4-5% and there are large age-group and regional differences in chronic HBV infection [2]. Hepatitis B infection may preserve its presence in the nuclei of hepatocytes even after serological recovery. Patients with a history of HBV infection are vulnerable to reactivation of HBV infection during or after immunosuppressive treatment. Therefore, identification of these patients and follow-up of viral infection markers are crucial for starting antiviral prophylaxis to avoid further morbidity and mortality [3].

Since the clinical presentation of HBV reactivation may vary from asymptomatic HBV DNA flares to fulminant or chronic hepatitis, HBV reactivation brings about serious risks in patient care and survival while causing interruption or cessation of chemotherapy [1]. Up to now, no standard care guidelines have been established for NHL patients with resolved HBV infection who received treatment with R-CT [4,5]. The possibility of HBV due to the use of R-CT has increased due to the use of this B-cell-targeting monoclonal antibody since it can decrease the titer of HBsAb and cause the failure of presentation of HBsAg to the cytotoxic T cells [6,7].

We aimed to determine the profiles of HBV infection markers in NHL patients receiving R-CT and to investigate the reactivation of HBV infection during and after R-CT. Furthermore, we assessed the efficacy of antiviral prophylaxis on HBV reactivation in these patients.

PATIENTS AND METHODS

Study design

This retrospective study was performed in the hematology department of a tertiary care center. Data were extracted from the medical files of 180 NHL patients (89 women, 91 men) who underwent R-CT. The patients were diagnosed and treated between January 2013 and December 2019. The indicators of HBV infection such as HBsAg, anti-HBc IgG and anti-HBs were obtained from the hospital database. The incidence of HBV reactivation and the effectivity of antiviral prophylaxis in this series were evaluated.

All of the clinical and laboratory examinations were performed in our hospital. The inclusion criteria for this retrospective study were pathological diagnosis of NHL including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), Burkitt ' s lymphoma, MALToma, splenic marginal zone lymphoma (SMZL); receipt of at least one cycle of R-CT including rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP). Patients who fulfilled these criteria were included in this retrospective analysis.

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Outcome measures

Baseline descriptives (age, sex), the subtype of NHL, tumor stage, chemotherapy regimen, no. of chemotherapy cycles, rate of remission, positivities for isolated anti-HBc IgG, HBsAg, anti-HBs, anti-HBc IgG, HBeAg, anti-HBe, HBV DNA, anti-HCV, anti-HIV, HDV antigen, anti-HDV, levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), administration and durations of antiviral prophylaxis, increase in levels of AST and ALT, seroconversion, HBV DNA reactivation, treatment for HBV DNA reactivation, the success rate of antiviral prophylaxis and HBV infection-related mortality rate were noted in this series.

The HBV reactivation rate was defined as serum HBV DNA appearance with or without the reappearance of serum HBsAg (HBsAg serore version). Chronic HBV infection was defined as the persistence of serum HBsAg for at least 6 months [1].

The definition of HBV reactivation was defined as the elevation of serum HBV DNA level>1 log IU/mL from baseline in HBsAg-positive patients. If HBsAg-positive patients showed an increase in alanine transaminase (ALT, P3 times the baseline value or an absolute value of P100 U/L) and/or required active treatment for hepatitis including hospitalization, they were defined as HBV reactivation unless other causes for hepatitis such as toxic hepatitis were found. In case of HBsAg-negative/HBcAb-positive patients, the positive conversion of HBsAg with or without any increase of ALT was defined as HBV reactivation [8].

The laboratory data representing HBV status before the R-CT were gathered including serologic profiles of HBV and the level of HBV DNA. The type and duration of antiviral prophylaxis were analyzed to seek its relationship with the reactivation of HBV. The type of antiviral prophylaxis was determined according to physicians' decisions.

Statistical analysis

Our data were analyzed with Statistical Package for Social Sciences version 21.0 for Windows software (SPSS Inc., Chicago, Illinois, USA). Descriptive data were presented as counts and percentages.

RESULTS

Our patient population consisted of 180 patients (89 women, 91 men) with an average age of 61.19 ± 14.02 (range: 21-94) years. An overview of diagnoses are presented in Table 1 and the most common types were DLBCL (n=108, 60%), MZL (n=25, 13.9%), CLL (n=18, 10%), and FL (n=15, 8.3%).

TABLE 1
A survey of diagnoses in our series.

Diagnosis	n (%)
Diffuse large B-cell lymphoma	108(60)
Marginal zone lymphoma	25(13.9)
Chronic lymphocytic leukemia	18(10)
Follicular lymphoma	15(8.3)
Mantle cell lymphoma	4(2.2)
Lymphoplasmocytic lymphoma	4(2.2)
Castleman disease	3(1.7)
Burkitt's lymphoma	1(0.6)
MALToma	1(0.6)
Splenic marginal zone lymphoma	1(0.6)
Total	180(100)

Abbreviation: MALToma: Mucosa Associated Lymhoid Tissue Associated Lymphoma.

The tumor stages were 1 (n=8, 4.4%), 2 (n=34, 18.9%), 3 (n=51, 28.3%), and 4 (n=87, 48.3%). The average number of CT cycles were 6.26 ± 2.10 (range: 1 to 18). The chemotherapy protocols are presented in Table 2.

TABLE 2
Chemotherapy protocols administered in our non-Hodgkin's lymphoma population.

Chemotherapy protocol	n (%)
R-CHOP+R- ESHAP+R-BENDAMUSTINE+IBRUTINIB	1 (0.6)
FC+R-BENDAMUSTINE	1 (0.6)
R	9 (5.0)
R-BENDAMUSTINE	13 (7.2)
R-BENDAMUSTINE+ESHAP	1 (0.6)
R-CHOP	118 (65.6)
R-CHOP, R-B	1 (0.6)
R-CHOP+8R	2 (1.1)
R-CHOP+R-BENDAMUSTINE	2 (1.1)
R-CHOP+R-BENDAMUSTINE+LEN/DEX+GDP+IBRUTINIB	1 (0.6)
R-CHOP+R-DHAP	1 (0.6)
R-CODOX-M/IVAC	1 (0.6)
R-CVP	21 (11.7)
R-CVP+R-BENDAMUSTINE	1 (0.6)
R-FC	5 (2.8)
R-CHLORAMBUCIL	2 (1.1)
Total	180

Abbreviations: R-CHOP: R: Rituximab; C: Cyclophosphamide, H: Doxorubicin hydrochloride, O: Vincristine sulfate, P: Prednisone; ESHAP: E: Etoposide, S: Solu-medrone, HA: high-dose cytarabine, P: Cisplatin; FC: F: Fludarabine, C: Cyclophosphamide; R: Rituximab; B: Bortezomib; Len/Dex: lenalidomide, Dexamethasone; R-DHAP: DH: Dexamethasone, A: Cytarabine; CODOX-M/IVAC: Cyclophosphamide, Vincristine, Doxorubicin, and High-Dose Methotrexate, Alternating with Ifosfamide, Etoposide, and Cytarabine; GDP: G: Gemcitabine, CVP: C: Cyclophosphamide, V: Vincristine, P: Prednisolone.

The most common CT regimen were R-CHOP (n=118, 65.6%), R-CVP (n=21, 11.7%), R-Bendamustine (n=13, 7.2%), and R (n=9, 5%). Complete and partial responses to treatment were noted in 138 (76.7%) and 12 (6.7%) patients, respectively. Seventeen patients (9.4%) were refractory to treatment and rate of mortality was 4.4% (n=8). The patients were still on the CT cycle and the response could not be evaluated in 4 patients (2.2%). One patient interrupted and refused to receive CT (0.6%).

Table 3 demonstrates the HBsAg, anti-HBs, anti-HBc IgG, HBeAg, anti-HBe, HBV DNA, anti-HCV, anti-HIV, HDV Ag, anti-HDV levels in our series. HBsAg, anti-HBs, anti-HBc IgG, HBeAg, anti-HBe, HBV DNA, anti-HCV, anti-HIV, HDV Ag, anti-HDV were positive in 8 (4.4%), 59 (32.8%), 53 (29.4%), 1 (0.6%), 11 (6.1%), 4 (2.2%), 3 (1.7%), 1 (0.6%), 0, and 1 (0.6%), respectively. Isolated antiHBc IG positivity was deteted in 14 (7.8%) cases.

TABLE 3
The HB profiles on consecutive tests are demonstrated.

Marker	Positive n (%)	Negative n (%)	Unknown n (%)	Total
HBsAg	8(4.4)	172(95.6)	-	180
Anti-HBs	59(32.8)	117(65)	4 (2.2)	180
Anti-HBc IgG	53(29.4)	105(58.3)	22 (12.2)	180

HBeAg	1(0.6)	126 (70)	53 (29.4)	180
Anti-HBe	11(6.1)	122(67.8)	47 (26.1)	180
HBV DNA*	5(2.8)	117 (65)	58 (32.2)	180
Anti-HCV	3(1.7)	176(97.8)	1 (0.6)	180
Anti-HIV	1(0.6)	179(99.4)	-	180
HDAg	1(0.6)	101(56.1)	78 (43.3)	
Anti-HDV	-	102(56.7)	78 (43.3)	180

Abbreviations: *: At Initial Diagnosis; Ag: Antigen

The serum levels of AST and ALT at initial diagnosis were 27.54 ± 24.38 and 23.44 ± 25.49, respectively. Antiviral prophylaxis was administered to 30 (16.7%) patients and the duration of antiviral prophylaxis was 12.50 ± 5.90 days. The agents used in antiviral prophylaxis were entecavir (n=21, 70%), lamivudine (n=8, 26.67%) and tenofovir (n=1, 3.33%).

An increase in HBV DNA was noted in 3 patients (1.67%), while 145 patients displayed no increase (80.56%). The changes in HBV DNA level were unknown in 32 (17.78%) cases. There was an increase in serum ALT levels in 2 patients (1.1%). Seroconversion was also detected in 2 patients (1.1%). HBV DNA reactivation was observed in 4 patients (2.2%) and these patients received entecavir (n=2), lamivudine (n=1), and tenofovir (n=1).

TABLE 4

The HBV DNA profiles on consecutive tests are demonstrated.

Follow-up no.	HBV DNA status			Total
	Positive	Negative	Unknown	
1	6	7	1	14
2	5	8	1	14
3	2	10	1	13
4	3	8	1	12
5	5	17	22	44

The antiviral prophylaxis was successful in 21 patients (84%), while it was unsuccessful in 3 cases (12%). The duration of antiviral prophylaxis was insufficient to assess the outcome in 1 patient (4%).

In this series, the rate of mortality related to HBV was 0.6% (n=1), while 37 patients were lost to follow-up (n=37, 20.6%).

DISCUSSION

Our results indicated that HBV reactivation in NHL patients during or after R-CT must not be overlooked and antiviral prohpylaxis must be started in patients under risk without delay. The HBV marker panel must be carefully examined and monitored during and after the administration of CT cycles. Even though rates of seroconversion and mortality associated with HBV reactivation were relatively low, we suggest that the popularization of R-CT regimens pose a challenge for HBV reactivation, particularly in endemic areas.

The utility of rituximab and similar agents, in case of use alone or in combination with cytotoxic therapy, has been linked with reactivation of HBV in lymphoma patients [9]. The importance of antiviral therapy to prevent HBV reactivation in HBsAg positive patients receiving rituximab-CT for onco-hematological diseases is well established [10-12]. Furthermore, reactivation of HBV is possible up to 27% of NHL patients with resolved HBV infection, after R-CT[13-15].

Viral reactivation constitutes a significant risk in these patients since a mortality rate as high as 50% can be detected despite the timely initiation of antiviral prophylaxis and interruption or cessation of R-CT [5,16]. There is no standard for the management of HBV reactivation in patients with resolved HBV infection and there is controversy on the selection of pre-emptive anti-HBV therapy or anti-HBV prophylaxis. There is a dispute on the utility of cheaper and less potent lamivudine versus the novel and more expensive agents such as entecavir or tenofovirdisoproxil fumarate [1]. Lioglio et al. regularly monitored levels of HBV DNA, HBsAg, anti-HBs, and ALT both during prophylaxis and after lamivudine discontinuation. They reported that approximately one-third of patients with protective levels of anti-HBs titers at baseline displayed a remarkable diminution in titres during R-CT and some patients changed into anti-HBs negative. Notably, there was not any HBsAg serore version during antiviral prophylaxis with lamivudine [1].

Marrone et al. monitored their patients with HBsAg only in the absence of serum HBV DNA, which makes the diagnosis of HBV reactivation less sensitive [17]. We suggest that sensitivity of follow-up of must be strengthened with the cost-effective use of multiple markers

In the setting of undetectable HBV DNA, the absence of anti-HBs in the presence of anti-HBc has been suggested to indicate occult infection. In healthy anti-HBc–positive, HBsAg-negative, and anti-HBs–negative donors of liver transplantation, although HBV DNA was undetectable, HBV was found to exist in the liver, resulting in HBV reactivation in the recipients after transplantation during immunosuppressive treatment [18].

In parallel with relevant publications, our findings imply that NHL patients scheduled for R-CT, who are HBsAg negative must be further screened for anti-HBc and anti-HBs. In order to prevent reactivation of HBV and its related morbidity and mortality, patients who are positive for anti-HBc and who are negative for anti-HBs must be closely monitored with HBV DNA and serum biochemistry during C-RT. This follow-up must last for at least 6 months after R-CT and the antiviral prophylaxis must be started thoroughly upon diagnosis of reactivation [18]. The reason for the persistence of high mortality rates linked with HBV reactivation during or after R-CT can be attributed to the delay in the administration of antiviral treatment [19].

However, reports using this approach have not been found to be universally successful, with HBV-associated mortality still being observed, possibly because of a delay in the antiviral administration. Furthermore, the potential intense monitoring modality may not be cost-effective and may be difficult to conduct in clinics that lack adequate laboratory support [9].

In conjunction with Loglio et al., we observed no remarkable side effects due to antiviral prophylaxis including lamivudine, entecavir, and tenofovir. Antiviral treatment protocols must be tailored with respect to safety profile and cost-effectivity. Lamivudine (LMV) can constitute a useful measure for HBV prophylaxis since it is safe, cheap and readily available. In addition, the likelihood of LMV resistance is quite low in patients with minimal HBV replication and with resolved infection, who may be immunocompromised in short-term [1].

Negative anti-HBs status and rituximab-containing regimens are both important factors for predicting chemotherapy or immunosuppressive therapy-related HBV reactivation in patients with resolved HBV infection [20]. However, the role of antiviral prophylaxis in preventing HBV reactivation by chemotherapy or immunosuppressive therapy in patients with resolved hepatitis B is unclear [20].

The risk of HBV reactivation from R-CT or immunosuppressive therapy has been speculated to be lower in HBsAg-negative, anti-HBc positive patients compared with HBsAg positive patients [21].

Consensus has been reached for routine screening of HBV serology in patients scheduled for chemotherapy, particularly in endemic areas. Prophylactic use of antiviral medication is the standard of care for lymphoma patients with chronic hepatitis B who will receive R-CT. On the other hand, the clinical benefit of antiviral prophylaxis for patients with previously resolved HBV infection could not be promptly confirmed [22].

Kim et al. reported that HBV reactivation was detected in 27.8% of HBsAg positive patients in B-cell lymphoma patients treated with R-CT. This reactivation was less common in patients receiving antiviral prophylaxis. Lamivudine was most frequently utilized, but more than 20% of HBsAg-

positive patients displayed HBV reactivation. There was a lower rate of HBV reactivation for entecavir compared with lamivudine [8].

Previously reported incidences of HBV reactivation in HBsAg-positive NHL patients who underwent C-RT under antiviral prophylaxis have varied from 3.4% to 80% [23,24]. The optimal duration of antiviral prophylaxis is controversial because of a lack of evidence from randomized clinical trials. The HBV reactivation was expected to occur more commonly after the withdrawal of lamivudine prophylaxis. Kim et al. demonstrated a more often occurrence of HBV reactivation in patients who received lamivudine.

Similar to the data reported by Kim et al., we suggest that follow-up using HBV DNA can suffice for screening the occurrence of HBV reactivation from HBsAg-negative/HBcAb-positive patients. The minor risk for HBV reactivation reminds that routine antiviral prophylaxis for HBsAg-negative/ HBcAb-positive patients is not indicated.

The definition and criteria of HBV reactivation and threshold values for HBV DNA assay may challenge interpretation and comparative analysis of results in various publications [15,25]. The rate of HBV reactivation is low in patients who are HBsAg negative/anti-HBc positive receiving R-CT without concomitant antiviral prophylaxis. However, elderly patients, particularly those without anti-HBs, are especially supposed to be under risk [9,26].

The main restrictions of the present study involve retrospective design, missing data, patients lost to follow-up, a small number of patients receiving antiviral prophylaxis, data limited to the experience of a single center and lack of long-term follow-up. Moreover, the lack of comparison of safety and cost-effectivity panels of different antiviral agents constitutes another weakness of this study.

CONCLUSION

To conclude, the development of guidelines is essential to detect and monitor HBV reactivation and administration of antiviral prophylaxis during or after R-CT. Lamivudine, entecavir, and tenofovir can be safely used for antiviral prophylaxis. Intense monitoring programs for HBV reactivation may not be cost-effective, thus institutions that lack sufficient facilities may not be able to carry out this action. On the other hand, the relationship between HBV reactivation and antiviral prophylaxis in cases with resolved HBV infection necessitates further well-designed, prospective, multi-centric trials on larger series.

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CONFLICT OF INTEREST STATEMENT

Authors declare that there is no conflict of interest in this article.

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