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Evaluation of the frequency of hepatitis B virus reactivation and the importance of hepatitis B prophylaxis in hematology patients receiving immunosuppressive therapy: a single-center study

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ABSTRACT

Aims: The aim of this study was to evaluate the rate of hepatitis B virus reactivation (HBVr) in hematology patients receiving immunosuppressive therapy in our center and the clinical characteristics of patients with HBVr. We will also investigate the importance of effective prevention of this potentially life-threatening event and management of hepatitis B virus (HBV) prophylaxis.

Methods: In this study, hepatitis B prophylaxis and its effects on patients over 18 years of age receiving immunosuppressive therapy in the hematology clinic were analyzed. 122 patients were included in the study. The HBV markers of the patients were determined by the chemiluminescence method. In the study, HbsAg(+) and isolated antiHbc IgG-positive patients received prophylactic antiviral treatment. The differential diagnosis of HBV reactivation and the criteria determined to define HBV reactivation were performed. Clinical characteristics and descriptive information of patients receiving HBV prophylaxis were analyzed using SPSS 25.0.

Results: The median age of 122 patients (59.8% male) was 58 years. It was determined that five HbsAg-positive patients had no prior follow-up and did not receive antiviral treatment. 117 patients had isolated anti-HBc IgG positivity. The median duration of prophylaxis was 15 (9-21.25) months, and the total follow-up period was 19.5 (11.75-30.25) months. 81.1% of the patients received regular HBV prophylaxis treatment; 59% of them received entecavir, and the rest received tenofovir disoproxil. Bone marrow transplantation was performed in 25 patients. HBV reactivation was detected in only 4 patients (3.3%); one of these patients had received allogeneic and one autologous bone marrow transplantation; and three patients had received chemoimmunotherapy including Rituximab. The diagnoses of the patients with HBVr were acute myeloid leukemia, lymphoma, and chronic lymphocytic leukemia. During the follow-up period, 29 patients (23.8%) died due to their primary disease, but there were no deaths due to HBV reactivation.

Conclusion: The data obtained in this study show that effective hepatitis B prophylaxis treatment is successful in preventing HBV reactivation in hematology patients. HBVr was observed in four patients who did not take HBV prophylaxis medication regularly.

Keywords: Hematology, immunosuppressive therapy, hepatitis B, prophylaxis, reactivation

INTRODUCTION

Hepatitis B carriage [HBsAg(+), Anti-HBs (-)] is a condition in which the patient has previously been exposed to the hepatitis B virus and has not developed immunity to it. Healed hepatitis B is a condition in which the patient has encountered hepatitis B at some point in his/her life and has developed immunity and antibodies [HBsAg(-), antiHc IgG(+)]. Over time, these antibodies decrease in the body, and when the patient is exposed to hepatitis B again

or uses immunosuppressive drugs such as chemotherapy, hepatitis B viremia occurs in the patient. Hepatitis B viremia leads to acute fulminant hepatitis, cirrhosis, and even hepatocellular cancer, resulting in fatal complications.[1,2] Cortisone, rituximab (anti-CD20), and other cytotoxic chemotherapy drugs, which are widely used in benign and malignant diseases of hematology, both reduce the number of cells involved in the immune system and weaken the immune system by dysfunctioning these cells, leading to hepatitis B virus reactivation (HBVr).[3] In addition, these life-saving chemotherapy treatments are interrupted when HBVr occurs. To prevent this situation, prophylactic antiviral treatment should be initiated to prevent HBVr in HbsAg positive carriers and in hematology patients who will receive immunosuppressive treatment such as chemotherapy and rituximab in isolated antiHbc IgG positive patients.[4] Hepatitis B prophylaxis is important in the treatment of these patients because HBVr has the potential to negatively affect clinical outcomes by reducing the chance of cure and preventing the completion of cancer treatment.[5] HBVr causes serious problems in branches such as hematology, oncology, dermatology, rheumatology, nephrology, and neurology receiving immunosuppressive therapy and hepatitis B virus screening before treatment is usually neglected. In this study, we aimed to raise awareness among clinicians by determining the reactivation rate and clinical characteristics of hematology patients receiving immunosuppressive therapy.

METHODS

The ethics committee approval of the study was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Research Ethics Committee on 22.05.2020 with the decision number 2020/03-50. The analyses in the study were performed according to the principles of the Declaration of Helsinki.

This study included patients aged ≥18 years who started immunosuppressive treatment and received hepatitis B prophylaxis in the hematology clinic between January 2016 and May 2020 at Van Yüzüncü Yıl University Medical Faculty Hospital. The information of the patients was retrospectively analyzed from the hospital's data processing system and patient files. Information on 134 patients was obtained in the study. A total of 12 patients were excluded from the study because 7 of these patients preferred another center for treatment in the following periods; 3 patients died in the first month of chemotherapy; and 2 patients did not have sufficient information in their file records. Thus, a total of 122 patients were included in the study. HbsAg, anti-Hbc IgG, anti-Hbs, anti-HIV, and anti-HCV status of patients receiving chemotherapy and immunosuppressive treatment such as rituximab were recorded from the patient records. These antiviral tests were performed by the chemiluminescence method (Abbott Diagnostics, ARCHITECT i1000 SR Immunoassay Analyzer, Germany). Age, gender, diagnoses, chemotherapies, number of cycles, number of transplanted patients, antiviral treatments, and duration were determined. Prophylactic antiviral treatment was initiated in patients with HbsAg(+) and isolated antiHbc IgG-positive patients. HBVr criteria were defined as transaminase elevation of at least five times or more, bilirubin increase, PT/INR increase, HBsAg or HBeAg reappearance, and HBV DNA increase. A differential diagnosis of HBV reactivation from sepsis, chemotherapy toxicity, and cholestasis was made. The number and clinical characteristics of patients with HBV reactivation were determined.

Statistical Analysis

SPSS version 25.0 (IBM SPSS, Chicago, IL) was used to calculate descriptive data on HBVr patient characteristics. Numerical data were presented as medians (Q25-Q75). Categorical variables were expressed as numbers and percentages (n, %).

RESULTS

A total of 122 patients, 73 (59.8%) of whom were male, were included in the study. The median age of the patients was 58 years. Five (4.1%) patients who were HbsAg positive had no previous clinical follow-up and were not receiving any antiviral treatment for HBV. Isolated anti-Hbc IgG positivity was detected in 117 patients in the study. The median duration of total prophylaxis was 15 months. 99 (81.1%) of the patients received antiviral prophylaxis treatment regularly. As antiviral treatment, 72 (59%) patients received entecavir, and the remaining patients received tenofovir disoproxil. Bone marrow transplantation was performed in 25 (20.5%) patients. The demographic and clinical characteristics of the patients are shown in Table I. The study population consisted of patients (n=114/ 93.4%), the majority of whom received chemotherapy for malignant diseases. The immunosuppressive treatments given to the patients consisted of cytotoxic chemotherapy, cytotoxic chemotherapy regimens with Rituximab, and Rituximab alone. Table II shows the hematologic diseases of the patients and the characteristics of the chemotherapy regimens they received. HBV reactivation occurred in only 4 (3.3%) of 122 patients. Two patients with HBV reactivation had undergone bone marrow transplantation, and both patients did not receive antiviral treatment regularly. Patients 3 and 4 with HBV reactivation were diagnosed with chronic lymphocytic leukemia and received Rituximab chemotherapy regimens. The clinical characteristics of patients with hepatitis B reactivation are shown in Table III. During follow-up, 29 (23.8%) patients died due to disease recurrence and complications. No patient died due to HBV reactivation.

DISCUSSION

Approximately 400 million people worldwide are chronically infected with HBV, which is defined as hepatitis B surface antigen (HBsAg) in serum.[1] Hepatitis B carriage [HbsAg (+), anti-HbsAg (-)] is observed at a rate of 2.6% in the Turkish population, and hepatitis B carriage in the Eastern and Southeastern regions is 3.2%.[6] In another study, while HBsAg positivity was found to be approximately 4% in Turkey, anti-HBc IgG positivity was found to be 30.6%.[7]

The risk of hepatitis B reactivation is present in hematology patients receiving chemotherapy or immunosuppressive therapy with chronic hepatitis B [HBsAg (+)] or cured infection (anti-HBc-positive).[5] The risk of HBVr in HBsAg (-), and anti-HBc IgG (+) individuals is 0.3-9%. Although reactivation is low in those with anti-HBs (+), the risk is present. The risk of reactivation in HBsAg (+) individuals ranges from 4-70% and is usually above 10%. In this study, two out of five HBsAg-positive patients (40%) had HBVr. The aim of hepatitis B prophylaxis is to prevent serious clinical

Table 1. Demographic and clinical characteristics of the patients

Clinical parameters	n (%) or median (Q1-Q3)
Age, years	58 (46.25-68)
Gender Male Female	 73 (59.8%) 49 (40.2%)
Disease group Malign Bening	 114 (93.4%) 8 (6.6%)
Serological status HbsAg(+)/antiHbc IgG(+) HbsAg(-)/antiHbc IgG(+)	 5 (4.1%) 117 (95.9%)
AntiHbs status AntiHbs(-) AntiHbs(+)	 89 (73%) 33 (27%)
Immunosuppressive treatment Cytotoxic CT Rituximab+ Cytotoxic CT Rituximab	 66 (54.1%) 48 (39.3%) 8 (6.6%)
Immunosuppressive exposure (months)	6 (5-8)
Duration of prophylaxis (months)	15 (9-21.25)
Total follow-up time (months)	19.5 (11.75-30.25)
Antiviral treatment Entecavir Tenofovir disoproxil	 72 (59%) 50 (41%)
Compliance with immunosuppressive therapy Received regularly Not taken regularly	 99 (81.1%) 23 (18.9%)
HSCT Transplanted Non-transplant	 25 (20.5%) 97 (79.5%)
Hepatitis B reactivation status Reactivated Non-reactivated	 4 (3.3%) 118 (96.7%)

CT, Chemotherapy; HSCT, Hematopoietic stem cell transplantation

Table 2. Hematologic diseases and chemoimmunotherapies

Primary disease	n (%)	Chemotherapies given
Multiple myeloma	26 (21.3%)	* VAD, VCD, VRD,
Chronic lymphocytic leukemia	21 (17.2%)	** R-FC, RB
NHL (DLBCL)	21 (17.2%)	** R-CHOP, R-DHAP, R-ICE
Acute myeloid leukemia	19 (15.6%)	*7+3, HIDAC, FLAG-IDA
Hodgkin's lymphoma	15 (12.3%)	*ABVD, DHAP, ICE
Acute lymphocytic leukemia	6 (4.9%)	*Hyper-CVAD(A/B), CALGB
NHL (Other)	6 (4.9%)	*CHOP, CHOEP, R-ESHAP
ITP	5 (4.1%)	Rituximab
TTP	2 (1.6%)	Rituximab
AIHA	1 (1.8%)	Rituximab

*Cytotoxic chemotherapy, **Rituximab + cytotoxic chemotherapy
NHL, non-hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; ITP, immune thrombocytopenic purpura; TTP, thrombocytopenic thrombotic purpura; AIHA, autoimmune hemolytic anemia

consequences of HBVr, such as acute-fulminant hepatitis and liver failure. Hepatitis B prophylaxis is necessary according to the indications and evidence provided by current international recommendations and to prevent interruption of life-saving anti-neoplastic therapies.[8] In this study, HBVr was observed in 4 (3.3%) patients, and only these patients had a morbidity burden. For prophylactic antiviral treatment to be effective, HBV prophylaxis should be started 2 weeks before immunosuppressive therapy or chemotherapy and continued for 12-18 months after the end of treatment.[4] In

Table 3. Characteristics of patients with hepatitis B reactivation

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	39	42	59	54
Gender	Female	Male	Male	Male
Malignant Disease	AML	DLBCL	CLL	CLL
Received CT	7+3, HIDAC, Busulfan+ Cyclophosphamide, Cyclosporin, FLAG-IDA	R-CHOP, R-DHAP, Busulfan+ Etoposide	R-FC, RB	R-FC, RB
Total number of CT cycles	6	8	9	10
Stem cell transplant	Yes, [1]ASCT	Yes, [2]ASCT	No	No
Initial hepatitis serology	HbsAg(-), antiHbs(-), antiHbc Ig G(+)	HbsAg(+), antiHbs(-), antiHbc Ig G(+)	HbsAg(-), antiHbs(-), antiHbc Ig G(+)	HbsAg(+), antiHbs(-), antiHbc Ig G(+)
Prophylaxis monitoring	Not taken regularly	Not taken regularly	Not taken regularly	Not taken regularly
How many months reactivated (month)	11	15	10	9
Total Duration of prophylaxis (months)	11	11	13	8
Total follow-up period (months)	16	28	26	18
Laboratory values when reactivated	ALT=522 U/L, AST=486 U/L, TB=9.85 mg/dl, INR=2.1	ALT=880 U/L, AST=821 U/L, TB=7.26 mg/dl, INR=1.9	ALT=670 U/L, AST=804 U/L, TB=5.02 mg/dl, INR=1.6	ALT=640 U/L, AST=530 U/L, TB=7.8 mg/dl, INR=2.3
HBV DNA monitoring	Reactivation onset: 82000 IU/mL	Reactivation onset: 214300 IU/mL	Reactivation onset: 104000 IU/mL	Reactivation onset: 326400 IU/mL
HBV treatment	Tenofovir	Tenofovir	Entecavir	Entecavir
The day chemotherapy is delayed	22 days after ASCT, (cyclosporine)	After OSCT, there was no delay	43	38
Latest status	Malignancy recurrence, Ex	Alive	Alive	R/R malignancy, Ex

CT, Chemotherapy; AML, Acute myeloid leukemia; DLBCL, Diffuse large B cell lymphoma; CLL, Chronic lymphocytic leukemia; TB, Total bilirubin; R/R, Relapse/Refractory; 1ASCT, Allogeneic stem cell transplantation; 2ASCT, Autologous stem cell transplantation

this study, HBV prophylaxis was started simultaneously with chemoimmunotherapy because the treatment of hematologic malignancies was urgent. HBVr was not observed in any of these patients because HBV prophylaxis was not started before chemotherapy. In our study, HBVr was observed in patients who did not use HBV prophylaxis regularly and discontinued it for a long time.

Apart from malignant hematologic diseases, HBV prophylaxis is also given to benign patients receiving immunosuppressive therapy. In a study by Xu et al.[9], the positivity of hepatitis B markers in 115 rheumatoid arthritis patients was evaluated, and all patients were given leflunomide, an immunosuppressive drug. In this study, HBVr was observed in five patients with chronic hepatitis B (HbsAg positive, antiHbc IgG positive, HBV DNA normal) who did not receive HBV prophylaxis. In our study, HBVR was not observed in patients receiving immunosuppressive treatment for benign disease because they received HBV

prophylaxis regularly. However, HBVr was observed in two patients with malignant hematologic disease who were HbsAg positive and did not receive HBV prophylaxis regularly.

Understanding the role of novel and specific antineoplastic agents such as the anti-CD 20 agent Rituximab in the generation of HBVr represents an important step forward in prevention strategies.[10] Rituximab is a biologic drug that suppresses the immune system by acting on B lymphocytes. In people at risk of hepatitis B reactivation, it may particularly trigger this condition.[11] Huai-Hsuan Huang et al.[12] conducted one of the largest studies in this field in 3702 adult non-Hodgkin lymphoma patients receiving rituximab-based chemoimmunotherapy. In this study, antiviral treatment was started for HBV prophylaxis in 711 patients. As a result of this study, the survival of patients who received HBV prophylaxis was significantly higher than that of patients who did not receive HBV prophylaxis. In our study, 39.3% of patients received chemoimmunotherapy including Rituximab, and 6.6% received Rituximab for benign disease. HBV prophylaxis was initiated in all of these patients. HBVr occurred in three patients who received Rituximab for malignant hematologic diseases. HBV prophylaxis includes antiviral drugs such as lamivudine, entecavir, and tenofovir disoproxil. In a study by Alessandro Loglio et al.[13] the efficacy of Lamivudine given for prophylaxis was evaluated in 85 non-Hodgkin lymphoma patients receiving Rituximab-based chemoimmunotherapy. In this study, patients were receiving lamivudine prophylaxis regularly. HBVr was observed in one patient, and ALT elevation was observed in five patients. In a study by Nikolaos Papadopoulosa et al.[14] data from 55 patients, the majority of whom had hematologic malignancy, were analyzed. HBVr was observed in one of 31 patients who received any of the antiviral drugs, including lamivudine, entecavir, and tenofovir disoproxil. However, HBVr was observed in all 24 patients who did not receive HBV prophylaxis. Patients in our study used nucleoside analogs such as entecavir and tenofovir disoproxil, which are more effective than lamivudine, and these drugs were not stopped due to any side effects. The data obtained from these studies, including our study, show that all antiviral drugs used in HBV prophylaxis are effective in preventing HBVr.

HBV-naive patients should be vaccinated against HBV before stem cell transplantation. Up to 54% reactivation has been reported in HBsAg-positive stem cell transplantation patients. Reverse seroconversion is common in cases with anti-HBc (+). In allogeneic stem cell transplant recipients, 7-15% of post-transplant liver disease is caused by viral hepatitis. In cases of suspicion, HBV DNA should be tested from both the blood and collected stem cells of the donor. Immunosuppression causes reactivation of HBV replication on circular closed covalent DNA (cccDNA) in hepatocytes.[15] Cyclosporine, tacrolimus, rituximab, anti-thymocyte globulin globulin, and mycophenolate mofetil are agents used to suppress the immune system after hematopoietic stem cell transplantation (HSCT). Since these drugs suppress the immune system, they increase the risk of HBVr in patients with HSCT.[16] A retrospective study investigated the incidence of HBVr in 413 patients with hematologic malignancy who underwent HSCT.[17] HBVr developed in all five patients with HSCT who were HBsAg-positive. HBVr was detected in 11 of 408 HBsAg-negative HSCT patients. These individuals had different serologic markers (anti-HBc and/or anti-HBs). In this study, all HBVr cases were controlled with lamivudine or entecavir administration. In our study, 25 (20.5%) patients underwent HSCT. HBVr developed in two patients, one of whom underwent ASCT and the other underwent OSCT. The patient who underwent ASCT was HbsAg negative and anti-Hbc IgG positive. The patient who underwent OSCT was HbsAg and anti-Hbc IgG positive. HBVr was controlled with tenofovir disoproxil in both cases. HBV prophylaxis was successful with entecavir and tenofovir disoproxil in other HSCT patients without HBVr.

Limitation: Since the number of patients with HBV reactivation was 4/122, it was not possible to statistically evaluate the factors affecting reactivation. At the beginning of the treatment of hematologic malignancy, HBV DNA was studied only in patients with HbsAg(+) and during the reactivation period of patients with HBV reactivation. However, HBV DNA was not regularly studied in patients with isolated antiHbc IgG positivity and in the follow-up of patients with HBV reactivation. A liver biopsy was not performed in any patient with HBVr.

CONCLUSION

Before starting treatment for hematologic malignancies, especially viral hepatitis, markers should be checked. Hepatitis B prophylaxis should be given to malignant and benign hematology patients with anti-HBc IgG positivity who will receive rituximab, cytotoxic chemotherapy, stem cell transplantation, and other immunosuppressive therapies. The risk of viral hepatitis transmission is particularly high in malignant hematology patients since blood and blood products are frequently given during treatment and follow-up. Therefore, viral hepatitis markers should be reassessed at the start of chemoimmunotherapy even if HBV prophylaxis is not needed. HBV DNA should be studied before starting prophylaxis treatment if the hospital has the facility. In this study, HBVr was not found in any patient who received antiviral prophylaxis regularly during and after chemotherapy. In our study, HBVr was seen in patients with malignant hematologic diseases such as leukemia and lymphoma who did not receive prophylaxis regularly. In addition, these patients received rituximab-based chemoimmunotherapy in addition to stem cell transplantation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee approval of the study was obtained from Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 22.05.2020, Decision No: 2020/03-50).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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