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ORIGINAL ARTICLE – OPEN ACCESS

Overlooked Prophylaxis of Hepatitis B in Patients Undergoing Hematopoietic Stem Cell Transplantation

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ABSTRACT

Objective: The reactivation rate of dormant hepatitis B virus (HBV) in the liver is between 4.1% and 41.5% in immune-compromised patients. The disappearance of hepatitis B surface antibody (anti-HBs) can be an alarm for hepatitis B reactivation. In this study, the changes in serological status, reactivation rates, and antiviral prophylaxis rates were evaluated.

Materials and Methods: A retrospective study was conducted involving patients who were followed up at Erciyes University HSCT Center between January 2018 and July 2019. The demographic data, type of hematological disease, pre- and post-transplant status of HBV, presence of antiviral prophylaxis, and frequency of hepatitis B flare were evaluated.

Results: One hundred and seven patients were included in this study. The median follow-up duration was 18 months. New chemotherapy protocols were initiated in 36 patients due to progression and in 23 patients with a diagnosis of graft-versus-host disease. Anti-HBs levels decreased in 60% of the patients, and anti-HBs levels decreased to below the protective level in 13% of the patients. Among the 107 patients, 38 had resolved hepatitis B infection before transplantation, and 20 and four of 18 patients (22%) who did not receive antiviral prophylaxis developed HBV seroconversion and hepatitis B flare. The median levels of anti-HBs titers after transplantation were 167 IU/L and 15 IU/L in groups that received and did not receive antiviral prophylaxis, respectively (p=0.028).

Conclusion: Antiviral prophylaxis should be administered in patients positive for hepatitis B core antibody before hematopoietic stem-cell transplantation. Measuring HBV serological parameters at regular intervals is essential in the high-risk group.

Keywords: Hepatitis B, hematopoietic setem cell transplantation, reverse seroconversion, HBV reactivation

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem affecting approximately 240 million people worldwide (1). The prevalence of hepatitis B surface (HBs) antigen (HBsAG) positivity varies between 4% and 6% in Turkey (2). HPV-related diseases can be seen as an acute infection, chronic infection, inactive carrier, reactivation, and hepatic flare (1). Hepatitis B flare may result in complications, including liver failure and mortality (3). Hepatitis B-induced reactivation occurs frequently in several cases such as those undergoing hematopoietic stem-cell transplantation (HSCT), renal transplantation, intensive chemotherapy, anti-tumor necrosis factor (TNF) treatment, or rituximab treatment (3–5).

After HSCT, the reactivation rate of hepatitis B varies between 6% and 54% in HBs antigen-negative and hepatitis B core antibody (anti-HBc)-positive patients (6). Furthermore, the reactivation rates may reach up to 50% in inactive carriers. The risk of hepatitis B reactivation is determined by a complex interplay between the host's immunity, viral factors, and immunosuppression related to HSCT. Therefore, initiating antiviral prophylaxis at least a week before HSCT is recommended in all patients, including inactive carriers or those with resolved hepatitis B infection (7, 8).

Anti-HBs levels after transplantation may decrease below the protective level. However, this decline is not correlated with seroconversion and hepatitis B reactivation. Regression in the anti-HBs level may be different according to gender and the type of hematological malignancy (9–11).

Thus, this study determines the HBV serology, rate of HBV infection resolution, antiviral prophylaxis, and hepatitis B reactivation rates in patients undergoing HSCT.

MATERIALS and METHODS

A retrospective study was conducted involving patients who were followed up at Erciyes University HSCT Center between January 2018 and July 2019. Erciyes University HSCT Center has a capacity of 35 beds and approximately performs 120 HSCT a year. In Erciyes University HSCT Center, the BEAM (carmustine, etoposide, cytar-

abine, and melphalan) protocol was used to the patients seven days before the first day of autologous HSCT. A chemotherapy protocol including gemcitabine, fludarabine, melphalan, methotrexate, and cyclosporine was used to patients who planned to undergo allogeneic HSCT before the sixth day after HSCT. The HBsAg, anti-HBs, anti-HBc levels of all patients and donors for allogeneic HSCT were evaluated and screened before transplantation. Furthermore, the HBV DNA levels of seropositive patients were screened. The patients were given antiviral prophylaxis, regardless of whether they had HBV DNA positivity or not. HBV DNA-positive patients were further investigated for chronic liver disease. Potent antivirals are mostly preferred for prophylaxis. Antiviral prophylaxis was continued as long as immunosuppression continued and one year after the last immunosuppressive therapy (8).

The demographic data, type of hematological disease, pre- and post-transplant levels of HBsAg, anti-HBs level, anti-HBc level, mean follow-up duration, presence of antiviral prophylaxis, and frequency of hepatitis B flare were evaluated based on the data received from the patients' records and hospital automation system.

The type of transplantation was recorded as allogeneic or autologous. The follow-up durations of the patients were recorded as months.

The presence of graft-versus-host disease (GVHD), localization, and treatments for GVHD after transplantation were recorded.

The first hepatitis B serology measurement time after transplantation, anti-HBs titers before and after transplantation and whether these titers were decreased, and the presence of anti-HBs titers below the protective level (<10 IU/ml) were recorded. Patients with a follow-up duration of less than ex months (death, lack of data, etc.) were excluded from the study.

Definition of terms used in the study (12):

Chronic Hepatitis B infection: HBsAg positivity for at least six months before transplantation; HBeAg/anti-HBe may be positive; liver damage determined by biopsy.

Resolved Hepatitis B infection: Anti-HBc positivity; HBsAg or anti-HBs does not have to be positive.

HBV seroconversion: HBsAg positivity in a patient with resolved hepatitis B infection.

Anti-HBc seroconversion: Anti-HBc positivity of seronegative patients after HSCT.

HBV reactivation: HBV DNA positivity that has not been detected previously in HBsAg-positive patients or HBs-Ag positivity in patients with resolved hepatitis B infection.

Hepatitis B flare: At least three-fold increase in transaminase levels in subjects with HBV reactivation or seroconversion.

Serological imaging for hepatitis B was performed using enzyme-linked immunosorbent assay (EUROIMMUN, Lübeck, Germany). The cut-off value for anti-HBs was 10 mIU/mL.

In the central biochemistry laboratory of the hospital, the upper limit for transaminases was 40 U/L.

Statistical Analyses

Data were analyzed using Statistical Package for the Social Sciences (version 22.0; IBM Corp., Armonk, NY, USA). Prognostic variables to determine hepatitis B flare were assessed using univariate (two for categorical data and the Mann–Whitney U test for continuous data) and multivariate analysis via a binary logistic regression model using a forward stepwise method. P values of <0.05 were used to denote statistical significance.

Ethics

This study was approved by the Noninvasive Clinical Research Ethics Committee of Erciyes University (date: 25.12.2019; number: 2019/883).

RESULTS

The demographic data, hematological malignancy, type of transplantation, and serological parameters before and after transplantation are provided in Table 1. During the study period, 148 patients were followed up. Among them, 39 were excluded because they could not be reached after HSCT hepatitis serology and two were receiving antiviral treatment for chronic hepatitis B. Therefore, 107 patients were included in the study (Fig. 1). The median age of the patients was 54, and 60% of them were male. The median follow-up duration was 18 months. Multiple myeloma (MM) was the most common hematological malignancy (32%), and autologous HSCT was performed in 55% of the patients. New chemotherapy protocols were initiated in 36 patients due to disease progression after HSCT, and 23 patients underwent immune-suppressive treatment for GVHD. The first anti-HBs measurement time after HSCT was 4 months (range, 1–16 months). The median levels of anti-HBs titers before and after HSCT were 80 mIU/mL (range, 2–4388 mIU/mL) and 31 mIU/mL (range, 2–5277 mIU/mL), respectively. The anti-HBs level decreased in 60% of the patients, and the anti-HBs level decreased to below the protective level in 13% of the patients. Among the patients, 38 had resolved hepatitis before transplantation. Approximately one-fifth of the patients (8/38) were anti-HBs-negative, and hepatitis B vaccine recommendation information was not available. Antiviral prophylaxis was administered to 20 patients (52%), and the median duration of antiviral prophylaxis was 16 months (range, 6–52 months). Four of the 18 patients (22%) who did not receive antiviral prophylaxis developed HBV seroconversion and hepatitis B flare during follow-up.

The differences between the patients with and without antiviral prophylaxis are shown in Table 2. Twenty patients received antiviral prophylaxis, whereas 18 of them did not. Of the patients who were given antiviral prophylaxis, nine were treated with tenofovir disoproxil fumarate, eight with entecavir, and three with tenofovir alafenamide. Significant differences in age, hematological malignancy, the transplantation type, the presence of GVHD, immunosuppressive therapy, and disease progression were not observed between the patients with and without antiviral prophylaxis. The median pre-transplant level of anti-HBs titers was 176 IU/L in the group with antiviral prophylaxis and 81 IU/L in the group without prophylaxis. The median levels of anti-HBs titers after transplantation were 167 IU/L and 15 IU/L in the groups with and without antiviral prophylaxis, respectively, and the difference was found to be significant ($p=0.028$). Patients who were not given antiviral prophylaxis had a higher rate of reduction in the anti-HBs titer level to below the protective level. Hepatitis B reactivation did not develop in patients receiving antiviral prophylaxis; however, hepatitis B reactivation and hepatitis B flare were observed in four patients

Table 1. The demographic features, type of hematological malignancy, and pre- and post-transplant hepatitis serology of the patients

	All patients n=107	
	n	%
Male gender	64	59.8
Age (year), median (min.–max.)	54 (17–85)	
Post-transplant follow-up time (month), median (min.–max.)	18 (6–68)	
Hematological malignancy		
AML	26	24.3
ALL	8	7.5
MM	35	32.7
Lymphoma	23	21.5
Other	15	14.0
Type of HSCT		
Autologous	59	55.1
Allogeneic	48	44.9
Post-transplant recurrence	36	33.6
Presence of GVHD	15	14.0
Localization of GVHD		
Skin	5	4.7
GIS	6	5.6
Liver	4	3.7
Presence of immunosuppression	23	21.5
Immunosuppressive treatment		
Cyclosporine	16	15.0
Mycophenolate	10	9.3
Prednisolone	5	4.7
Anti-HBc positivity before HSCT	38	35.5
Presence of anti-HBs titer reduction after HSCT	64	59.8
Presence of anti-HBs titer below protective level after HSCT	14	13.1
Transaminase increase after HSCT (for all reasons)	45	42.1
HBV seroconversion	4	3.7
Hepatitis B reactivation	2	1.8
Hepatitis B flare	4	3.7
Exitus	16	15.0

min: Minimum; max.: Maximum; GIS: Gastrointestinal System; AML: Acute myeloid leukemia; MM: Multiple myeloma; ALL: Acute lymphoblastic leukemia; MM: Multiple myeloma; HSCT: Hematopoietic stem-cell transplantation; GVHD: Graft-versus-host disease; HBV: Hepatitis B virus

in the group without antiviral prophylaxis. The demographic data, HSCT protocol, and laboratory values of the patients who developed HBV seroconversion are provided in Table 3.

DISCUSSION

In this study, the occurrence rates of chronic hepatitis B and anti-HBc positivity are similar to those in the general population

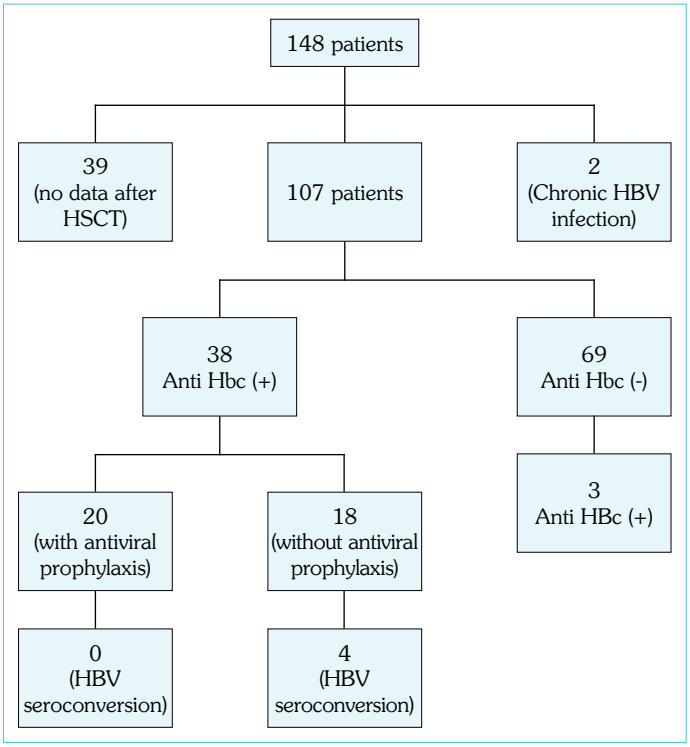

Figure 1. Flowchart of the study design

(13). Three of the patients (1.3%) became anti-HBc-positive in their post-transplant period. This rate was reported in 1.3% of 69 patients with malignant lymphomas and MM with autologous transplantation (14). The rate of anti-HBc seroconversion was reported as 0.8% in patients who had chemotherapy due to hematological malignancy (15). Anti-HBc seroconversion may be due to the serostatus of the donor for allogeneic transplants. Alternatively, another study examining the hepatitis B serology of 289 patients who underwent allogeneic HSCT has reported that 14 patients became anti-HBc-positive after transplantation although all donors were seronegative (16). In this study, two of three patients underwent autologous HSCT. No clear information exists about why anti-HBc positivity developed in patients who underwent autologous or allogeneic HSCT with seronegative donors.

Resolution of hepatitis before transplantation is known as a risk for HBV reactivation. The current guidelines recommend antiviral prophylaxis to patients with resolved and chronic hepatitis B (17, 18). Clinicians may overlook the serology of anti-HBc positivity more than HBsAg positivity. In this study, 18 of 38 patients were anti-HBc-positive; however, they did not receive any antiviral prophylaxis during the HSCT period. Hepatic reactivation developed only in patients who did not receive antiviral prophylaxis (22%). In a retrospective study evaluating 764 patients who underwent allogeneic HSCT, hepatic reactivation was observed in 14 (10%) of 137 patients with resolved hepatitis after a median follow-up duration of 19 months. The use of rituximab and cyclosporine was a risk factor for hepatic reactivation [4]. In this study, approximately half of the patients who underwent HSCT continued immunosuppressive treatment due to GVHD or post-HSCT disease progression. Moreover, they also experienced a high risk of reactivation due to the presence of GVHD and progression of the primary hematological disorder.

Table 2. Comparison of patients with and without antiviral prophylaxis

	With antiviral prophylaxis N=20		Without antiviral prophylaxis N=18		p
	n	%	n	%	
Male gender	10	50.0	14	77.8	0.101
Age (year), median (min–max)	58 (24–74)		55 (17–69)		0.496
Hematological malignancy					
AML	8	40.0	2	11.1	
ALL	1	5.0	0	0.0	
MM	6	30.0	9	50.0	0.212
Lymphoma	3	15.0	3	16.7	
Other	2	10.0	4	22.2	
Type of HSCT					
Autologous	11	55.0	13	72.2	0.328
Allogeneic	9	45.0	5	27.8	
Presence of GVHD	3	15.0	1	5.6	0.606
Localization of GVHD					
GIS	2	10.0	0	0.0	0.737
Liver	1	5.0	1	5.6	
Post-transplant progression of hematological malignancy	6	30.0	5	27.8	0.999
Presence of immunosuppression	6	30.0	1	5.6	0.093
Immunosuppressive treatment					
Cyclosporine	5	83.3	0	0.0	0.286
Mycophenolate	2	33.3	1	100.0	0.429
Prednisolone	1	16.7	1	0.0	0.999
Pre-transplant anti-HBs titer (IU/L) median (min–max)	176 (2–2951)		81 (2–1000)		0.331
Post-transplant anti-HBs titer (IU/L) median (min–max)	167 (2–1000)		15 (2–398)		**0.028**
Presence of anti–HBs titer reduction after HSCT	11	55.0	13	72.2	0.328
Presence of anti-HBs titer below protective level after HSCT	1	5.0	4	22.2	0.170
Transaminase increase after HSCT	3	15.0	7	38.9	0.144
HBV seroconversion	0	0.0	4	22.2	

min: Minimum; max.: Maximum; GIS: Gastrointestinal System; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; MM: Multiple myeloma; HSCT: Hematopoietic stem-cell transplantation; GVHD: Graft-versus-host disease; HBV: Hepatitis B virus

Since there is no explanation of the reactivation mechanism in MM, thus it was predicted that the steroid dose given in chemotherapy and the suppression of MM itself by the humoral immune system significantly contributed in the mechanism of hepatitis B reactivation (9). When the risk factors for hepatitis B reactivation were evaluated in 107 patients who underwent autologous HSCT, MM was found to be a risk factor (1). In this study, the hematological malignancy type of most patients who developed HBV seroconversion was MM (3/4). Ceneli et al. (11) have evaluated the HBV serology of 90 patients who underwent allogeneic HSCT and reported that MM was an independent risk factor in 14 patients who developed HBV and anti-HBc seroconversion.

Post-HSCT duration seems to be an important criterion for reactivation. This period has been reported as between 10 and 48 months for allogeneic and autologous transplant patients (19). In this study, the median time for reactivation was 12 months. Seto et al. (10) have evaluated 65 patients who underwent allogeneic HSCT with resolved hepatitis and reported that the median time for reactivation was 44 months. HBV reactivation in anti-HBc-positive patients increases over time even if they received immunosuppressive agents. In addition, following up patients periodically after HSCT for reactivation is crucial, especially for patients receiving ongoing immunosuppressive therapy. In this study, the median follow-up period was 18 months. In the literature, the reactivation rate increases even more when the follow-up period is kept longer. Therefore, the hepatitis B reactivation rate in this study was relatively low. However, antiviral prophylaxis was started immediately after this study, especially in patients with isolated anti-HBc positivity who did not receive antiviral prophylaxis.

Table 3. Clinical characteristics of four patients with HBV seroconversion after HSCT

At the time of HSCT	Patient 1	Patient 2	Patient 3	Patient 4
Age	30	68	56	60
Sex	Male	Male	Male	Male
Diagnosis	AML	MM	MM	MM
Type of HSCT	Allogenic	Autologous	Autologous	Autologous
HBV serology at HSCT (HBsAg/anti-HBc/anti-HBs)	-/+/+	(-/+/-)	(-/+/+)	(-/+/+)
Anti-HBs titer (IU/L)	470	2	28	17
HBV-DNA (IU/mL)	Negative	N A	Negative	N A
ALT (U/L)	20	17	23	12
HBV prophylaxis	No	No	No	No
Presence of GVHD	Yes	No	No	No
Localization of GVHD	Liver	–	–	–
Immunosuppressive treatment	Mycophenolate mofetil	–	–	–
CTx after HSCT	No	Yes	Yes	Yes
At the time of HBs Ag reversion				
HBV serology (HBs Ag/anti-HBc/anti-HBs)	+/+/-	(+/+/-)	(+/+/-)	(+/-/-)
No. of months after HSCT	12	12	7	54
HBV-DNA (IU/mL)	Not available	240,000,000	380,000,000	2,500,000
Anti-HBs titer (IU/L)	2.48	2.00	2.00	2.00
Peak ALT (U/L)	170	168	268	520
HBV treatment	Entecavir	Tenofovir	Tenofovir	Entecavir
Outcomes	Recovered	Recovered	Recovered	Recovered

HBs Ag: Hepatitis B surface antigen; HSCT: Hematopoietic stem cell transplantation; AML: Acute myeloid leukemia; MM: Multiple myeloma; NA: Not available; Anti-HBs: Hepatitis B surface antibody; HBV: Hepatitis B virus; ALT: Alanine transaminase; GVHD: Graft versus host disease; CTx: Chemotherapy; Anti- HBc: Hepatitis B core antibody

In this study, 60% of the patients experienced a significant decrease (from 80 IU to 31 IU) in median level of anti-HBs titers, and four patients (3.7%) had a decreased anti-HBs titer level to below the protective level. In a five-year retrospective analysis of 15 patients who underwent allogeneic HSCT, 12 patients were reported have decreased anti-HBs levels below the protective level, and seven of them developed HBV seroconversion (75%) (3). Uhm et al. (9) have evaluated the HBV serology of patients undergoing autologous HSCT and reported that almost one-third of patients who were positive for anti-HBs before transplantation had a decreased anti-HBs level below the protective level. In another study in which 12 patients who underwent allogeneic HSCT were evaluated for six years retrospectively, five of the patients had decreased anti-HBs levels and two had anti-HBs levels below the protective level (15). Anti-HBs titer may be a predictor for hepatitis B reactivation, especially for patients treated with intensive immunosuppressive agents and those with GVHD and progressive primary hematological disorder.

In conclusion, the HSCT process has a risk for hepatitis B reactivation due to intensive immunosuppressive treatments applied during and after the transplantation period. This study is important for ignoring antiviral prophylaxis despite guidance recommendations in patients with isolated anti-HBc positivity. Antiviral prophylaxis was significantly efficient in reducing such a risk in patients with resolved hepatitis B. However, regardless of whether anti-HBs is positive or negative, the risk of seroconversion and hepatitis B reactivation remains as patients receive ongoing immunosuppressive treatment. Periodic monitoring of HBsAg, anti-HBs, and anti-HBc is required for these patients.

Ethics Committee Approval: This study was approved by the Non-invasive Clinical Research Ethics Committee of Erciyes University (date: 25.12.2019; number: 2019/883).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ZT, AUK; Design – ZT, GKÜ, AUK; Supervision – ZT, AUK, MK; Materials – ZT, HNK; Data Collection and/or Processing – ZT, HNK; Analysis and/or Interpretation – ZT, AUK, MK; Literature Search – ZT, GKÜ; Writing – ZT, AUK; Critical Reviews – ZT, AUK, MK.

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