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Original Investigation

The frequency of hepatitis B virus reactivation in patients with bone marrow transplantation

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ABSTRACT

Objective: All patients with serologic evidence of a previous hepatitis B virus (HBV) infection have the risk of reactivation. The present study aimed to determine the prevalence of HBV infection/reactivation and to identify possible factors causing reactivation in patients who underwent bone marrow transplantation.

Methods: In total, 442 patients who underwent allogeneic and autologous peripheral stem cell transplantation between April 2011 and December 2016 were included. Hepatitis B virus serologies, chemotherapy regimens received, and antiviral treatments were retrospectively evaluated.

Results: The number of HBsAg-positive patients was 36 (8.1%) and that of HBsAg-negative/anti-HBc-positive patients was 74 (16.7%); antiviral treatment was given to all patients. There was no HBV reactivation at the median follow-up of 21 months.

Conclusion: All patients receiving immunosuppressive therapy should be screened for HBV infection and evaluated for the prophylactic treatment of HBV. Thus, the risk of HBV reactivation is minimized, and a preventive approach should always be considered for patients.

Keywords: Bone marrow transplantation, hepatitis B reactivation, immunosuppressed host

INTRODUCTION

Worldwide, approximately 2 billion people are infected with hepatitis B virus (HBV) and more than 240 million people have chronic hepatitis B (CHB) infection (1). Looking at our country in term of hepatitis B virus infection, the frequency of HBsAg (Hepatitis B surface antigen) was found between 0.8%-5.7% (2). In Eastern and Southeastern Anatolia, a higher rate of positivity than other regions was reported with 6.2% (3). This elevation may be referred to the differences in socioeconomic and education level. When these rates are taken into consideration, our hematology clinic faces a higher risk patient group compared to other regions.

In patients for whom immunosuppressant treatment is planned, HBV serologic testing (by HBsAG and Anti-HBc (hepatitis B core antigen antibody) prior to the treatment have become a routine practice in almost all clinics (4). All patients with serological evidence of previous HBV infection faces reactivation risk if they receive immunosuppressant treatment. In literature, the frequency of HBV reactivation was reported in up to 70% of patients who received chemotherapy (5-8). In our study, we aimed to determinate the frequency of HBV infection/reactivation and possible factors that cause reactivation in patients undergoing bone marrow transplantation.

METHODS

A total of 442 patients who underwent allogeneic and autologous peripheral stem cell transplantation (PSCT) due to hematological malignancy or hematologic diseases between January 2009 and December 2016 were enrolled to the study. Patients with inadequate serologic parameters and follow-up were not included in the study. From files and laboratory registry system of these patients, Hepatitis B virus serology, chemotherapy that they received and antiviral treatments were checked retrospectively. Based on the Health Practice Communique, one lamivudine (LAM) 100 mg, tenofovir (TEN) 245 mg tablet or entecavir (ETV) 0.5 mg daily were given orally to the patients that have CHB infection (HBsAg positive) or previous HBV infection (HBsAg negative, Anti-HBc positive). Patients were evaluated for reactivation and treatment effi-

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ciency taking into consideration HBV DNA and alanine transaminase (ALT) and aspartate transaminase (AST) levels. The study was performed in accordance with the 1975 Declaration of Helsinki Principles as revised in 2008 and the Approval of the Ethics Committee Commission dated/numbered 25.01.2017/19. All patients signed the informed consent form and approved the study.

Statistical Analysis

The Statistical Package for Social Sciences 16.0 (SPSS Inc.; Windows 16.0, Chicago, IL, USA) was used for statistical analysis of the data obtained at the end of the study. The results are given as mean (±) standard deviation and percentage. Chi-square test was used for categorical variables, and student-t test was used for the variables that can be averaged. The chi-square test was used for intra-group categorical comparisons. For all tests, $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 442 patients being 257 men and 185 women that underwent transplantation were evaluated for hepatitis serology. No HBV reactivation was detected during the post-transplantation follow-up of median 27 months for autologous PSCT patients and median 21 months for allogeneic PSCT patients. HBsAg positive patients were evaluated with HBV DNA. The demographic data of patients, preparation regimens used for transplantation and mortality rates are shown in detail in Table 1.

As reactivation risks are classified according to the variety of medications that patients received, a comparison with the chemotherapy regimens they received is presented in Table 2. 3 patients in the highest risk group with both rituximab use and HBsAg positivity were found and antiviral treatment was started. Two of these patients responded to tenofovir treatment. As the patient who received lamivudine treatment did not respond adequately, lamivudine resistance was considered and the patient was switched to tenofovir treatment and responded during follow-up.

During allogeneic PSCT, among the patients who received ATG regimen (anti-thymocyte globulin) 1 patient refused the treatment, 1 patient refused the treatment alteration and 2 patients died without receiving treatment. One patient who did not receive ATG regimen refused the treatment. The HBV DNA results are expected in 2 patients among patients who underwent autologous PSCT.

When evaluating whether HBsAg positivity has an impact on duration of neutrophile and platelet engraftments and total

Table 1. HBV-related general characteristics of patients undergoing hematopoietic stem cell transplantation

		Allogeneic PHSCT	Autologous PHSCT	p
Number of patients		160	282	
Age at diagnosis*		29 (15–63)	54 (17–76)	
Male (%)		96 (60%)	161 (57%)	
Diagnosis	AML	82	12	
	ALL	43	–	
	NHL	9	91	
	AA	26	–	
	MM	–	179	
Preparation regimen	BuCyc	71	12	
	Bu/CycFuATG	89	–	
	Melphalan	–	179	
	R/BEAM	–	38/91	
Neutrophile engraftment*		15 (10–61 days)	11 (9–20 days)	
Platelet engraftment*		13 (9–61 days)	12 (9–61 days)	
HBsAg (+)		15/160 (9.4%)	21/282 (7.4%)	0.590#
AntiHBc-IgG (+)/HBsAg (–)		34/145 (23.4%)	40/261 (15%)	
HBV reactivation		–	–	
Follow-up period median (months)		21 (3–81)	27 (3–85)	

&Log rank test; #Fisher's Exact Test; *median; HL: Hodgkin's lymphoma; AA: aplastic anemia; NHL: non-Hodgkin lymphoma; MM: multipl myeloma; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; BuCyc: busulfan, cyclophosphamide; Bu/CycFuATG: busulfan, cyclophosphamide, fludarabine, anti-thymocyte globulin; R/BEAM: rituximab/carmustine, etoposide, sitarabine, melphalan; PHSCT: peripheral hematopoietic stem cell transplantation

Table 2. The reflection of chemotherapy regimens of patients with hematopoietic stem cell transplantation and HBV association on engraftments

		HBsAg (+)	HBsAg (–)	p	Treatment
Number of patients		36/442 (8.1%)			
Age at diagnosis		51 (26–74)	46 (15–76)		
Male (%)		26 (72%)	231 (56%)		
Autologous PHSCT	Rituximab (+)	3/38	35/38		2 T, 1 L→T
	Rituximab (–)	18/244	226/244		8 L, 3L→T, 1L→E, 4T
Allogeneic PHSCT	ATG (+)	11/89	78/89		1 L–T, 2 L, 4 T
	ATG (–)	4/71	67/71		1 E, 1 T, 1 L–T
Neutrophile engraftment* (days)		12 (8–61)	12 (10–61)	0.930#	
Platelet engraftment* (days)		13 (9–61)	13 (8–61)	0.322#	
3–year total survival %		67	69	0.227&	

&Log rank test; *median; #median test; ATG: anti–thymocyte globulin; T: tenofovir; L: lamivudine; E: entecavir; PHSCT: peripheral hematopoetic stem cell transplantation

survival, no significant difference was detected between HBsAG negative and positive group (Table 2).

As it is known that the HBsAg positive group is at high reactivation risk, the treatments that they received, and HBV DNA levels before and after the treatment were shown in detail. Of 36 HBsAg-positive patients, 7 patients started treatment with lamivudine. But these patients did not respond as expected, and treatment was switched to tenofovir. Initially, entecavir 0.5 mg/day was started in 1 patient and then the dose was switched to 1 mg/day due to inadequate response. Although all risks were described, 2 patients did not accept the treatment. The HBV DNA results are expected and the prophylactic treatments are planned in 2 patients; antiviral treatment was started in 5 patients but these patients died from malignancy-related causes and response evaluation could not be made. The malignancy of 2 patients progressed aggressively and patients died without receiving antiviral treatment (Table 3).

The patient diagnosed with acute myeloid leukemia (AML) and planned for allogeneic transplantation never had HBV and because the donor was HBsAg-positive, the patient and the donor were given antiviral treatment.

DISCUSSION

Hepatitis B reactivation is a condition that occurs after loss of immunity control in HBV infection in a patient who is inactivated or healed (9). Immunosuppression-related iatrogenic hepatitis B reactivation may appear as acute symptomatic hepatitis that can cause death by developing asymptomatic biochemical hepatitis or fulminant presentation (10). Therefore, the paths to follow should be determined by grouping the patients who receive immunosuppressant treatment according to their serological characteristics and the type of treatment they will receive.

As an overall opinion, it was found suitable to serologically screen all patients who will receive immunosuppressant treatment, start antiviral prophylaxis to the patients who require such treatment after screening, monitor the treatment of infected patients by HBV DNA monitoring and to protect the patient against CHB complications (11, 12). In some studies, it was suggested to screen only high-risk patients for cost-effectiveness (13, 14). Despite all the screening recommendations, we see that routine practice does not involve screening before immunosuppressant treatment in clinics; the trials that were conducted in oncology patients within this context in 2010 and 2011 showed that hepatitis serology screening rate was below 20% (15, 16).

The patients undergoing bone marrow transplantation due to hematologic disease or malignancy receive long-term immunosuppressant treatment and if acute/chronic GVHD (graft-versus-host disease) develops, these patients receive longer-term treatment (particularly corticosteriods).

In a study that evaluated HBV reactivation risks by diseases, it was shown that the highest-risk group consists of patients undergoing bone marrow transplantation and these patients were followed by solid organ transplant patients (17). When evaluated overall, the fact that our center is in the endemic region and that our transplantation patients are exposed to immunosuppressant treatment for a long time puts all our patients in the high risk group and makes it necessary for serological screening.

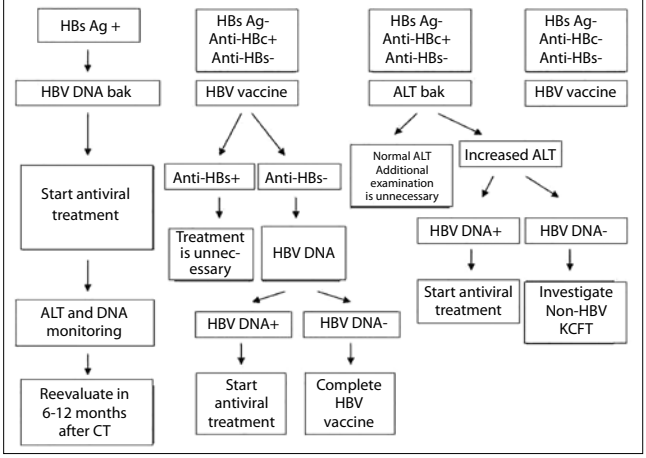
Reactivation risk was found to be associated with the given immunosuppressant agent and HBsAg positivity (9, 18). Although anti-HBs negativity or low titre was found to be associated with HBV reactivation, it was shown that Anti-HBs (antibody against hepatitis B surface antigen) did not impact the

Table 3. General characteristics of HBsAg-positive patients undergoing hematopoietic stem cell transplantation

Patient no.	Diagnosis	HSCT Type	Age	Gender	Anti- HBc IgG (+)	Anti- HBs Ig (+)	HBV DNA Baseline (IU/mL)	Antiviral Treatment	HBV DNA follow-up year 1	HBV DNA Last follow-up
1	MM	Auto	63	M	+	-	1.1×10^6	Lam→Etv	416	<20
2	MM	Auto	43	M	+	-	1170	Lam	0	0
3	AML	Allo	26	F	+	-	3.2×10^6	Lam→Ten	3350	<20
4	MM	Auto	57	F		-	170×10^6	Ten	335×10^3	ex
5	AML	Allo	34	M	+	-	678×10^3	Ent	342	<20
6	MM	Auto	58	F	+	-	1.6×10^6	Lam→Etv	ex	ex
7	MM	Auto	44	M	+	-	1170	Lam	0	0
8	NHL	Auto	51	M	+	-	134	Ten	<20	<20
9	NHL	Auto	47	M	+	-	134	Ten	<20	<20
10	NHL	Auto	59	M	+	+	70	Ten	ex	ex
11	AML	Allo	22	M	-	-	170×10^6	Ten	<20	0
12	MM	Auto	56	M		+	170×10^6	Ten	536×10^3	ex
13	MM	Auto	55	F	+	-	21.3×10^6	Lam→Ten	4.8×10^6	67
14	MM	Auto	63	M	+	-	374×10^3	Lam	<20	0
15	MM	Auto	54	M	+	+	399×10^3	Lam→Ten	<20	0
16	MM	Auto	62	M	+	-	40	Lam	<20	<20
17	AML	Allo	48	M	+	+	57	Lam	<20	<20
18	NHL	Auto	41	F	+	+	586×10^3	Lam	<20	<20
19	AML	Allo	53	F	+	-	686×10^3, Donor HbsAg (+)	Lam, (Donor: Ten)	372	ex
20	NHL	Auto	55	M	+	-	141	Lam→Ten	92	70
21	MM	Auto	49	M	+	+	783×10^3	Lam	<20	0
22	HL	Auto	42	M	+	+	0	Lam	0	0
23	AML	Allo	58	M	-	+	0	Refused treatment	0	0
24	MM	Auto	61	M	+	-	50	Lam	<20	0
25	AML	Allo	51	M	+	-	>170×10^6	Lam→Ten	47×10^3	0
26	NHL	Auto	56	F	-	-	0	Ten	0	0
27	AML	Allo	52	F	+	-	38×10^3	Ten	0	0
28	AML	Allo	49	M	-	-	22.2×10^6	Ten	<20	<20
29	AML	Allo	46	F	+	-	<20	Ten	<20	<20
30	MM	Auto	56	F	-	-	Result is expected			
31	MM	Auto	74	M	-	-	Result is expected			
32	ALL	Allo	28	M	+	-	170×10^6	Refused treatment		ex
33	AA	Allo	27	M		+	ex			ex
34	AA	Allo	31	M	+	+	170×10^6	Ten	16×10^3	
35	AML	Allo	57	M	-	+	ex			ex
36	AA	Allo	32	M	+	+	16×10^3	Ten		

HL: Hodgkin's lymphoma; NHL: non-Hodgkin lymphoma; MM: multipl myeloma; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; AA: aplastic anemia; HSCT: hematopoietic stem cell transplantation; Auto: autologous; Allo: allogeneic; M: male; F: female; Ten: tenofovir; Lam: lamivudine; Etv: entecavir; Ex: exitus

Figure 1. HBV management, prophylaxis and treatment algorithm in patients who will receive immunosuppressant treatment



reactivation risk in recent meta-analyses (19). Experts consider that the use of anti-CD20 agents (rituximab, ofatumumab) pose the highest risk for reactivation (5). In a study, patients diagnosed with lymphoma received chemotherapy with and without rituximab and reactivation was found to be greater in patients receiving rituximab when activation risk assessment was performed (20). Since there is no reactivation in our study, there is no significant difference. Also anthracyclines and high dose corticosteroids (prednisone 20 m/day usage for longer than 4 weeks) are other agents that is considered as high risk (5, 21).

After serological screening of patients, as Anti-HBs, HBsAg, Anti-HBc (hepatitis B core antibody) negative patients have never been exposed to the virus, vaccination should be recommended to these patients (9). Antiviral treatment should be started to HBsAg and/or Anti-HBc positive patients prior to chemotherapy regimens (10). Patients should be followed periodically with examinations such as HBV DNA, ALT and AST for the course of disease and treatment efficiency. Moreover, antiviral treatment should be started in anti-HBc positive and HBsAg-negative patients that were previously exposed to HBV since it is known that cccDNA remains in hepatocytes or other tissues (22, 23). In some studies, it was determined that Anti-HBc positive/HBsAg negative patients who underwent transplantation showed fatal HBV reactivation as much as HBsAg-positive patients (24-26). In the same study which was conducted in 2003, it was seen that reactivations occurred particularly within 12 months post-transplant (24). Another study which was conducted in 2013 was designed in chemotherapy patients and it was shown that HBV reactivations occurred in a duration of 4 to 36 weeks after treatment initiation (27). Of 764 bone marrow transplantation patients, 137 patients (18%) were HBsAg negative/Anti-HBc-positive and in 14 (10%) of these patients HBV reactivation was detected in median 19 months post-transplant (28). In our study, the number of HBsAg-positive patients was 36 (8.1%) and the number of HBsAg negative/Anti-HBc positive patients was 74 (16.7%); all patients received antiviral treatment and no reactivation was detected during a follow-up of median 21 months.

During HBV infection or reactivation periods, immunosuppressant treatment is delayed in patients and this affects the course of their diseases. Engraftment, which means the placement of the stem cells given in transplant patients in the bone marrow, is one of the milestones of the transplantation phase. Every event the patient is exposed to impacts engraftment. When evaluating whether HBsAg positivity has an impact on the duration of neutrophile and platelet engraftments and total survival in our study, no significant difference was detected between the HBsAG negative and positive groups.

It is inevitable to start antiviral treatment in HBsAg-positive patients. HBV DNA levels should be examined in these patients. The high level of HBV DNA is known to be associated with the development of hepatocellular carcinoma (HCC) and cirrhosis and to increase mortality in a patient (29). It is recommended to make an assessment once every 3 months during the first year, thereafter every 6-12 months and transplant patients are followed with the same assessments in our clinic.

In general, the patient should be assessed according to their serological status prior to immunosuppressant treatment, and once categorized, the algorithm should be followed as shown in Figure 1 (14, 30, 31).

CONCLUSION

Given the current evidence-based guidelines, all patients who will receive immunosuppressant treatment should be screened for HBV and assessed for prophylactic treatment. Thus, a preventive approach should always be employed for patients by minimizing HBV reactivation risk. Although the transplantation is performed in high-risk group patients in an endemic region, the fact that there is no reactivation in any of the patients who accept antiviral treatment is important for our clinic.

In conclusion, the frequency of HBsAg in patients who underwent bone marrow transplantation was similar to the frequency of HBsAg in the community and there was no reactivation detected in any of the patients who received antiviral treatment. This study suggested antiviral treatment was effective and safe in those who underwent bone marrow transplantation.

Ethics Committee Approval: Ethics committee approval was received for this study from Gaziantep University School Medicine Clinical Research Ethics Committee (25.01.2017/19).

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

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