The Importance of Antiviral Prophylaxis in Anti Hbc Positive Patients with Autologous Haematopoietic Stem Cell Transplantation

Otolog Hematopoetik Kök Hücre Nakli Olan Anti Hbc Pozitif Hastalarda Antiviral Profilaksinin Önemi

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ÖZET

GİRİŞ ve AMAÇ: Bu çalışmanın amacı, otolog hematopoietik kök hücre nakli (HSCT) olan hastalarda HBV reaktivasyonunu etkileyen faktörleri araştırmak ve HBs Ag negatif/AntiHbc IgG pozitif hastalarda hepatit profilaksisinin gerekliliğini değerlendirmektir.
YÖNTEM ve GEREÇLER: Çalışma, 500 yataklı bir eğitim hastanesinde yapılan retrospektif gözlemsel kohort çalışmasıdır. HSCT için immünosüpresif tedavi alması planlanan hastalar Hbs Ag, Anti HBs ve Anti Hbc IgG bakılarak HBV açısından tarandı. Çalışma popülasyonu Mayıs 2012 - Aralık 2018 tarihleri arasında hastanemizde otolog HSCT olan ve Anti Hbc IgG için pozitif olan hastalardan oluşmaktaydı.
BULGULAR: HSCT uygulanan 328 hastanın HBs Ag, Anti Hbs ve Anti Hbc IgG test sonuçları incelendi. Ortanca yaş 59'du (Aralık: 23-66 yaş) ve hastaların 63'ü (% 65,6) erkekti. HBs-Ag negatif / Anti Hbc IgG pozitif hastaların beşinde (gizli hepatit) HBV-DNA pozitifliği saptandı. Bu hastalara nükleoz(t)id (NA) profilaksisi uygulandı. Hbs Ag negatif hastaların toplam 52'si (% 61.9) NA profilaksisi aldı. Herhangi bir antiviral profilaksi almayan 32 hastanın dördünde (% 12.5), nakilden sonraki ortanca 9. ayda (6-13 ay) HBV reaktivasyonu görüldü.
TARTIŞMA ve SONUÇ: HBs Ag negatif/anti-HBc IgG pozitif olan otolog HSCT alıcılarına, HBV reaktivasyonu riski göz önüne alınarak, antiviral profilaksi uygulanmalıdır. Lammivudin (LAM) bu hastalar için profilaksideki potent NA'lar kadar etkilidir ve 12 aylık süre profilaksi için yeterlidir
Anahtar Kelimeler: Hepatit B virüsü, HBV reaktivasyonu, Otolog hematopoietik kök hücre nakli, antiviral profilaksi

ABSTRACT

INTRODUCTION: The aim of the study is to investigate the factors affecting HBV reactivation in patients with autologous hematopoietic stem cell transplantation (HSCT) and to evaluate the necessity of hepatitis prophylaxis in HBs Ag negative/AntiHbc IgG positive patients
METHODS: The study is a retrospective observational cohort study conducted in a 500-bed teaching hospital. Patients who were planned to get immunosuppressive therapy for malignancy were screened for HBV by Hbs Ag, Anti HBs, and Anti Hbc IgG levels. The study population was consisted of patients, who had autologous HSCT in our hospital between May 2012 and December 2018, and were positive for Anti Hbc IgG.
RESULTS: HBs Ag, Anti Hbs, and Anti Hbc IgG test results of 328 patients who underwent HSCT were examined. The median age was 59 years (Range: 23-66 years) and 63 (65.6%) of them were male. HBV-DNA was detected in low values in five (5.9%) of HBs Ag negative/Anti Hbc IgG positive patients (occult hepatitis). Nucleot(s)ide analogue (NA) prophylaxis was administered to those patients. Totally 52 (61.9%) of the Hbs Ag negative patients received NA prophylaxis. HBV reactivation occurred in four (12.5 %) of 32 patients who did not receive any antiviral prophylaxis, in a median of 9 months (6-13 months) after transplantation

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DISCUSSION AND CONCLUSION: Antiviral prophylaxis should be administered to autologous HSCT patients, who are HBs Ag negative/anti-HBc IgG positive, taking into consideration the risk of HBV reactivation. Lamivudine (LAM) is as effective as the potent NAs in the prophylaxis for those patients, and 12 months is enough for prophylaxis.
Keywords: Hepatit B virus, HBV reactivation, autologous HSCT, antiviral prophylaxis

Introduction

Hepatitis B is a common public health problem worldwide. Approximately 2 billion people have been exposed to the Hepatitis B virus (HBV), and 240 million of them are chronically infected (1, 2). Hepatitis B reactivation may occur even after years of HBsAg loss due to the persistence of covalently closed circular DNA of the virus in hepatocytes in patients with a resolved infection under certain conditions (3). Hepatitis B reactivation can occur asymptomatic, with only reappearance or increase of levels of HBV-DNA in the blood, as well as in different clinical pictures, including acute hepatitis and fulminant liver failure. It may even cause death (4). The treatment of the patient's primary disease may also be disrupted, as chemotherapy is discontinued due to HBV reactivation. Therefore, all candidates for immunosuppressive therapy should be screened for HBV infection by checking HBsAg, anti-HBs, and anti-HBc IgG before the treatment (5). Patients who are anti-HBc IgG positive should also be tested for HBV-DNA levels and patients with positive HBV-DNA levels should get antiviral prophylaxis with nucleos(t)ide analogs (NAs). In patients with negative HBs Ag and HBV-DNA, prophylaxis decision is made by the level and duration of the immunosuppressive therapy (2).

HBV reactivation can develop in HSCT recipients as they receive profound and prolonged immunosuppressive therapy, especially in allogeneic HSCT (2). However, data about autologous HSCT patients are limited.

Our study aims to investigate the factors affecting HBV reactivation in patients with autologous HSCT and to evaluate the necessity of hepatitis prophylaxis in HBs Ag negative and AntiHbc IgG positive patients. Also, the clinical features and treatment response of patients with HBV reactivation will be evaluated.

Methodology

This is a retrospective observational cohort study conducted in a 500-bed teaching hospital. Patients who were planned to get immunosuppressive therapy for malignancy were screened for HBV by Hbs Ag, Anti HBs, and Anti Hbc IgG levels. Patients with positive anti-HBc IgG were referred to the Department of Infectious Diseases. The patients either received an antiviral treatment/prophylaxis or were followed without treatment according to the HBs Ag positivity, HBV-DNA level and the type, and duration of the immunosuppressive treatment.

Antiviral prophylaxis was administered one week before the immunosuppressive therapy, if that was possible, or at least on the same day. Patients, who did not receive prophylaxis, were followed up with HBV-DNA at least once every 3 months during, and one year after the completion of their immunosuppressive treatment. Patients, who received antiviral prophylaxis, were also followed up with HBV-DNA every 3-6 months for 1 year after discontinuation of the drug.

The study was carried on the Anti Hbc IgG positive patients, who had autologous HSCT in our hospital between May 2012 and December 2018. The data of the patients were recorded retrospectively from the hospital automation system and the patient files. Patients, who were older than 17 years and followed up for at least one year after autologous HSCT, were included in the study. Exclusion criteria were a negative test for anti-HBc IgG and to be under 17 years old. Patients, who could not be followed up for one year after transplantation for various reasons, were not included in the study either. Demographic data such as age and gender of the patients, underlying disease, and the conditioning regimen used for transplantation were recorded. Laboratory tests like HBe Ag, Anti HBe, HBV-DNA level, and Anti-HBs titer were also recorded.

Serological tests were performed by Cobas Roche Diagnostics using an electrochemiluminescence immunological assay. HBV-DNA quantification by real-time

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polimerase chain reaction (PCR) was performed in Rotor-Gene Q (Qiagen, Germany). The analytical detection limit of HBV DNA is 31.6 IU/mL (linear range: 31.6-20000000 IU/mL).

Anti-HBs titer ≥ 10IU was sustained as positive. The patients with a value of Anti-HBs titer ≥100 IU were evaluated additionally, to assess whether this titer was protective to prevent reactivation. If antiviral prophylaxis was initiated, the name of the antiviral drug, HBV reactivation status, the administered treatments after reactivation, response to the treatment and follow-up time (months) were also recorded.

HBs Ag positive/Anti-HBc IgG positive and HBs Ag negative/Anti-HBc IgG positive patients were evaluated as two separate groups. All of the autologous HSCT patients with positive HBs Ag received antiviral prophylaxis/therapy, while patients who were Hbs Ag negative, did not have a standard procedure until 2016. For this reason, while some patients received prophylaxis, some were followed without prophylaxis.

Definitions:

HBV reactivation: HBs Ag seroconversion (positive when previously negative) or ≥10 fold increase HBV DNA level

Hepatic exacerbation: An increase in alanine aminotransferase (ALT) levels> 3 times the upper limit of normal or > 100 IU / L

Severe hepatitis: An increase in ALT levels > 10 timesthe upper limit of normal, or an increase in total bilirubin>1.5 times the upper limit of normal (6,7).

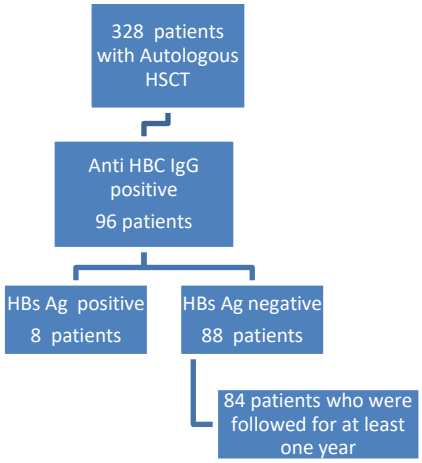

Figure -1: The serological status of patients included in the study

Clinical data, laboratory values, antiviral drugs used for antiviral treatment, and the outcome of the treatment of the patients with HBV reactivation was recorded. Local ethics committee approval was received. (2020-06/673)

Statistics:

The data were analyzed by SPSS 22.0 (Chicago, IL, USA). The continuous variables are described as the mean ± the standard deviation and the range. The percentages were described up to three decimals. The Chi-squared test or Fischer' s exact test was carried out to analyze the nominal variables.P-value <0.05 was considered as significant

Results:

In the study, HBs Ag, Anti Hbs, and Anti Hbc IgG test results of 328 patients who underwent HSCT were examined. The median age was 59 years (Range: 23-66 years), Sixty-three (65.6%) of the patients were male. The underlying malignancies of patients were multiple myeloma (MM) (65.6%), non-Hodgkin lymphoma (NHL) (20.8%), and Hodgkin lymphoma (HL) (10.4%), respectively. Anti-HBc IgG was positive in 96 (29.2%) the patients and HBs Ag was positive in eight (8.3%) of the 96 patients, whereas 50 (52%) of them had anti-HBs positivity. HBe Ag was positive in only one patient and 35 of them were anti-HBe positive. The demographic data and clinical features of those patients were summarized in Table-1.

Five of eight HBs Ag positive patients were receiving antiviral drug due to chronic hepatitis B (CHB) before admission. TDF was administered to the remaining three patients for prophylaxis. HBV reactivation did not occur in those patients, except one patient who discontinued TDF at 11th month after HSCT. The findings of HBs Ag positive patients were summarized in Table-2.

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Table-1: Characteristics of the Anti-HBc IgG Positive Patients

	(n=96)
Age, median (min-max)	59 (23-66)
Male sex, n(%)	63(65.6)
Malignity **HodgkinLymphoma, n(%)** **Non Hodgkin Lymphoma, n(%)** **Multipla Miyeloma, n(%)** **Solid Tumor, n(%)**	 10(10.4) 20(20.8) 63(65.6) 3(3.1)
HBsAg positive, n (%)	8(8.3)
HBeAg positive, n (%)	1(1)
Anti Hbe positive, n (%)	35(36.4)
Anti HBs positive, n (%)	50(52)

In the first year of transplantation, four patients from HBs Ag negative group died of various reasons other than HBV reactivation, so 84 HBs Ag negative patients were included in the study. The median age of these patients was 55 years (range: 20-69 years) Fifty-eight (69%) of the patients of them were male. HBV-DNA was detected in low values in 5.9% of those patients (occult hepatitis). NA prophylaxis was administered to those patients due to occult hepatitis. Totally 52 (61.9%) of the Hbs Ag negative patients received NA prophylaxis. Twenty-eight (33.3%), 20 (23.8%), and 4 (4.7%) patients received lamivudine (LAM), tenofovir disoproxil fumarate (TDF) and entecavir (ETV), for prophylaxis, respectively. All of the drugs were well tolerated and there were no recorded serious side effects that caused discontinuation of the treatment.

HBV reactivation occurred in four of 32 patients who did not receive any antiviral prophylaxis, in a median of 9 months (6-13 months) after transplantation. The age of patients with HBV reactivation was between 45-64 years and three of them were male. The underlying diseases of the three patients were multiple myeloma (MM) and one was NHL. Severe hepatitis developed in three patients, but none of them died.

Three patients received ETV and one received LAM for the treatment of HBV reactivation. The development of HBV reactivation in the prophylaxis group and non-prophylaxis group were found statistically different (p=0.024).The age, gender, underlying malignancy, given regimen, and anti-HBs positivity of the patients were not statistically different for both groups in terms of reactivation. The clinical and laboratory findings of the prophylaxis group and non-prophylaxis group were summarized in Table-3.

The patients were followed up for 37.75 ± 21.27 months. Three patients remained to be HBs Ag positive during the follow-up. One of the patients became HBs Ag negative and Anti-HBs positive in the sixth month of the treatment. Clinical and laboratory findings of the patients with HBV reactivation were summarized in Table-4

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Table-2: The findings of HBsAg Positive Patients

Patient Number	Age	Sex	Malignity	HBV DNA (copies/ml) Before HSCT	Former NA Therapy	NA therapy during HSCT	Follow-up time (months)	HBV reactivation
P1	65	M	MM	0	LAM	LAM	36	No
P2	68	M	NHL	0	LAM	LAM	71	No
P3	30	M	NHL	0	TDF	TDF	24	No
P4	69	M	NHL	4000	LAM	TDF	26	No
P5	62	F	MM	0	LAM	LAM	4 (Died)	No
P6	29	F	NHL	519	-	TDF	24	No
P7	24	M	HL	153	-	TDF	19	No
P8	64	F	MM	5755	-	TDF (discontinued)	19	Yes

M: Male, F: Female, MM: Multipla Miyeloma NHL: Non-Hodgkin Lymphoma: HL Hodgkin Lymphoma**,** LAM: Lamivudine, TDF: Tenofovir disoproxil fumarate, HBV: Hepatitis B virus

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Table-3: The findings of the HBs Ag negative/Anti-HBc IgG positive patients with or without HBV Reactivation

	Total (n=84)	**Patients without HBV Reactivation (n=80)**	**Patients with HBV Reactivation (n=4)**	**p**
Age, median (min-max)	55 (20-69)	55(20-69)	63 (45-64)	0,326
Male sex, n(%)	58(69)	55 (68.7)	3 (75)	0,845
Malignite: **Hodgkin lenfoma, n (%)** **Non Hodgkin lenfoma, n (%)** **Multipl Miyelom, n (%)** **Solid Tumor, n (%)**	 9 (10.7) 14 (16.6) 58 (69) 3 (3.5)	 9 (11) 13 (16) 55 (68.7) 3 (3.7)	 0 (0) 1 (25) 3 (75) 0 (0)	0.719
Conditioning regimen **Melfalan, n(%)** **BEAM, n(%)** **TECA, n(%)** **CY-TBI, n(%)**	 57 (67.8) 22 (26.1) 3 (3.5) 2 (2.3)	 54(67.5) 2126.2() 3(3.7) 2(2.5)	 3(75) 1(25) 0(0) 0(0)	0.908
Occult hepaitis, n(%)	5 (5.9)	5 (6.2)	0 (0)	0.779
HBeAg positive, n (%)	0 (0)	0 (0)	0 (0)	
Anti Hbe positive, n (%)	25 (29.7)	24 (30)	1 (25)	0.657
Anti HBs positive (≥ 10IU), n(%)	48 (57.1)	46 (57.5)	2 (50)	0.27
Anti HBs ≥ 100, n(%)	25 (29.7)	23 (28.7)	2 (50)	0.574
Patients with NA Prophylaxis, (%)	52 (61.9)	52 (65)	0 (0)	0.179
Drug for Prophylaxis: **No prophylaxis** **Lamivudin** **Tenofovir Disoproxil Fumarate** **Entecavir**	 32 (38,1) 28 (33.3) 20 (23.8) 4 (4.7)	 28 (35) 28 (35) 20 (25) 4 (5)	 4 (100) 0(0) 0(0) 0(0)	**0.024**
Follow-up time (months)	37,75±21,27	38,01±21,41	30,75±19,61	0.503

BEAM: carmustine etoposide cytarabine melphalan, TECA: Thiotepa, carboplatin, etoposide, CY-TBI: Cyclophosphamide- Total body irradiation

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Tablo-4: The findings of Patients With HBV Reactivation

	R1	**R2**	**R3**	**R4**
Age	64	63	61	45
Sex	Female	Male	Male	Male
Maligniity	MM	MM	MM	NHL
Conditioning Regimen	Melfelan	Melfelan	Melfelan	BEAM
HBV Prophylaxis	No	No	No	No
Reactivation time (months)	13	6	8	9
Serology during HBV Reactivation HBsAg Anti HBcIgM HBeAg Anti HBe Anti HBs	 Positive Positive Positive Negative Positive	 Positive Negative Positive Negative Negative	 Positive Positive Negative Positive Negative	 Positive Positive Positive Negative Negative
HBV DNA (copy/ml)	$4x10^4$	$1.4X10^8$	$1.6x10^4$	$3.2x10^6$
ALT	696	194	2554	713
AST	416	152	654	567
Total bilirubin	5	0.55	14.3	2.5
Antiviral treatment	Lamivudin 100 mg	Entecavir 0.5 mg	Entecavir 0.5 mg	Entecavir 0.5 mg
Follow-up time (month)	23	15	58	30
Outcome	HBV DNA Negative LFTs: Normal HBsAg Positive Anti HBs Positive	HBV DNA Negative LFTs: Normal HBsAg Positive Anti HBs negative	HBV DNA Negative LFTs: Normal HBs Ag neg Anti HBs positive	HBV DNA Negative LFTs: Normal HBsAg positive Anti HBs negative
Mortality Related to HBV Reactivation	No	No	No	No
MM: Multipla Miyeloma NHL: Non Hodgkin Lymphoma , BEAM: carmustine etoposide cytarabine melphalan, LFTS: Liver Function Tests				

Discussion

According to the world health organization (WHO), Turkey is in the middle endemicity region, like most of the Mediterranean countries, the Middle East, and some countries in South America, where HBV prevalence is between 2-8% in terms of HBV.

HBs Ag prevalence was reported to be 4-5% in blood donors in 2011 and it was reported as 2% in another recent study (8, 9). In a study investigating the HBV seroprevalence in Turkey, HBs Ag was reported to be positive in 4% of the population. Anti-HBc IgG was positive in 30.6% of them and Anti-HBs was 31.9% of the people in this study (10). In a study conducted in cancer patients in 2011, Hbs Ag, Anti HBs and Anti-HBc IgG seropositivity were reported to be 4.2%, 34.6% and 38.4% , respectively (11). In our study, HBs Ag positivity was 2.4% and Anti-HBc IgG of 29.2%. The prevalence of HBs Ag in our study was lower than those in the previous studies. This might be attributed to the positive effect of the hepatitis B vaccination program in Turkey since 1998 (12).

HBV-DNA was found to be positive 5.9% of patients with resolved HBV infection, in our study. Those rates were reported to be between 5-22% in different studies (13,14).

In a study conducted in Korea, MM was reported to be an underlying disease and a risk factor for seroconversion after a resolved HBV infection in autologous HSCT patients (15).

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We did not find a significant difference between the underlying diseases of the patients who had reactivation.

HBV reactivation rate was reported as 6.5% in a study where MM patients with autologous HSCT were evaluated (13). In the study of Mikulska et al. HBV reactivation was detected in 14 (10%) of 137 allogeneic HSCT patients with resolved HBV infection (16). Ramos et al reported HBV reactivation in 11.6% of 73 allogeneic HSCT patients within 3 years. The median time of reactivation was 17 months (range: 8 - 31 months) in this study (17). HBV reactivation occurred in a median of 9 months (range: 6-13 months) after transplantation in our study.

HBV reactivation time was 16 months after HSCT in median (range: 7-37 months) in the study of Varma et al, and 19 months (range:9-77 months) in the study of Mikulska et al (13,16). Since the immunosuppression is prolonged because of GVHD prophylaxis in allogeneic HSCT patients, HBV reactivation may occur after years in allogeneic HSCT patients (16, 18).

Twenty-eight of HBs negative patients were under LAM as the prophylaxis and none of them had HBV reactivation during or after treatment in our study. LAM prophylaxis was administered to 63 allogeneic HSCT patients with resolved HBV infection in a study from Italy. Twenty-five percent of patients were under rituximab prophylaxis for the prevention of Epstein-Barr virus (EBV) associated post-transplant lymphoproliferative disease (PTLD). None of these patients had HBV reactivation under prophylaxis. Only one patient experienced reactivation after eight months of discontinuation of prophylaxis (19). LAM prophylaxis was effective against the HBV reactivation in HSCT patients with resolved HBV infection like in our study.

Although potent NAs, such as ENT, TDF, and TAF are recommended for the prophylaxis in HBs Ag positive patients in the EASL guideline, LAM is recommended for HBs Ag negative patients (2). LAM could be preferred to decrease the cost related to antiviral prophylaxis in patients with autologous HSCT in whom immunosuppressive therapy is shorter than alllogeneneic HSCT.

There are different suggested treatment durations between 6-18 months depending on the status and duration of the immunosuppression (2, 20-22). Our patients received NA prophylaxis for 12 months and HBV reactivation did not occur. Yoo et al reported HBV reactivation in 4.1% of 96 HSCT patients (59 allogeneic, 37 autologous), who had NA prophylaxis for a median of seven months. Therefore, short-term antiviral prophylaxis was reported to be not sufficient to prevent HBV reactivation (23). In a study conducted in autologous and allogeneic HSCT patients from our country, NA prophylaxis was administered to HBs Ag negative patients, and no reactivation was reported, during the median follow-up duration of 21-months. Antiviral prophylaxis duration was not revealed in this study (24). The duration of antiviral prophylaxis was 12 months after cessation of immunosuppressive treatment in our study.

The limitation of our study is that it is a retrospective study, so that the data, such as the stage of the malignancy and the status of relapse after HSCT were not included.

Conclusion:

Antiviral prophylaxis should be administered to autologous HSCT patients, who are HBs Ag negative/anti-HBc IgG positive, taking into consideration the risk of HBV reactivation. LAM is as effective as the potent NAs in the prophylaxis for those patients, and 12 months is enough for prophylaxis.

There is no conflict of interest.

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