

## Hepatitis B-related events in autologous hematopoietic stem cell transplantation recipients

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### Abstract

**AIM:** To investigate the frequency of occult hepatitis B, the clinical course of hepatitis B virus (HBV) reactivation and reverse seroconversion and associated risk factors in autologous hematopoietic stem cell transplantation (HSCT) recipients.

**METHODS:** This study was conducted in 90 patients undergoing autologous HSCT. Occult HBV infection was investigated by HBV-DNA analysis prior to transplantation, while HBV serology and liver function tests were screened prior to and serially after transplantation. HBV-related events including reverse seroconversion and reactivation were recorded in all patients.

**RESULTS:** None of the patients had occult HBV prior to transplantation. Six (6.7%) patients were positive

for HBV surface antigen (HBsAg) prior to transplantation and received lamivudine prophylaxis; they did not develop HBV reactivation after transplantation. Clinical HBV infection emerged in three patients after transplantation who had negative HBV-DNA prior to HSCT. Two of these three patients had HBV reactivation while one patient developed acute hepatitis B. Three patients had anti-HBc as the sole hepatitis B-related antibody prior to transplantation, two of whom developed hepatitis B reactivation while none of the patients with antibody to HBV surface antigen (anti-HBs) did so. The 14 anti-HBs- and/or anti-HBc-positive patients among the 90 HSCT recipients experienced either persistent (8 patients) or transient (6 patients) disappearance of anti-HBs and/or anti-HBc. HBsAg seroconversion and clinical hepatitis did not develop in these patients. Female gender and multiple myeloma emerged as risk factors for loss of antibody in regression analysis ( $P < 0.05$ ).

**CONCLUSION:** Anti-HBc as the sole HBV marker seems to be a risk factor for reactivation after autologous HSCT. Lamivudine prophylaxis in HbsAg-positive patients continues to be effective.

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**Key words:** Autologous stem cell transplantation; Hepatitis B reactivation; Occult hepatitis; Multiple myeloma; Lymphoma

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## INTRODUCTION

Hepatitis B virus (HBV) infection is one of the major human health problems in the world. It is estimated that 350-400 million (approximately 5%) people worldwide are affected by HBV infection<sup>[1,2]</sup>. Turkey is one of the endemic areas for HBV infection. The spectrum of HBV-related disease ranges from asymptomatic HBV carrier state, chronic hepatitis B, acute hepatitis B, to rarely fulminant hepatitis. Chronic HBV infection is also associated with cirrhosis and hepatocellular carcinoma<sup>[1]</sup>. A new clinical status of persistence of HBV genomes in the liver tissue and/or serum in HBV surface antigen (HBsAg)-negative individuals is designated as "occult HBV infection"<sup>[3,4]</sup>. Though suspected to exist since the early 1980s, this peculiar form of chronic viral infection has been better identified during the past 10 years. The availability of highly sensitive molecular biology techniques made it possible to disclose several of its virological aspects and to show its worldwide distribution, as well as revealing its possible implications in various clinical contexts<sup>[5,6]</sup>.

Intensive chemotherapy, radiotherapy, monoclonal antibody treatment and autologous and allogeneic hematopoietic stem cell transplantation (HSCT) give rise to immune dysfunction which consequently exposes the patients to the risk of many infections, including viral hepatitis<sup>[7,8]</sup>. Exacerbation of hepatitis B is a serious cause of morbidity and mortality in patients undergoing cytotoxic or immunosuppressive therapy, particularly in areas where chronic HBV infection is endemic<sup>[9]</sup>. Iwai *et al*<sup>[10]</sup> reported lethal hepatic failure in an immunosuppressed patient after allogeneic bone marrow transplantation due to reactivation of latent HBV. The patient had antibody to HBV surface antigen (anti-HBs) and no viral DNA detected in the serum prior to transplantation<sup>[10]</sup>. Carpenter *et al*<sup>[11]</sup> described a patient with chronic myelogenous leukemia whose pretransplantation evaluation revealed normal serum aspartate and alanine aminotransferase levels, a negative serum for HBsAg, anti-HBs, antibody to HBV core antigen (anti-HBc), and HBV-DNA assessed by a sensitive real-time polymerase chain reaction (PCR). The donor was seropositive for anti-HBc, but serum HBV-DNA was negative by PCR. This case went on to develop acute HBV infection 7 mo after transplantation<sup>[11]</sup>.

To date, there have been several reports of reverse seroconversion/HBV reactivation in patients previously positive for anti-HBs after allogeneic or autologous HSCT<sup>[12-19]</sup>. There is also growing evidence regarding increased frequency of occult HBV infection in areas where hepatitis B is endemic<sup>[5,20-22]</sup>. However, information pertaining to prevalence of occult hepatitis B prior to HSCT and frequency of reverse seroconversion/HBV reactivation after HSCT has been scant.

This study aimed to determine: (1) prevalence of occult HBV infection in patients with various hematologic malignancies who are candidates for autologous HSCT; (2) frequency, course and results of HBV reactivation

and reverse seroconversion after autologous HSCT; and (3) risk factors for HBV reactivation and reverse seroconversion in patients undergoing autologous HSCT for various malignancies.

## MATERIALS AND METHODS

### Study population

Ninety consecutive patients who underwent autologous HSCT at the Stem Cell Transplantation Unit of Gazi University with the diagnosis of various hematological malignancies from September 2003 through July 2008 were included in the study.

### Detection of hepatitis markers and HBV-DNA

HBV serology and liver function tests were screened before transplantation, at day +30 and every 3 mo thereafter. HBV-DNA was tested in all patients prior to transplantation, and after transplantation in the patients who had reverse seroconversion/reactivation of HBV or acute HBV infection. HBV serology (HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe) was tested by ELISA. HBV-DNA was extracted using the MagAttract Virus Mini M48 kit (Qiagen, Hamburg, Germany) on the Bio-Robot M48 workstation (Qiagen, Hamburg, Germany) following the manufacturer's instructions. Besides HBV markers, all patients were screened for antibody to hepatitis C virus (anti-HCV) and anti-human immunodeficiency virus antibodies prior to transplantation.

### Definitions of HBV-related events

Hepatitis was defined as a serum alanine aminotransferase level greater than 100 IU/mL on two consecutive determinations more than 5 d apart<sup>[23]</sup>.

Occult hepatitis B was defined as the presence of HBV-DNA and the absence of HBsAg in plasma<sup>[3]</sup>.

HBV reactivation was defined as seroconversion from HBsAg-negative to positive for HBsAg with an increase in HBV-DNA levels compared with baseline HBV-DNA levels, in the absence of clinical and laboratory features of acute infection with hepatitis A, hepatitis C, or other systemic infection<sup>[24]</sup>.

Reverse seroconversion was defined as appearance of HBsAg and disappearance of anti-HBs after HSCT in patients who had no HBsAg but did have anti-HBs or anti-HBc before transplantation<sup>[14,19]</sup>.

Loss of antibody was defined as disappearance of anti-HBs and/or anti-HBc after transplantation.

### Lamivudine prophylaxis

All patients with a positive HBsAg received 100 mg/d lamivudine prophylaxis before the transplantation conditioning regimen. Lamivudine prophylaxis was maintained for at least 1 year after transplantation. Liver function tests were within normal limits in all patients before starting the conditioning regimen.

This study was approved by the Institutional Board of Gazi University Medical School.

### Statistical analysis

Statistical analysis was performed using the program of SPSS for Windows, version 11.5. Relative risks for reactivation of HBV and loss of antibodies were calculated by logistic regression analysis.  $P < 0.05$  was considered to be statistically significant.

## RESULTS

### Patient characteristics

Among the ninety (59 male and 31 female) patients included in the study, forty-six had multiple myeloma (MM), 23 Hodgkin's lymphoma (HL), 15 non-HL (NHL), 4 acute myeloblastic leukemia, 1 acute lymphoblastic leukemia, 1 primitive neuroectodermal tumor (PNET). The median age at transplantation was 48 years (range: 16-71 years). The median follow-up after autologous HSCT was 15 mo (range: 6-36 mo). Patients with MM comprised the most common subgroup (46 patients, 51.1%) as shown in Table 1.

### Changes in HBV serologic markers

Pre-transplantation surveillance of HBV infection showed that 6 patients (6.7%) were HbsAg-positive; three of these patients were HBV-DNA-positive. None of the patients in our cohort had occult hepatitis B. Total numbers of patients with anti-HBs and anti-HBc were 30 (33.3%) and 23 (25.6%), respectively. Forty-nine patients (54.4%) had neither anti-HBs nor anti-HBc; 12 patients (13.3%) had both (Table 2).

Clinical hepatitis B infection was detected in three patients. Two of these infections were HBV reactivation while one patient developed acute hepatitis B. While none of the patients with positive HBsAg reactivated after autologous HSCT, 2 of the 3 patients with negative HBsAg and positive anti-HBc had hepatitis B reactivation. On the other hand, none of the patients with negative HBsAg and positive anti-HBs reactivated.

Six patients with pretransplantation HBsAg received prophylactic lamivudine. Autologous HSCT was performed under lamivudine prophylaxis in those 6 patients; none of whom had HBV reactivation in the post-transplantation period.

**Reactivation case 1:** A 55-year-old male patient with MM had anti-HBc antibody as the sole HBV-related marker at pretransplantation screening. HBsAg, anti-HBs, HBeAg, anti-Hbe and HBV-DNA were all negative. The patient had received four cycles of VAD (vincristine, adriamycin, dexamethasone) as first line treatment, and four cycles of thal-dex (thalidomide-dexamethasone) as second line treatment. Cyclophosphamide-etoposide and melphalan were administered as mobilization and conditioning regimens, respectively. At day 110 after autologous HSCT, HBsAg and HBV-DNA became positive. He was in partial remission at the time of hepatitis B reactivation. Lamivudine treatment was started on the same day. Although ALT was within normal limits ini-

Table 1 Clinical characteristics of patients

Characteristic	n (%)
Total	90 (100.0)
Gender (M/F)	59 (65.6)/31 (34.4)
Median age (yr)	48 (range: 16-71)
Underlying disease	
Multiple myeloma	46 (51.1)
Hodgkin's lymphoma	23 (25.6)
Non-Hodgkin's lymphoma	15 (4.4)
Acute myeloblastic leukemia	4 (4.4)
Acute lymphoblastic leukemia	1 (1.1)
Primitive neuroectodermal tumor	1 (1.1)
Conditioning regimen	
Melphalan	47 (52.2)
BEAM	35 (38.9)
Busulfex-Cy	4 (4.4)
Busulfex-Melphalan	1 (1.1)
TBI-Cy-Thiotepa	1 (1.1)
Thiotepa-Cy-Bu	1 (1.1)
Z-BEAM	1 (1.1)

BEAM: The combination of Carmustine (BCNU), Etoposide, Cytarabine (Ara-C) and Melphalan; Z-BEAM: The combination of Ybritumomab Tiuxetan (Zevalin®), Carmustine (BCNU), Etoposide, Cytarabine (Ara-C) and Melphalan; Cy: Cyclophosphamide; TBI: Total body irradiation.

tially, it increased to 590 U/L (0-49 U/L, reference value) at day 225 post-transplantation. Subsequently ALT levels decreased gradually and normalized within 2 wk. Anti-HBc was still positive at the time of HBV reactivation and it remained positive during follow-up period. Anti-HBe and anti-HBs have not become positive during the follow-up. HBsAg and HBV-DNA disappeared in the first year after autologous HSCT. HBV-DNA titer was  $1.1 \times 10^6$  copies/mL at day +110,  $1.9 \times 10^6$  copies/mL at day +183,  $0.9 \times 10^6$  copies/mL at day +225, 1100 copies/mL at day +256 and negative at day 365 after autologous HSCT.

**Reactivation case 2:** A 55-year-old male patient with MM had anti-HBc antibody as the sole HBV-related marker at pretransplantation screening. HBsAg, anti-HBs, HBeAg, anti-Hbe and HBV-DNA were all negative in this patient as well. At day 148 after autologous HSCT, HBsAg and HBV-DNA became positive. Lamivudine treatment was started the same day. ALT level was normal initially, but it was measured as 1157 U/L at day +198. Subsequently, ALT level decreased gradually and returned to normal limits within 2 wk. HBV-DNA titer was 1000 copies/mL at the time of reactivation, then decreased gradually and it became negative at day +225. HBsAg also disappeared in patient's serum on day 365 after autologous HSCT. Anti-HBc was still positive at the time of HBV reactivation and it remained positive during follow-up. Anti-HBe and anti-HBs became positive at day +198 and day +457 after autologous HSCT, respectively. He was in complete remission at the time of hepatitis B reactivation.

**Acute HBV infection case 1:** A 48-year-old female

**Table 2** Pretransplant HBV serologic results and HBV-related events after transplantation *n* (%)

Pretransplantation HBV serologic result					HBV-related events after transplantation	
HBsAg	Anti-HBs	Anti-HBc	Anti-HBe	Patients	HBV reactivation/total patients	Loss of antibody/total patients
Negative	Negative	Negative	Negative	45 (50.0)	1/45	1/45
Negative	Positive	Negative	Negative	15 (16.7)	-	8/15
Negative	Negative	Positive	Negative	3 (3.3)	2/3	1/3
Negative	Negative	Negative	Positive	1 (1.1)	-	-
Positive	Negative	Negative	Negative	3 (3.3)	-	-
Positive	Negative	Positive	Positive	3 (3.3)	-	-
Negative	Negative	Positive	Positive	5 (5.6)	-	-
Negative	Positive	Negative	Positive	3 (3.3)	-	-
Negative	Positive	Positive	Negative	6 (6.7)	-	4/6
Negative	Positive	Positive	Positive	6 (6.7)	-	-

HBV: Hepatitis B virus (HBV); HBsAg: HBV surface antigen; anti-HBs: Antibody to HBV surface antigen; anti-HBc: Antibody to HBV core antigen.

**Table 3** Characteristics and serologic marker details of the patients with loss of antibody

Patients No.	Age (yr)	Gender	Antibody disappearance time (post-transplantation months)		Time of antibody reappearance (mo)	Disease
			Anti-HBs	Anti-HBc		
#1	71	F	+6	-	+18	MM
#6	59	F	+6	-	-	MM
#8	50	M	+12	-	+18	MM
#10	48	F	+9	-	-	MM
#12	52	F	+24	+6	-	MM
#27	46	F	+1	-	+12	MM
#28	59	M	+1	-	+8	MM
#39	59	M	+1	-	-	MM
#40	30	M	-	+1	+6	NHL
#41	68	M	-	+3	-	MM
#43	16	F	+1	-	-	PNET
#48	56	F	+1	+1	+6 (anti-HBc)	MM
#55	64	M	+6	-	-	MM
#89	23	F	+3	-	-	HD

MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; PNET: Primitive neuroectodermal tumor.

patient with MM received methylprednisolone for autologous graft-versus-host disease (GVHD) treatment at day 18 post-transplantation. HBsAg, anti-HBs, anti-HBc, HBeAg, anti-Hbe and HBV-DNA were all negative prior to transplantation in this patient. On day +210 post-transplantation, HBsAg, HBeAg and HBV-DNA became positive. Lamivudine treatment was started. ALT level, which initially was normal, gradually increased to 534 U/L at day 287 post-transplantation. She remained on steroid treatment for the treatment of grade IV chronic dermal GVHD. HBV-DNA titer was  $5.3 \times 10^7$  copies/mL on the day of reactivation,  $1 \times 10^6$  copies/mL at day +287,  $3.3 \times 10^4$  copies/mL at day +365, and 2000 copies/mL at day 580 after autologous HSCT. On day 580 post-transplantation when the data of this study were analyzed, she was positive for HBsAg, HBeAg and HBV-DNA (gradually decreasing titer, YMDD mutation negative).

**Loss of antibody**

The 14 anti-HBs- and/or anti-HBc-positive patients who underwent autologous HSCT experienced persistent (8 patients) or transient (6 patients) disappearance of anti-

HBs and/or anti-HBc. Interestingly, neither seroconversion for HBsAg nor clinical hepatitis developed in these patients. Eleven of these 14 patients had MM, 1 had NHL, 1 had HL, and 1 had PNET. Anti-HBs or anti-HBc reappeared in 5 of these patients within 6 to 8 mo. Characteristics of these patients and details of the changes in serologic markers are shown in Table 3.

Possible risk factors for reactivation and loss of antibodies, including age, gender, underlying disease, the number of pre-transplant chemotherapy cycles and the mobilization and conditioning regimens, were tested both in univariate and multivariate logistic regression analysis. No specific risk factors were found for reactivation of HBV. Female gender ( $P = 0.04$ , OR = 3.4, CI: 1.17-9.81) and MM ( $P = 0.035$ , OR = 4.29, CI: 1.29-16.2) emerged as risk factors for loss of antibody in univariate analysis; whereas only MM was an independent risk factor in multivariate analysis ( $P = 0.043$ , OR = 3.6, CI: 1.1-14.4).

**DISCUSSION**

HBV carriers have increased liver-related morbidity and

mortality during chemotherapy of hematological disorders<sup>[25]</sup>. Reactivation in patients supposedly immune to hepatitis B has also become an emerging problem during the treatment of various hematologic disorders with chemotherapeutic agents, monoclonal antibodies, immunosuppressive agents and HSCT<sup>[26]</sup>. HBV is a latent virus which may persist for a long time despite the presence of anti-HBs and/or anti-HBc antibodies. Reverse seroconversion/reactivation may occur which results in increased liver-related morbidity and mortality<sup>[25]</sup>, particularly in areas with high hepatitis B prevalence. Turkey is among the middle-endemic regions for hepatitis B with a mean seroprevalence for hepatitis B among healthy blood donors reported as 4.19% (3.9%-12.9%)<sup>[2,27]</sup>.

Occult HBV infections are defined as the presence of HBV-DNA and the absence of HBsAg in liver tissue, plasma or serum of HBV-infected patients<sup>[3-5]</sup>. The risk of reactivation and fulminant course is particularly high in this group of patients. We investigated the prevalence of occult HBV infection in patients with various hematologic malignancies who were candidates for autologous HSCT. We also investigated the frequency and the risk factors associated with HBV reactivation/reverse seroconversion after autologous HSCT.

Pre-transplantation surveillance of HBV infection showed that six patients (6.7%) were HbsAg-positive, three of whom were also HBV-DNA-positive. The 6.7% HBsAg seropositivity among patients with hematologic malignancies in the presented study seems to be similar to the frequency in the normal population.

There are several reports describing effective lamivudine prophylaxis in HbsAg-positive patients receiving chemotherapy or HSCT<sup>[9,28-30]</sup>. None of our patients with HBsAg, with or without positive HBV-DNA, had hepatitis reactivation under lamivudine prophylaxis. Our study results might suggest an efficacy of lamivudine prophylaxis in HbsAg-positive patients undergoing autologous HSCT, although lamivudine resistance has also been reported in other series<sup>[23,31,32]</sup>.

Reactivation of HBV in patients previously positive for anti-HBs and/or anti-HBc, so called “reverse seroconversion”, has been reported in immunosuppressed patients including patients with acquired immunodeficiency and recipients of organ transplantation or HSCT<sup>[14,33,34]</sup>. In particular, patients with lymphoma receiving rituximab with or without chemotherapy have an increased risk of reactivation<sup>[26]</sup>. The precise frequency of reactivation in the setting of HSCT in anti-HBs- and/or anti-HBc-positive and HbsAg-negative patients is not known, though previous reports mention a frequency of 7% to 12%<sup>[18,35,36]</sup>. Two among the 3 patients (66.7%), who had anti-HBc as the “only” hepatitis B-related marker prior to transplantation developed HBV reactivation after autologous HSCT. The cause of the hepatitis in the two patients presented above seems to be reactivation of a previous infection. Similarly, Matsue *et al*<sup>[37]</sup> found an increased risk of reactivation in their patients who had anti-HBc antibodies, while none of the patients in their

series with anti-HBs developed a reverse seroconversion. In the absence of HBV-DNA prior to transplantation, patients with anti-HBc as the sole HBV-related marker might be a variant or subgroup of patients with occult hepatitis where the infection is limited to the liver. Our results suggest that patients with anti-HBc in the absence of anti-HBs seem to be a high risk group requiring monitoring and even prophylaxis, though these data warrant verification with further prospective randomized studies. In contrast to the patients presented by Matsue *et al*<sup>[37]</sup>, whose HBV reactivation was after corticosteroid therapy for chronic GVHD, our patients who had HBV reactivation were not receiving corticosteroids and were in remission from their underlying diseases. The immunosuppressive effect of autologous HSCT *per se* might be responsible from the reverse seroconversion in our cases.

At present, HBV serological markers including HBsAg, anti-HBs and anti-HBc may not be adequate to perceive the existence of HBV. Recent studies have demonstrated that improvement of PCR methods have favored the recognition of occult HBV infections in an increasing number of clinical settings and geographical areas. To date, documentation of occult HBV prevalence rates has been limited to blood or organ donors and selected patient populations such as hemodialysis patients with HCV<sup>[38-40]</sup>, AIDS patients and hemophiliacs. The prevalence of HBV viremia in adult hemodialysis patients is 3.8%-15%, or 4-20 times higher than what standard monoclonal antibody-based HBsAg testing would have suggested. It is possible that host immune mechanisms and viral interactions can maintain HBV infection in a latent state until more profound immunosuppression ensues<sup>[38-40]</sup>. Recently, occult HBV prevalence has also been investigated in community-based populations<sup>[21]</sup>. The prevalence of occult hepatitis was found to be 15.3% in a cohort of 124 consecutive HbsAg-negative stem cell donors in Hong Kong, which suggests occult hepatitis is a matter of concern in endemic areas<sup>[13]</sup>.

None of the patients presented in this study with various hematological malignancies had occult hepatitis B prior to transplantation. Uhm *et al*<sup>[7]</sup> similarly have not detected occult HBV infection in their patients with hematologic malignancies in Korea, which is also an endemic area for HBV infection. Absence of occult hepatitis in a relatively high risk group of patients requires further elucidation. On the other hand, patients with anti-HBc as the only HBV marker might be a variant subgroup with occult hepatitis. More sensitive methods such as detection of covalently closed circular DNA - the key intermediate of replication of the virus - in liver biopsy specimens may be required in patients with immunosuppression, in order to exclude occult infection.

The rates of disappearance of anti-HBs, anti-HBc, and both (loss of antibody) were 40% (12/30 patients), 6.7% (2/30 patients), and 6.7% (2/30 patients), respectively, in our series. Total rate of disappearance of anti-HBs and/or anti-HBc was 46.7% (14/30 patients). Loss

of antibody was transient in 6 of these patients. Anti-HBs reappeared after 8-18 mo (median 15 mo) in 4 patients and anti-HBc reappeared after 6 mo in 2 patients (Table 3). The most common underlying disease among the patients who had loss of antibody (11/14 patients) was MM. MM was discovered to be an independent risk factor for loss of antibody in multivariate analysis ( $P = 0.043$ , OR = 0.27). The reason why the loss of antibody emerges more in MM patients who have undergone autologous HSCT remains to be elucidated.

None of the patients who lost their hepatitis B antibodies developed HBsAg seroconversion or clinical hepatitis during the median 15 mo follow up period. The actual risk of disappearance of anti-HBs and reverse seroconversion was estimated to be 75% and 39.8% at 2 years, and 100% and 70% at 5 years, respectively, in allogeneic HSCT recipients in the study of Onozawa *et al.*<sup>[19]</sup>. Lower rates of disappearance of antibody and reverse seroconversion in our study could be explained by the fact that our study population consisted of patients who had undergone autologous HSCT which is less immunosuppressive than allogeneic HSCT.

In conclusion, HBV-related events such as reactivation, acute hepatitis and loss of antibody can develop in patients undergoing autologous HSCT. Patients with anti-HBc antibody as the only HBV-related serologic marker might be a special risk group where antiviral prophylaxis should be considered. Loss of anti-HBs and/or anti-HBc after transplantation is not a rare complication of autologous HSCT, especially in MM patients, and does not necessarily progress to reverse seroconversion and clinical hepatitis. Further prospective and randomized studies are required to validate the prognostic significance and treatment of anti-HBc-positive patients.

## COMMENTS

### Background

Hepatitis B virus (HBV) infection is one of the major human health problems in the world. Turkey is one of the endemic areas for HBV infection. Intensive chemotherapy, radiotherapy, monoclonal antibody treatment, and autologous and allogeneic hematopoietic stem cell transplantation (HSCT) give rise to immune dysfunction which consequently expose the patients to the risk of many infections, including viral hepatitis. Exacerbation of hepatitis B is a serious cause of morbidity and mortality in patients undergoing cytotoxic or immunosuppressive therapy, particularly in areas where chronic HBV infection is endemic.

### Research frontiers

This study aimed to determine the prevalence of occult HBV infection in patients with various hematologic malignancies who are candidates for autologous HSCT. Frequency, course of disease, results of HBV reactivation and reverse seroconversion after autologous HSCT, and the risk factors for HBV reactivation and reverse seroconversion in patients undergoing autologous HSCT for various malignancies were also determined.

### Innovations and breakthroughs

HBV-related events such as reactivation, acute hepatitis and loss of antibody can develop in patients undergoing autologous HSCT. Patients with anti-HBc antibody as the only HBV-related serologic marker might be a special risk group where antiviral prophylaxis should be considered. Loss of antibody to HBV surface antigen (anti-HBs) and/or anti-HBc after transplantation is not a rare complication of autologous HSCT, especially in multiple myeloma patients, and does not necessarily mean progression to reverse seroconversion and clinical

hepatitis. Further prospective and randomized studies are required to validate the prognostic significance and treatment of anti-HBc-positive patients.

### Applications

Presence of anti-HBc as the sole HBV-related marker seems to be a risk factor for reactivation. Loss of anti-HBs and anti-HBc are frequently seen after autologous HSCT, not necessarily having a poor prognostic significance. Lamivudine prophylaxis in HBV surface antigen (HBsAg)-positive patients, and treatment in patients with HBV reactivation, continues to be effective.

### Terminology

HBV reactivation was defined as seroconversion from HBsAg-negative to positive for HBsAg with an increase in HBV-DNA levels compared with baseline HBV-DNA levels, in the absence of clinical and laboratory features of acute infection with hepatitis A, hepatitis C, or other systemic infection. Reverse seroconversion was defined as appearance of HBsAg and disappearance of anti-HBs after HSCT in patients who had no HBsAg but did have anti-HBs or anti-HBc before transplantation. Loss of antibody was defined as disappearance of anti-HBs and/or anti-HBc after transplantation.

### Peer review

In this paper, the authors provide consistent data which may help better understanding of the yet unsolved topic of HBV reactivation after immunosuppression, even if they do not change significantly current practices in this field.

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