

The effect of anticancer therapy on anti-hepatitis B antibody titres in patients with haematological malignancies and solid tumours

Bahiddin Yilmaz¹, Dilek Erdem², Fatih Teker³,
Ibrahim Goren⁴, Beytullah Yildirim⁴,
Engin Kut¹, Derya Sarikaya¹, Memis H Atay⁵
and Idris Yucel¹

Abstract

Objective: To investigate the effect of immunosuppressive anticancer therapy on titre levels of anti-hepatitis B surface antibodies (anti-HBs) in hepatitis B surface antigen (HBsAg) negative and anti-HBs positive patients with haematological malignancies or solid tumours.

Methods: This retrospective study reviewed the medical records of patients with haematological malignancies or solid tumours. Pretreatment HBsAg negative and anti-HBs positive patients were included in the analysis. Anti-hepatitis B core antibody status was used to evaluate vaccinated patients and those with resolved HBV infections.

Results: The medical records of 237 patients were reviewed retrospectively. The median anti-HBs titre decreased significantly after anticancer therapy compared with the pretreatment median anti-HBs titre in all patients (71 mIU/ml versus 57 mIU/ml). Anti-HBs titre decreased significantly in patients with haematological malignancies (70 mIU/ml versus 37 mIU/ml) and in patients administered rituximab-based chemotherapy (67 mIU/ml versus 33 mIU/ml) following chemotherapy, whereas there was no significant change in patients with solid tumours. After chemotherapy, patients with low pretreatment anti-HBs titres (<100 mIU/ml) were more likely to become seronegative (<10 mIU/ml).

¹Department of Medical Oncology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey

²Division of Medical Oncology, Medical Park Hospital, Samsun, Turkey

³Division of Medical Oncology, Gazi Yasargil Education and Research Hospital, Diyarbakir, Turkey

⁴Department of Gastroenterology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey

⁵Department of Haematology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey

Corresponding author:

Bahiddin Yilmaz, Department of Medical Oncology, School of Medicine, Ondokuz Mayıs University, Samsun 55139, Turkey.

Email: bahiddin.yilmaz@omu.edu.tr



Conclusion: High levels of anti-HBs may have a protective effect against the reactivation of HBV especially in patients with haematological malignancies who received immunosuppressive anticancer therapy.

Keywords

Hepatitis B virus reactivation, hepatitis B surface antibody, chemotherapy, solid tumour, haematological malignancy

Date received: 15 December 2015; accepted: 23 February 2016

Introduction

Infection with the hepatitis B virus (HBV) is a major public health concern, with around two billion people worldwide having been exposed to the virus.¹ Although vaccination is effective, approximately 350 million people have chronic HBV infection, and more than one million patients are estimated to die every year as a result of cirrhosis and/or hepatocellular carcinoma caused by HBV.^{1,2} As in other developing countries, HBV is a serious health problem in Turkey, where the prevalence of hepatitis B surface antigen (HBsAg) seropositivity is 4.2–8.2%.^{3,4}

Hepatitis commonly affects cancer patients who receive immunosuppressive anticancer agents for both haematological malignancies and solid tumours and reactivation of the HBV is a serious complication.^{5–7} Reactivation of HBV is characterized by elevated transaminases, clinical hepatitis and raised levels of serum HBV DNA.⁵ HBsAg positive carriers have a particularly high risk of reactivation of the virus.^{5,6} Among HBV carriers, the incidence of reactivation is 20–70% and the associated mortality rate is 5–40% in patients receiving anticancer therapy.⁸ The rate of reactivation is lower in patients with solid tumours receiving standard cytotoxic chemotherapy than it is in patients with haematological malignancies;⁹ and those with non-Hodgkin's lymphoma (NHL) that are treated with rituximab-based schedules have an

especially high risk.¹⁰ Over the past decade, studies have demonstrated that patients who are HBsAg negative, hepatitis B core antibody (anti-HBc) positive with or without hepatitis B surface antibodies (anti-HBs), which indicates a resolved infection, may develop HBV reactivation following immunosuppressive anticancer therapy, and that their reactivation risk is between 2.3% and 23.8%.^{11–17} HBV reactivation can result in anicteric hepatitis leading to severe hepatic failure and death, even with the use of effective prophylactic antiviral therapy.^{5,11}

The potential usefulness of performing anti-HBs screening prior to a patient undergoing anticancer therapy is unclear due to insufficient evidence.^{9,18} The present study investigated the effects of anticancer therapy on the levels of anti-HBs in HBsAg negative and anti-HBs positive patients with haematological malignancies or solid tumours. In addition, it investigated whether there was a chemotherapy-induced change in the anti-HBs titres of vaccinated patients and in patients who had had previous exposure to HBV.

Patients and methods

Patient population

This retrospective study reviewed the medical records of consecutive adult patients with haematological malignancies or solid tumours who received immunosuppressive anticancer therapy at the Department of

Medical Oncology and the Department of Haematology, School of Medicine, Ondokuz Mayıs University, Samsun, Turkey between January 2005 and December 2014. Information on each patient's age, sex, type of cancer and chemotherapy regimen, and HBV serum markers, including HBsAg, anti-HBs, and anti-HBc, was obtained from their medical records. The patients that tested negative for HBsAg and positive for anti-HBs secondary to vaccination or HBV infection prior to the initiation of the chemotherapy were evaluated for the study. Anti-HBc positive patients were defined as those with resolved HBV infection and anti-HBc negative patients were defined as vaccinated patients.⁹ Those patients who received ≥ 3 courses of chemotherapy and those who had HBsAg and anti-HBs measurements after the chemotherapy were enrolled in the study. Patients < 15 years of age, those who had undergone an allogeneic transplantation, and those with severe renal and liver insufficiency or hepatocellular carcinoma were excluded from the study. The study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (no. OMU KA EK 2014/898). As this was a retrospective study that analysed data from the medical records, there was no need for informed patient consent.

Serum HBV marker data collection

Hepatitis B markers were measured from serum samples using an enzyme-linked immunosorbent assay (ELISA) and the results were obtained from the medical records. All analyses were performed using a cobas[®] e 601 analyser (Roche Diagnostics, Mannheim, Germany) following the manufacturer's instructions. The minimum detectable concentrations were 2.0 IU/l for anti-HBs, 0.8 PEI U/ml for anti-HBc and 0.1 IU/l for HBsAg. Intra- and interassay

coefficients of variation for all ELISAs were $< 8\%$ and $< 12\%$, respectively. Post-treatment changes in anti-HBs titres and a return to negative titres were evaluated in the different patient subgroups (i.e. those with haematological malignancies, solid tumours, and those that had received rituximab-based therapy). As the upper limit for anti-HBs titres was 100 mIU/ml in the laboratory that undertook the analyses, this was accepted as the cut-off level for the pretreatment value when analysing the post-treatment seronegativity rates in two subgroups based on this cut-off level. A post-treatment titre of anti-HBs of ≥ 10 mIU/ml was defined as positive and a titre of < 10 mIU/ml was defined as negative. The anti-HBc status of the subgroups was also evaluated with the cut-off level of ≤ 1 IU/ml being defined as positive and > 1 IU/ml being defined as negative. The HBsAg status was also evaluated with the cut-off level of < 1 IU/ml being defined as negative and ≥ 1 IU/ml being defined as positive.

Statistical analyses

All statistical analyses were performed using the SPSS[®] statistical package, version 21.0 (SPSS Inc., Chicago, IL, USA) for Windows[®]. The Shapiro–Wilk test was used to analyse the variables that were normally distributed. Variables that were not normally distributed were analysed using the Wilcoxon signed-rank test and Mann–Whitney *U*-test. Fisher's exact test was used for the evaluation of the categorical variables. The results are presented as the median (min–max) and *n* of patients (%). A *P*-value < 0.05 was considered statistically significant.

Results

This retrospective study examined the medical records of 3740 consecutive adult

patients with haematological malignancies or solid tumours who received immunosuppressive anticancer therapy. Of these 3740 patients, 237 patients met the criteria for inclusion. A total of 122 (51.5%) were male and 115 (48.5%) were female. The median age of the patients was 54 years (range 15–86 years). The median interval between the pretreatment and post-treatment measurements of the anti-HBs titre was 295 days (range 38–1715 days). The most common haematological malignancies were acute leukaemia and lymphoma, and the most common solid tumours were colorectal, breast, lung and gynaecological tumours. The demographic and clinical characteristics of the patients are presented in Table 1.

When all patients were analysed, the post-treatment median anti-HBs titres decreased significantly compared with the

pretreatment values ($P < 0.001$) (Table 2). In the subgroup analysis, the post-treatment median anti-HBs titres decreased significantly in those with haematological malignancies ($P < 0.001$), but not in those with solid tumours. Furthermore, the median anti-HBs titres decreased significantly after rituximab-based therapy ($P = 0.006$). As the upper limit for anti-HBs titres was 100 mIU/ml in the laboratory that undertook the analyses, this was accepted as the cut-off level. After chemotherapy, 34.6% (45 of 130) of patients who had a pretreatment anti-HBs titre of < 100 mIU/ml had a value of < 10 mIU/ml (i.e. seronegative). In contrast, only 7.5% (eight of 107) of those who had a pretreatment anti-HBs titre of ≥ 100 mIU/ml had a post-treatment value of < 10 mIU/ml. The difference between the two groups was statistically significant ($P < 0.001$). There was also a significant difference within the haematological malignancies, solid tumours, and rituximab-based therapy subgroups ($P < 0.05$ for all comparisons).

The anti-HBc total antibodies were measured in 125 of the 237 patients (52.7%) (Table 2). Among these patients, 51 were anti-HBc positive and 74 were anti-HBc negative. There was a significant decrease in the anti-HBs titres in both the anti-HBc positive and negative groups after treatment ($P < 0.05$ for both comparisons). Moreover, the decrease of the anti-HBs was measured for each individual patient and the median values of the decrease in the anti-HBc positive and negative groups were compared (13 versus 0 mIU/ml, respectively; $P = 0.044$). In the haematological malignancy group, there was only a significant decrease in the median anti-HBs titres in the anti-HBc positive patients ($P < 0.001$). The rate of becoming seronegative after chemotherapy in the anti-HBc positive and negative groups was significantly higher in patients with an anti-HBs titre of < 100 mIU/ml than in those with an anti-

Table 1. Demographic and clinical characteristics of patients ($n = 237$) diagnosed with haematological malignancies or solid tumours who underwent immunosuppressive anticancer therapy and who participated in this study to investigate the impact of chemotherapy on hepatitis B reactivation.

	Patient group $n = 237$
Age, years	54 (15–86)
Sex, male/female	122/115
Haematological malignancies	111 (46.8)
Multiple Myeloma	15 (6.3)
Lymphoma	36 (15.2)
Acute leukaemia	50 (21.1)
Chronic leukaemia	10 (4.2)
Solid tumours	126 (53.2)
Colorectal carcinoma	26 (11.0)
Oesophagogastric carcinoma	16 (6.8)
Gynaecological cancer	20 (8.4)
Head and neck carcinoma	14 (5.9)
Breast cancer	25 (10.5)
Lung cancer	20 (8.4)
Others	5 (2.1)

Data presented as median (min–max range) or n of patients (%).

Table 2. Results of subgroup analyses of hepatitis B markers before and after immunosuppressive anticancer therapy in patients (n = 237) diagnosed with haematological malignancies or solid tumours.

Subgroups	n	Pretreatment		Post-treatment		Statistical significance ^b		Post-treatment seronegativity rates of anti-HBs ^a		Statistical significance ^c
		median anti-HBs, mIU/ml	median (min–max) anti-HBs, mIU/ml	median (min–max) anti-HBs, mIU/ml	median (min–max) anti-HBs, mIU/ml	anti-HBs < 100 mIU/ml	anti-HBs ≥ 100 mIU/ml	anti-HBs < 100 mIU/ml	anti-HBs ≥ 100 mIU/ml	
All patients	237	71 (10–100)	57 (0–100)	45/130 (34.6%)	8/107 (7.5%)	P < 0.001	P < 0.001			P < 0.001
Haematological malignancies	111	70 (11–100)	37 (0–100)	29/62 (46.8%)	7/49 (14.3%)	P < 0.001	P < 0.001			P < 0.001
Solid tumours	126	71 (10–100)	82 (0–100)	16/68 (23.5%)	1/58 (1.7%)	NS	NS			P < 0.001
Rituximab-based therapy	22	67 (11–100)	33 (2–100)	6/13 (46.2%)	0/9 (0.0%)	P = 0.006	P = 0.046			P = 0.046
Anti-HBc (+) patients ^d	51	74 (10–100)	43 (0–100)	15/28 (53.6%)	4/23 (17.4%)	P < 0.001	P = 0.01			P = 0.01
Anti-HBc (–) patients ^d	74	79 (14–100)	53 (0–100)	14/38 (36.8%)	3/36 (8.3%)	P = 0.016	P = 0.005			P = 0.005
Anti-HBc (+) haematological malignancies	33	79 (11–100)	28 (0–100)	11/18 (61.1%)	3/15 (20.0%)	P < 0.001	P = 0.033			P = 0.033
Anti-HBc (–) haematological malignancies	40	92 (15–100)	48 (0–100)	9/20 (45.0%)	3/20 (15.0%)	NS	NS			NS
Anti-HBc (+) solid tumours	18	72 (10–100)	70 (0–100)	4/10 (40.0%)	1/8 (12.5%)	NS	NS			NS
Anti-HBc (–) solid tumours	34	66 (11–100)	59 (0–100)	5/18 (27.8%)	0/16 (0.0%)	NS	P = 0.046			P = 0.046

^aAnti-HBs titres that became < 10 mIU/ml were defined as seronegative.

^bWilcoxon signed-rank test.

^cFisher's exact test.

^dAnti-HBc was measured in 125 of 237 patients.

Anti-HBs, anti-hepatitis B surface antibody; Anti-HBc, anti-hepatitis B core antibody.

HBs titre of ≥ 100 mIU/ml ($P < 0.05$ for both comparisons). The results of the subgroup analysis of the anti-HBc positive and negative patients are shown in Table 2.

The characteristics of 53 patients who became anti-HBs negative are summarized in Table 3. Thirty-six of these patients had haematological malignancies and 17 had solid tumours. Among the haematological malignancies, there were 22 patients with acute leukaemia and eight with lymphoma. The most common solid tumours were gynaecological and breast cancers.

Only three patients with haematological malignancies developed treatment-related HBV reactivation and their details are listed in Table 4. In one of the patients, the HBV was reactivated after undergoing fludarabine plus cyclophosphamide treatment. The virus was deactivated following treatment with lamivudine, and the patient is still alive. A second patient remained in remission regarding her malignant disease, but subsequently died due to fulminant hepatitis despite the administration of antiviral therapy. The third patient had received vincristine, doxorubicin and dexamethasone therapy for multiple myeloma, but when this progressed, the patient was switched to bortezomib and then lenalidomide. Upon initiation of the lenalidomide therapy, HBV reactivation occurred, and the lamivudine therapy was continued for another 2 years. Tenofovir was added to the therapy when the patient developed resistance to lamivudine. However, the patient ultimately died due to primary disease progression.

Discussion

The results of the present study suggest that a low pretreatment level of anti-HBs is a risk factor for becoming negative for anti-HBs, particularly in patients with haematological malignancies who have undergone immunosuppressive anticancer therapy. This could contribute to HBV reactivation. HBV

Table 3. Demographic and clinical characteristics of patients ($n = 53$) diagnosed with haematological malignancies or solid tumours who became seronegative for anti-hepatitis B surface antibodies following immunosuppressive anticancer therapy.

	Patient subgroup $n = 53$
Age, years	46 (15–79)
Sex, male/female	25/28
Haematological malignancies	36 (67.9)
Multiple Myeloma	4 (11.1)
Lymphoma	8 (22.2)
Acute leukaemia	22 (61.1)
Chronic leukaemia	2 (5.6)
Chemotherapy regimens used in the haematological malignancies	
Idarubicin + cytosine arabinoside	7 (19.4)
CALGB protocol	6 (16.7)
R-CHOP	6 (16.7)
VAD \pm immunomodulators + proteasome inhibitors	4 (11.1)
Fludarabine + cyclophosphamide	2 (5.6)
BFM protocol	2 (5.6)
Other protocols	9 (25.0)
Solid tumours	17 (32.1)
Colorectal carcinoma	1 (5.9)
Oesophagogastric carcinoma	3 (17.6)
Gynaecological cancer	5 (29.4)
Head and neck carcinoma	3 (17.6)
Breast cancer	4 (23.5)
Lung cancer	1 (5.9)
Chemotherapy regimens used in the solid tumours	
Paclitaxel + carboplatin	5 (29.4)
Cisplatin + 5-fluorouracil	3 (17.6)
Doxorubicin + cyclophosphamide	2 (11.8)
Epirubicin + cisplatin + 5-fluorouracil	2 (11.8)
Other protocols	5 (29.4)

Data presented as median (min–max range) or n of patients (%).

CALGB, Cancer and Leukemia Group B; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VAD, vincristine, doxorubicin, dexamethasone; BFM, Berlin, Frankfurt, Munster.

Table 4. Demographic and clinical characteristics of three patients diagnosed with haematological malignancies who developed immunosuppressive anticancer therapy-related hepatitis B (HBV) reactivation.

Patient	Age, years	Sex	Disease	Chemotherapy	Baseline HBV markers			Post-treatment HBV markers				Outcome				
					HBsAg	Anti-HBs (mIU/ml) ^a	Anti-HBc	HBV DNA	HBsAg (mIU/ml) ^a	Anti-HBs	Anti-HBc		HBV DNA	Antiviral treatment		
1	59	F	CLL	FC	-	+	(67)	NA	NA	-	-	(0.7)	+	+	Lamivudine	Alive, reactivation recovered. HBV DNA became negative.
2	62	F	AML-M ₃	Ida+ATRA	-	+	(>100)	NA	NA	+	+	(0.01)	+	+	Lamivudine	Died due to HBV reactivation.
3	65	M	MM	VAD + bortezomib ^b lenalidomide ^b	-	+	(44.1)	+	NA	+	+	(0.08)	-	+	Lamivudine + tenofovir	HBsAg and HBV DNA became negative. Died due to malignant disease progression.

HBsAg, hepatitis B surface antigen; Anti-HBs, anti-hepatitis B surface antibody; Anti-HBc, anti-hepatitis B core antibody; F, female; CLL, chronic lymphocytic leukaemia; FC, fludarabine, cyclophosphamide; NA, not available; AML-M₃, acute myeloblastic leukaemia-promyelocytic leukaemia; Ida, idarubicin; ATRA, all trans retinoic acid; M, male; MM, multiple myeloma; VAD, vincristine, doxorubicin, dexamethasone.

^aAntibody titre level.

^bThese drugs were used with dexamethasone.

reactivation is defined as an increase in the alanine aminotransferase (ALT) level at least three-fold higher than the baseline value or any ALT level > 100 IU/l and a ten-fold increase of baseline HBV DNA or reappearance of detectable HBV DNA.^{5,9} HBV reactivation related to immunosuppressive anticancer therapy is a well-documented and common complication, especially among HBsAg positive carriers.^{5,6} Other conditions, such as occult or resolved HBV infections, can also result in reactivation.^{9,11-13} Lymphomas, male gender, younger age, hepatitis B envelope antigen seropositivity, and a high viral load are also known risk factors for HBV reactivation after immunosuppressive anticancer therapy.^{5,9,11}

Although the mechanism behind HBV reactivation remains unclear, several possible mechanisms have been proposed. For example, the administration of immunosuppressive chemotherapy affects the balance between the host's immune system and viral replication, thus suppressing normal immunological responses and affecting cellular and humoral immune responses.¹⁹⁻²¹ Moreover, the function of T lymphocytes may also be suppressed and a deficient immune response to viral antigens may lead to reactivation.¹⁹ Likewise, immunosuppressive chemotherapy, particularly rituximab-based chemotherapy, may suppress antibody-producing B lymphocytes, thereby resulting in a decrease in the production of immunoglobulins and antibodies against HBV.^{19,21} Another possible mechanism of HBV reactivation is the withdrawal of cytotoxic therapy.^{5,19} This leads to enhanced viral replication that can then induce a rebound immune response (hyper-immune response), which leads to the destruction of hepatocytes.^{13,19}

There are a limited number of studies on the anti-HBs status of patients with resolved HBV infections who received immunosuppressive anticancer therapy.^{11,16,22-24} Of

those studies that do exist, almost all have focused on haematological malignancies, particularly NHL, in patients who received rituximab-based therapy.^{11,16,22} HBV reactivation occurred in five (23.8%) of 21 NHL patients who received rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), and the anti-HBs were negative before treatment in these five patients with HBV reactivation.¹¹ In this study, anti-HBs titres were not considered quantitatively.¹¹ Therefore, the absence of anti-HBs has been identified as a risk factor for HBV reactivation, in addition to the use of rituximab.

A previous study suggested that anti-HBs titres significantly decreased after rituximab-based therapy in B-cell lymphoma patients.²² The authors reported that anti-HBs titres were more likely to decline (< 10 mIU/ml) in patients with pretreatment anti-HBs titres of < 100 mIU/ml.²² In their study, eight of 19 patients with pretreatment anti-HBs titres of < 100 mIU/ml became negative for anti-HBs titres, and HBV reactivation developed in only one of these patients.²² In contrast, none of the 10 patients with pretreatment anti-HBs titres > 100 mIU/ml became negative for anti-HBs after rituximab-based therapy.²² The researchers concluded that a low pretreatment level of anti-HBs was an independent risk factor for the loss of anti-HBs and HBV reactivation in patients with resolved HBV infection receiving rituximab-based therapy.²²

The impact of chemotherapy on anti-HBs titres was studied in 75 patients with resolved HBV infections who had haematological malignancies.²³ The study reported that the anti-HBs titres significantly decreased after chemotherapy, especially in patients with acute leukaemia, male patients, and patients receiving intensive chemotherapy.²³ The findings of a prospective study conducted on patients with resolved HBV infections undergoing

rituximab-based therapy, suggested that the rate of HBV reactivation was significantly higher in anti-HBs negative patients when compared with anti-HBs positive patients.¹⁶ Another study reported that although there was an overall decrease in anti-HBs titres, none of the titres of the 43 patients with haematological malignancies who had resolved HBV infection became negative.²⁴

Consistent with these reports, the present study found that the anti-HBs titres of all the patients were significantly decreased after the therapy compared with before the therapy (a median 57 versus 71 mIU/ml, respectively; $P < 0.001$). The seronegativity rate of the anti-HBs titres post-treatment was significantly higher in the patients with pretreatment titres of < 100 mIU/ml than in those with pretreatment titres of ≥ 100 mIU/ml ($P < 0.001$). The subgroup analysis of the patients revealed that the increase in post-treatment anti-HBs seronegativity was greatest in the group with haematological malignancies. In contrast, it has been reported that HBV reactivation may occur in patients that are positive for anti-HBs.^{25,26} In a case report, a patient who had received R-CHOP presented with high titre levels that were positive for anti-HBs at the time of a fatal reactivation of HBV.²⁵ Additionally, in a prospective study conducted on patients who had received immunosuppressive or cytotoxic therapy, one patient out of eight that had developed a reactivation of HBV was positive for anti-HBs at the time of the reactivation of the virus.²⁶ According to both reports,^{25,26} these issues were associated with mutations in the HBsAg coding region (escape mutation).

Various studies have reported that the risk of HBV reactivation is increased in HBsAg positive patients undergoing cytotoxic chemotherapy for solid tumours.^{5,27-29} Other studies have reported that the prophylactic use of antiviral agents prior to chemotherapy in these patients may reduce levels of reactivation-related morbidity and

mortality.³⁰⁻³² The clinical data regarding resolved HBV infection rates are insufficient. In a French study that included both haematological malignancies and solid tumours, HBV reactivation occurred in seven of 84 HBsAg negative and anti-HBc positive patients, none of whom had solid tumours.³³ Consistent with the findings of that study, the present data demonstrated that the patients with solid tumours who were HBsAg negative, regardless of their anti-HBs and anti-HBc status, did not have a high risk of HBV reactivation.

In the present study, HBV reactivation occurred in three patients, and all three had haematological malignancies; chronic lymphocytic leukaemia, acute myeloblastic leukaemia-promyelocytic leukaemia, and multiple myeloma. HBV reactivation did not occur in any of the 22 patients that were administered rituximab-based therapy or in any of the 126 patients with solid tumours. Two patients had pretreatment anti-HBs of < 100 mIU/ml, and one patient had a value ≥ 100 mIU/ml. Two of these three patients were anti-HBc positive after the chemotherapy treatment, and one patient who had been anti-HBc positive prior to chemotherapy was negative after the treatment. One of the patients who had been HBsAg negative before the treatment was still negative after the treatment, whereas the other two patients were positive after the treatment. Despite the prompt treatment of all three patients, one of them died while the other two patients recovered in terms of HBV reactivation. According to the literature, the risk of reactivation is greater in men.^{5,11,34} However, in the present study, two of the three patients with HBV reactivation were women.

In accordance with the current literature,^{11,22-24} this present study found that chemotherapy decreased anti-HBs titres, particularly in those patients with haematological malignancies and those that had received rituximab-based chemotherapy. The present study investigated the

post-chemotherapy changes in anti-HBs titres not only in patients that had recovered from a previous HBV infection but also in those that had acquired anti-HBs seropositivity through vaccination. The present data show that chemotherapy results in a decrease in anti-HBs titres but that it increases the risk of reactivation in patients with haematological malignancies, especially those with pretreatment anti-HBs of <100 mIU/ml. Furthermore, the chemotherapy-induced decline in anti-HBs titres was more significant in the patients with resolved hepatitis B infections (i.e. anti-HBc positive patients) compared with that of the vaccinated patients (i.e. anti-HBc negative patients). These findings might be explained by possible pathophysiological differences between vaccination-induced versus HBV infection-related immunity.

This present study had a number of strengths and limitations. It included a large number of patients, demonstrated the effects of chemotherapy on anti-HBs titres in solid and haematological malignancies, and evaluated the changes in antibody positivity due to HBV vaccination and resolved HBV infection. However, the limitations included the retrospective nature of the study, the absence of HBV DNA data in some instances, and the heterogeneity of the chemotherapy regimens used to treat the malignancies.

In conclusion, consistent with the current literature on the subject,^{16,22,23} the results of the present study suggest that pretreatment low-level positivity of anti-HBs is a risk factor for becoming negative for anti-HBs, particularly in patients with haematological malignancies who have undergone immunosuppressive anticancer therapy. Moreover, high levels of anti-HBs may have a protective effect against the reactivation of HBV. When making a decision about prophylactic antiviral therapy, the patient's anti-HBs status and anti-HBs titre, together with their HBsAg and anti-HBc levels, should

be considered, particularly in high-risk patients such as HBV carriers, those who have occult or resolved HBV infection and patients receiving immunosuppressive anticancer therapy. However, further prospective trials are needed to clarify this issue.

Declaration of Conflicting Interests

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; 11: 97–107.
2. Liaw YF and Chu CM. Hepatitis B virus infection. *Lancet* 2009; 373: 582–592.
3. Mehmet D, Meliksah E, Serif Y, et al. Prevalence of hepatitis B infection in the southeastern region of Turkey: comparison of risk factors for HBV infection in rural and urban areas. *Jpn J Infect Dis* 2005; 58: 15–19.
4. Gurol E, Saban C, Oral O, et al. Trends in hepatitis B and hepatitis C virus among blood donors over 16 years in Turkey. *Eur J Epidemiol* 2006; 21: 299–305.
5. Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; 62: 299–307.
6. Lok AS, Liang RH, Chiu EK, et al. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991; 100: 182–188.
7. Sagnelli E, Pisaturo M, Martini S, et al. Clinical impact of occult hepatitis B virus infection in immunosuppressed patients. *World J Hepatol* 2014; 6: 384–393.

8. Chen WC, Cheng JS, Chiang PH, et al. A comparison of entecavir and lamivudine for the prophylaxis of hepatitis B virus reactivation in solid tumor patients undergoing systemic cytotoxic chemotherapy. *PLoS One* 2015; 10: e0131545.
9. Hwang JP, Vierling JM, Zelenetz AD, et al. Hepatitis B virus management to prevent reactivation after chemotherapy: a review. *Support Care Cancer* 2012; 20: 2999–3008.
10. Méndez-Navarro J, Corey KE, Zheng H, et al. Hepatitis B screening, prophylaxis and re-activation in the era of rituximab-based chemotherapy. *Liver Int* 2011; 31: 330–339.
11. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009; 27: 605–611.
12. Koo YX, Tay M, Teh YE, et al. Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis. *Ann Hematol* 2011; 90: 1219–1223.
13. Fukushima N, Mizuta T, Tanaka M, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. *Ann Oncol* 2009; 20: 2013–2017.
14. Ji D, Cao J, Hong X, et al. Low incidence of hepatitis B virus reactivation during chemotherapy among diffuse large B-cell lymphoma patients who are HBsAg-negative/HBcAb-positive: a multicenter retrospective study. *Eur J Haematol* 2010; 85: 243–250.
15. Hsu C, Tsou HH, Lin SJ, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. *Hepatology* 2014; 59: 2092–2100.
16. Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014; 32: 3736–3743.
17. Matsue K, Kimura S, Takanashi Y, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. *Cancer* 2010; 116: 4769–4776.
18. Artz AS, Somerfield MR, Feld JJ, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol* 2010; 28: 3199–3202.
19. Dong HJ, Ni LN, Sheng GF, et al. Risk of hepatitis B virus (HBV) reactivation in non-Hodgkin lymphoma patients receiving rituximab-chemotherapy: a meta-analysis. *J Clin Virol* 2013; 57: 209–214.
20. Xu L, Tu Z, Xu G, et al. Epirubicin directly promotes hepatitis B virus (HBV) replication in stable HBV-expressing cell lines: a novel mechanism of HBV reactivation following anticancer chemotherapy. *Mol Med Rep* 2014; 9: 1345–1350.
21. Wursthorn K, Wedemeyer H and Manns MP. Managing HBV in patients with impaired immunity. *Gut* 2010; 59: 1430–1445.
22. Pei SN, Ma MC, Wang MC, et al. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. *Ann Hematol* 2012; 91: 1007–1012.
23. Yağci M, Suyani E and Kizil Çakar M. The impact of chemotherapy on hepatitis B antibody titer in patients with hematological malignancies. *Turk J Haematol* 2015; 32: 251–256.
24. Francisci D, Falcinelli F, Schiaroli E, et al. Management of hepatitis B virus reactivation in patients with hematological malignancies treated with chemotherapy. *Infection* 2010; 38: 58–61.
25. Westhoff TH, Jochimsen F, Schmittl A, et al. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. *Blood* 2003; 102: 1930.
26. Tamori A, Hino M, Kawamura E, et al. Prospective long-term study of hepatitis B virus reactivation in patients with hematologic malignancy. *J Gastroenterol Hepatol* 2014; 29: 1715–1721.
27. Yeo W, Chan PK, Hui P, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a

- prospective study. *J Med Virol* 2003; 70: 553–561.
28. Kim MK, Ahn JH, Kim SB, et al. Hepatitis B reactivation during adjuvant anthracycline-based chemotherapy in patients with breast cancer: a single institution's experience. *Korean J Intern Med* 2007; 22: 237–243.
 29. Dai MS, Wu PF, Shyu RY, et al. Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. *Liver Int* 2004; 24: 540–546.
 30. Katz LH, Fraser A, Gafter-Gvili A, et al. Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. *J Viral Hepat* 2008; 15: 89–102.
 31. Yeo W, Ho WM, Hui P, et al. Use of lamivudine to prevent hepatitis B virus reactivation during chemotherapy in breast cancer patients. *Breast Cancer Res Treat* 2004; 88: 209–215.
 32. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; 148: 519–528.
 33. Borentain P, Colson P, Coso D, et al. Clinical and virological factors associated with hepatitis B virus reactivation in HBsAg-negative and anti-HBc antibodies-positive patients undergoing chemotherapy and/or autologous stem cell transplantation for cancer. *J Viral Hepat* 2010; 17: 807–815.
 34. Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004; 90: 1306–1311.