Hepatitis B Reactivation in HBsAg-negative/Anti-HBc-positive patients receiving cytotoxic chemotherapy for solid tumors

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Abstract:

***Purpose* : The prevalence of hepatitis B virus (HBV) reactivation in HBsAg-negative/anti-HBc-positive patients receiving chemotherapy for solid tumors is not fully known. The aim of this study was to investigate the incidence and outcomes of HBV reactivation in these patients.**

***Methods* : Data among 645 HBsAg-negative/ anti-HBc-positive patients who underwent intravenous chemotherapy were retrospectively analyzed. Patients were categorized into two groups, based on received antiviral prophylaxis (n = 43) or not (n = 602). HBV reactivation was defined as the presence of detectable serum HBV DNA or HBsAg seroconversion from negative to positive, with or without increased liver enzymes.**

***Results* : HBV reactivation was detected in 3 patients (0.49%) among non-antiviral prophylaxis group and in none of those with antiviral prophylaxis. Two of the HBV reactivation detected patients were successfully treated with rescue therapy, while the third died due to liver failure.**

***Conclusions* : HBV reactivation is rare in HBsAg-negative and anti-HBc-positive patients receiving chemotherapy for solid tumors. However, considering the fatal outcomes patients must be closely monitored in terms of HBV-DNA positivity and/or HBsAg seroreversion and pre-emptive antiviral therapy must be initiated as soon as HBV reactivation occurs.** (Acta gastroenterol. belg., **2020**, 83, **426-431**).

Key words : hepatitis B virus reactivation, solid tumours, prophylactic antiviral therapy, chemotherapy

Introduction

Hepatitis B virus (HBV) infection is one of the most important health problems worldwide. There are some 350 million chronic HBV carriers in the world, and serologically confirmed HBV infection is present in 30% of the global population (1,2). Hepatitis B surface antigen (HBsAg) positivity has been determined in 4% of the general population in Turkey, total hepatitis B core antibody (anti-HBc) positivity in 30.6%, and hepatitis B surface antibody (anti-HBs) positivity in 32% (3). Interaction between viral replication and the host immune response plays an important role in the natural course of HBV. Even if HBV infection has resolved entirely in individuals infected with HBV, the viral genomic structure remains in the hepatocyte nucleus of all infected patients (4,5). Patients infected with HBV, who are HBsAg positive and/or anti-HBc positive and receive chemotherapy or immunosuppressive therapy are therefore at risk of HBV reactivation and acute flare-up (6). Reactivation may occur during or after chemotherapy. HBV reactivation can cause chemotherapy to be delayed, and can sometimes result in fulminant liver failure, or even death (7,8).

The reported risk of HBV reactivation in patients with solid tumor receiving chemotherapy is about 4-68% (mean 25%), the risk of reactivation has a dependence on the chemotherapy regimen and hepatitis serology (6). The risk of reactivation is lower in patients receiving antiviral prophylaxis (0.9-31.4% [mean 4.1%]) (6). Since there is a high risk of HBV reactivation in patients receiving systemic chemotherapy and HBsAg positivity, the current guidelines recommend antiviral prophylaxis for these (9,10,11). However, limited data are available concerning the management of HBV and risk of reactivation in patients receiving chemotherapy due to solid tumor and, with resolved HBV infection (negative HBsAg, positive anti-HBc, variable anti-HBs, and negative HBV-DNA). Hence, the purpose of this study was to determine the incidence of hepatitis B reactivation in patients with resolved HBV infection undergoing chemotherapy for solid tumors. We also compared the results of patients receiving antiviral prophylaxis with those patients not receiving such prophylaxis.

Materials and Methods

Patients and data collection

Data from 4547 patients diagnosed with solid tumors and receiving intravenous cytotoxic chemotherapy between January 2012 and January 2017, at Karadeniz Technical University Medical Faculty, divison of medical oncology were retrospectively analyzed. Patients with concomitant hepatitis, C and D or HIV infection, isolated anti-HBs (+) with immunization, receiving immunosuppressive therapy other than chemotherapy, with known cirrhosis of the liver, or receiving antiviral therapy before chemotherapy were excluded from the study. Six hundred forty-five patients who were anti-HBc positive and HBsAg-negative at the start of chemotherapy were finally included. Demographic and

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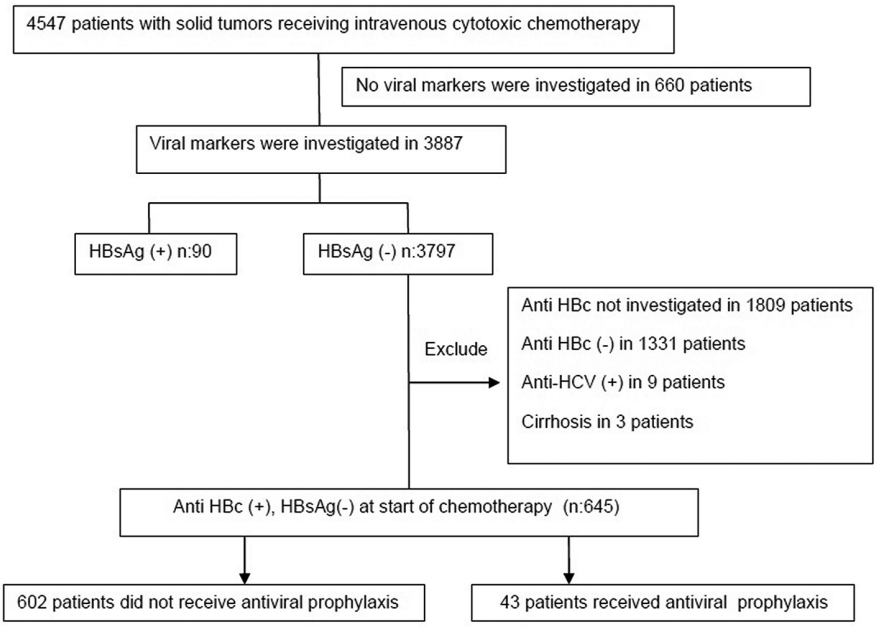

Abbreviations : HBsAg, Hepatitis B surface antigen ; anti-HBc, Hepatitis B core antibody ; Anti-HCV, Hepatitis C antibody.

Figure 1. — Study flow chart

clinical characteristics, applied chemotherapy regimens, hepatitis serology during and for at least six months after chemotherapy, and whether antiviral therapy was administered were evaluated from patients' records and laboratory record system. Patients with resolved HBV infection were divided into two groups, subjects who received antiviral prophylaxis and those who did not. A flow chart of the study population is given in Figure 1. The study was carried out in line with the principles of the Declaration of Helsinki and was approved by the local Ethical Committee (approval number: No. 2017/557).

Definitions

Hepatitis was defined as a three-fold greater increase in serum alanine aminotransferase (ALT) levels exceeding the upper limit of normal (ULN) 45 U/L for serum ALT. HBV reactivation-related hepatitis was defined as an increase more than one log higher than that of the baseline serum HBV DNA level, or serum HBV DNA turning from negative to positive, without evidence of hepatitis attributable to other causes, including viral hepatitis A, C, D, E and drug-induced liver disease. Acute liver failure was defined as sudden and severe impairment of liver function (with coagulopathy and hepatic encephalopathy). HBV reactivation was defined as the presence of detectable serum HBV DNA or HBsAg seroconversion from negative to positive, with or without increased liver enzymes (12,13).

Laboratory examinations

Routine biochemical parameters were assayed using a Roche Hitachi Cobas 8000 autoanalyzer (Roch, Germany) in a routine setting. Serum HBsAg, anti-HBs and anti-HBc levels were measured using electrochemiluminescence immunoassay on a Roche Cobas E601 device (Japan). Serum HBV DNA levels were measured using the real-time PCR method on a Roche Cobas AmpliPrep device (Japan) (lower limit of detection, 12 IU/mL).

Statistical analysis

Statistical analysis of the data obtained was performed using Statistical Package for Social Sciences 16.0 (SPSS Inc., Windows 16.0, Chicago, IL, USA) software. The results were expressed as mean, standard deviation, and percentage values. Categorical variables were analyzed using the chi square test, while the Mann Whitney *U* test was applied for variables for which mean values could be elicited. p values ≤ 0.05 were regarded as statistically significant for all tests.

Results

Baseline characteristics

Data regarding six hundred forty-five patients with solid tumors and a history of HBsAg-negative, anti-HBc-positive (anti-HBs positive or negative) serology before starting chemotherapy were analysed. The cohort was consisted of 344 men and 301 women, with a median age of 60 years. Six hundred two (93.3%) of these patients treated in this period did not receive antiviral prophylaxis and 43 (6.6%) were given antiviral prophylaxis. The basic demographic and clinical characteristics of the patients included in the study are shown in Table 1.

Table I. — **Patients' baseline demographic and clinical characteristics**

	Non-prophylaxis group (N=602) [n/N (%)]	Prophylaxis group (N=43) [n/N (%)]	p
Age [median (range)] (years)	60 (29-85)	59 (35-80)	0.544
Gender, male/female	322/280	22/21	0.926
Diagnosis			
Breast cancer	132 (21.9)	6 (13.9)	0.299
Lung cancer	124 (20.5)	7 (16.2)	0.628
Colorectal cancer	113 (18.7)	7 (16.2)	0.839
Gastric cancer	74 (12.3)	7 (16.2)	0.600
Gynecological Cancers	53 (9.7)	7 (16.2)	0.106
Urological cancers	38 (6.3)	3 (6.9)	0.748
Other gastrointestinal tract cancers*	44(7.3)	4 (9.3)	0.551
Others	24(3.9)	2(4.6)	0.689
Anti-HBs positive (%)	463/602 (77)	26/43 (60.4)	0.015
Hepatitis (%)	156/ 602 (25.9)	12/43 (27.9)	0.774
HBV-related hepatitis (%)	2 (0.33)	0	1.000
HBV reactivation (%)	3 (0.49)	0	1.000
Liver failure	1	0	1.000
Antiviral prophylaxis	** Tenofovir (2) ** Entecavir (1)	Entecavir (15) Lamivudine (4) Tenofovir (24)	
General mortality	199/602 (33)	14/43 (32.5)	0.946
HBV-related mortality (%)	1/602 (0.16)	0	1.000

Abbreviations : HBV, hepatitis B virüs ; anti-HBs, hepatitis B surface antibody. * Pancreatic cancer (37 patients). Esophageal cancer (11 patients). **As rescue antiviral treatment for HBV reactivation.

HBsAg and anti-HBs were monitored on a regular basis in the great majority of patients. Anti-HBs positivity was present before chemotherapy in 463 (463/602, 77%) of the patients not receiving antiviral prophylaxis and in 26 (26/43, 60.4%) of those receiving prophylaxis. Serum HBV-DNA levels were measured before chemotherapy in 20 (3.3%) patients who received no antiviral prophylaxis, and in 15 (34.8%) of patients who had received prophylaxis and HBV-DNA was negative in these patients. Hepatitis was diagnosed in 156 (156/602, 25.9%) of the patients in the non-prophylaxis group and in 12 (12/43, 27.9%) of the prophylaxis group. The hepatitis developed in two patients in the non-antiviral prophylaxis group was regarded as HBV-related. No HBV-related hepatitis was observed in the group receiving antiviral prophylaxis.

Characteristics of Cases Developing HBV Reactivation

HBV reactivation was determined in only three (0.49%) of the 645 patients who received chemotherapy for solid tumors in the study. These three patients were in the group who did not received antiviral prophylaxis.

Case 1 : The first patient developing reactivation was a 46-year-old woman with adenocarcinoma of the colon. This patient received FOLFIRI combination chemotherapy (irinotecan 180 mg/m² (288 mg), leucovorin 400 mg /m² (640 mg), fluorouracil 400 mg /m² (640 mg)) + bevacizumab 5 mg /kg (335 mg) due to peritoneal carcinomatosis and hepatic metastases. At the start of chemotherapy, her values were HBsAg(-), anti-HBs (-), anti-HBc-IGG (+), ALT : 9 U/L, AST : 15 U/L, INR : 1,07 and total bilirubin: 0.8 mg/dl. Viral marker and HBV-DNA monitoring were not performed during chemotherapy. One month after receiving six courses of chemotherapy her values were HBsAg(+), anti-HBs (-), ALT : 266 U/L, AST : 103 U/L, INR : 1,52, total bilirubin: 6.3 mg/dl and HBV-DNA : 276,000,000 IU/ml. This was interpreted as reactivation, and entecavir therapy was initiated. Disease progression was subsequently observed, the dosage was reduced and chemotherapy was maintained. However, generally impaired condition and hepatic encephalopathy developed on the sixth month of antiviral therapy. Shrinking in the hepatic metastases was observed at abdominal tomography. No metastasis was observed at cerebral tomography. The patient's test results in this period were total bilirubin: 19.5 mg/dl and ammonia: 137 umol/L, and the patient died due to liver failure.

Case 2 : The second patient who developed HBV reactivation was a 57-year-old man with high-grade glial tumor. The patient received adjuvant radiotherapy to the brain for one month, and was operated due to recurrence. Following surgery, the patient was started on antiedema therapy in combination with temozolomide (300 mg/5 days). Findings at the start of chemotherapy were HBsAg (-), anti-HBs (+), antiHBc-IGG (+), ALT : 16 U/L, and AST: 12 U/L. Following three courses of temozolomide, irinotecan 125 mg/m² (240 mg) + bevacizumab 10 mg/kg (700 mg) chemotherapy was initiated due to disease progression. Test results after the first course of chemotherapy were HBsAg (+), anti-HBs (+), ALT : 19 U/L, AST : 18 U/L, and HBV-DNA (-). These were

Table 2. — **Clinical outcomes of patients developing HBV reactivation**

Subject	1	2	3
Age (years)	46	57	79
Sex	F	M	F
Diagnosis	Adenocarcinoma of the Colon	High Grade Glial Tumor	Adenocarcinoma of the Pancreas
Chemotherapy regimen	FOLFIRI + Bevacizumab	3 courses temozolomide + anti-edema treatment then bevacizumab + irinotecan	Gemcitabine
Cycles of chemotherapy	6	8	4
Baseline ALT (U/L)	9	16	19
Baseline HBV DNA (IU/ml)	?	?	?
Initial HBV status HBsAg/anti-HBs/anti HBc-IGG	-/-/+	-/+/+	-/-/+
Timing of HBV reactivation (month)	7	4	3
HBV status during HBV reactivation HBsAg/anti-HBs/anti HBc-IGG	+/ - /+	+/+/+	+/ - /+
HBV DNA level during HBV reactivation (IU/ml)	276000000	negative	3200
ALT level during HBV reactivation (U/L)	266	19	545
Rescue treatment	Entecavir	Tenofovir	Tenofovir
Hepatic failure	Yes	No	No
Outcome	Died due to hepatic failure	Survived	Died due to disease progression

Abbreviations : HBV, hepatitis B virüs ; HBsAg, hepatitis B surface antigen ; anti-HBs, hepatitis B surface antibody ; anti HBc, hepatitis B core antibody ; ALT, serum alanine aminotransferase ; FOLFIRI, fluorouracil + irinotecan.

interpreted as HBV reactivation, and tenofovir therapy was initiated. Chemotherapy was maintained without interruption during reactivation, and seven courses of bevacizumab and irinotecan combination chemotherapy were added. HBsAg seroconversion developed on the fourth month of antiviral therapy.

Case 3 : The third patient who developed HBV reactivation was a 79-year-old woman with pancreas cancer. Following pancreatic surgery, she was started on adjuvant gemcitabine 1000 mg /m² (1400 mg) chemotherapy. Her pre-chemotherapy test results were HBsAg (-), anti HBs (-), anti HBc-IGG (+), ALT: 19 U/L, and AST: 20 U/L. Her test results after three courses of chemotherapy were HBsAg (+), anti HBs (-), ALT: 545 U/L, AST: 719 U/L, total bilirubin: 0.4 mg/dl, and HBV-DNA: 3200 IU/ml, and these were interpreted as reactivation, and tenofovir therapy was initiated. Results on the third month of antiviral therapy were HBsAg (-), anti-HBs (+) and HBV-DNA (-). However, the patient died due to progression of pancreatic cancer three months after receiving four courses of chemotherapy.

The clinical characteristics and laboratory data for the patients who developed HBV reactivation are summarized in Table 2.

Discussion

The European Association for the Study of the Liver (EASL) recommends antiviral prophylaxis before chemotherapy in the event of a high risk of HBV reactivation (detectable HBV-DNA, drug use causing B lymphocyte depletion, stem cell transplantation) in patients with serological evidence (negative HBsAg, positive Anti-HBc) of previous HBV infection and scheduled for chemotherapy due to solid tumor. Patients who are not started on antiviral prophylaxis at the beginning of chemotherapy must be monitored at 1-3-month intervals in terms of HBV-DNA positivity and/or HBsAg seroreversion. Antiviral prophylaxis should be started in the event that HBV-DNA positivity or HBsAg seroreversion are observed in these patients. However, prophylaxis rather than pre-emptive treatment is recommended in patients receiving long-term immunosuppression or who cannot be closely monitored in terms of HBV-DNA or HBsAg seroreversion (9). However, in our study HBV-DNA was assessed at the start of chemotherapy in only 3.3% of patients in the group not receiving antiviral prophylaxis, compared to 34.8% in the prophylaxis group. On the other hand, HBV-DNA monitoring was not performed at appropriate intervals in the great majority of patients whose with basal HBV-DNA assessment.

HBV reactivation is well known in patients with HBsAg negative and anti-HBc positive serology undergoing bone marrow transplantation and receiving chemotherapy for hematological cancers (14,15). However, the prevalence of HBV reactivation and antiviral prophylaxis requirements in patients receiving chemotherapy for solid tumor are still unclear. The number of patients diagnosed with solid tumors are continually rising in parallel with improvements in diagnostic methods, and several novel chemotherapeutic agents are entering into use in the treatment of these patients. It is therefore of great importance to know the prevalence and characteristics of HBV reactivation. Our study reflects real life experience in patients with solid tumors with serological evidence of past HBV infection. To the best of our knowledge, our study represent the highest number of patients from this group. HBV reactivation developed in only three patients (0.49%) not receiving antiviral prophylaxis in our study,

and no reactivation was observed in any patient receiving antiviral prophylaxis. Two patients who developed HBV reactivation were successfully treated with rescue therapy, while one died due to liver failure. In their study of 321 HBsAg negative and anti-HBc positive patients with solid tumor and 354 patients with hematological malignity, Kim *et al.* (16) reported HBV reactivation in only one patient (0.3%) with solid tumor. That was similar to the HBV reactivation rate in our study. However, in their prospective study involving 27 solid tumor patients with previous HBV infection, Hagiwara *et al.* reported HBV reactivation in the first month of chemotherapy in two patients (7.4%). The reactivation rate in that study involving a low number of patient was much higher than that in our study. Serum HBV-DNA was measured once monthly during chemotherapy in order to monitor HBV reactivation in that study. No flare-up of hepatitis was observed in two patients developing reactivation, and these were successfully treated with entecavir rescue therapy (17). One case report described how a patient with HBV infection and adenocarcinoma of the rectum developed HBV reactivation following a bevacizumab, fluorouracil and irinotecan chemotherapy regimen, and reported that despite subsequently receiving entecavir therapy the patient died due to liver failure (18). Thus, very few studies have investigated HBV reactivation in solid tumor patients with past HBV infection, and the results from these are inconsistent. Prospective studies involving larger number of patient are now clearly needed in order to determine the prevalence of reactivation in this patient group.

The risk of HBV reactivation in hematological malignity patients with serological evidence of previous HBV infection is higher in subjects who are anti-HBs negative before chemotherapy than in those who are anti-HBs positive (16,19,20). To the best of our knowledge, there are no previous studies showing that anti-HBs positivity in solid tumor patients decreases the risk of HBV reactivation. HBV reaction developed in two (1.43%) (cases 1 and 3) of the 139 patients who were anti-HBs (-) before chemotherapy, and clinical hepatitis and serum HBV-DNA positivity was determined in both. However, reactivation was observed in one (0.2%) (case 2) of the 463 patients who were anti-HBs (+) before chemotherapy, and no clinical hepatitis and serum HBV-DNA positivity was determined in that patient, despite development of HBsAg seroreversion. This finding suggested that anti-HBs positivity before chemotherapy can reduce both the risk of HBV reactivation and hepatitis flare-up in solid tumors, as in hematological malignities.

The risk of HBV reactivation is significantly lower in patients with resolved HBV infection compared to HBsAg-positive patients (8,21). In addition, since anti-HBc positivity is much more common in the general population than HBsAg positivity, patients with resolved HBV infection must not be overlooked (3). However, to the best of our knowledge, no previous studies have compared subjects with antiviral prophylaxis and those not receiving it in terms of HBV reactivation in solid tumor patients with resolved HBV infection. We performed such a comparison, and no HBV reactivation was observed in patients receiving antiviral prophylaxis. HBV reactivation was observed at a very low level in patients not receiving prophylaxis (0.49%). This finding suggests that pre-emptive therapy will be appropriate in this patient group, as recommended in the treatment guidelines (9).

The best way to prevent chemotherapy-induced HBV reactivation is to screen for HBV before chemotherapy and initiate antiviral prophylaxis in appropriate patients. To reduce chemotherapy-induced HBV reactivation, it is necessary to increase the awareness of HBV reactivation among doctors who apply chemotherapy. In recent years, a computer warning program has been used to increase HBV screening rates before initiation of chemotherapy (22,23). In a study which included the patients receiving biological therapy conducted by Sampedro *et al*.showed that screening rates for HBsAg and HBcAb increased from 50% to 94%, and from 30% to 85% respectively, by the use of an alarm system before treatment (22). Recently, Köksal *et al*. reported that HBsAg and anti-HBc IgG screening rates increased by 65.8% and 5.1%, respectively, in oncology patients receiving chemotherapy using the computer alert program (23).

There are some limitations to this study. The most important of these is its retrospective nature. The diagnoses and chemotherapy regimens of the patients therefore differed widely. In addition the numbers of patients given and not given prophylaxis also differed significantly. Another important limitation is that HBV-DNA and other viral serological markers were not monitored on a regular basis.

In conclusion, our study shows that HBV reactivation is rare in patients with resolved HBV infection receiving cytotoxic chemotherapy for solid tumor. However, since reactivation in these patients could have fatal consequences, patients should be monitored closely (every 1–3 months) in terms of HBV-DNA positivity and/or HBsAg seroreversion, and rescue antiviral therapy must be initiated as soon as HBV reactivation occurs.

Conflict of interest

The authors declare that they have no conflict of interest.

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