

Research Article

Anthracycline-Induced Hepatitis B Reactivation in Solid Organ Cancers: A Multicenter Study

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Abstract

Objectives: Hepatitis B reactivation is extremely rare in HBsAg-negative/Anti-HBcIgG-positive patients receiving chemotherapy for solid organ cancer in our current practice. In our study, we aimed to investigate the frequency of reactivation and associated risk factors in patients with solid tumors receiving anthracycline-based chemotherapy.

Methods: In the study, the records of 3147 patients with solid tumors receiving anthracycline chemotherapy were examined retrospectively. HBsAg negative/Anti-HBcIgG positivity was detected in 196 (6.2%) of the patients.

Results: Elevated liver enzymes were found in 45 patients, with the identified causes being adverse effects of chemotherapeutics in 18 (9.1%), liver metastasis in 11 (5.5%), use of antibiotics and analgesics in 7 (3.6%), herbal medications in 7 (3.6%), and Hepatitis B reactivation in 2 (1%) patients. Patients who developed Hepatitis B reactivation had Rheumatoid Arthritis and Systemic Lupus Erythematosus, and were on steroids.

Conclusion: In our study, the rates of hepatitis B reactivation after anthracycline chemotherapy in HBsAg negative/Anti-HBcIgG positive solid tumor patients were found to be lower than those reported in the literature. Our results suggest that prophylactic strategies for hepatitis B reactivation should be repeatedly considered in this group of patients.

Keywords: Antiviral prophylaxis, hepatitis b virus, hepatic reactivation, solid malignancies

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Hepatitis B virus (HBV) is a global health problem. It is estimated that approximately 2 billion people worldwide are exposed to this virus during their lifetime, and an estimated 250 million of them develop chronic HBV infection.^[1] The global prevalence of HBV is estimated to be approximately 3.2%, despite the large-scale HBV vaccination efforts carried out by the World Health Organization with the goal of HBV elimination and the increase in access to antiviral treatments for people infected with chronic HBV.^[2]

Currently, there are potent antiviral therapies developed for HBV. However, complete cure still remains to be achieved due to the natural replication process of the HBV virus.

HBV is a hepatotropic virus. The HBV genome and its replication are quite unique and the conversion of the relaxed circular DNA (rcDNA) to the more stable covalently closed circular DNA (cccDNA) is critical in the course of infection.^[3] Despite serologic clearance (disappearance of HBsAg and appearance of anti-HBc) years after acute infection, cccD-

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NA persists in the host hepatocyte nuclei.^[4] In the presence of a condition (immunosuppressive disease or treatment) that suppresses immune control of the virus, persistent cccDNA is a potential reservoir for virus replication.^[2] HBV reactivation essentially refers to the initiation of the viral replication process in HBsAg-positive or HBsAg-negative/Anti-HBcIgG-positive individuals, characterized by loss of control of the virus by the immune system, increase in basal HBV DNA, and elevated liver enzymes.^[5]

Although HBsAg-negative/Anti-HBcIgG positive patients are more prevalent than HBsAg-positive patients, the risk of HBVr is approximately eight-fold greater in HBsAg-positive patients than in HBsAg negative/Anti-HBcIgG positive patients.^[6] Factors determining the risk of HBVr include type of malignancy, viral serology, mutant subgroups of the virus, HBV-DNA level, and type of chemotherapeutic drug, as well as inflammatory and autoimmune diseases. HBsAg-positive patients undergoing organ or bone marrow transplantation and those with hematopoietic malignancies are in the high-risk group for HBVr, whereas patients with solid organ malignancies are considered to have intermediate risk.^[7]

The risk of HBVr in solid organ malignancies varies according to the chemotherapeutic agents used.^[8] For example, drugs affecting the number and function of T- and B-lymphocytes are in the high-risk group (reactivation risk >10%) in HBsAg-negative/Anti-HBcIgG-positive hematologic malignancies and bone marrow transplant recipients, whereas they are in the intermediate risk group (reactivation risk 1-10%) in solid organ malignancies. In solid organ malignancies, anthracycline-based drugs are defined in the American Gastroenterological Association Institute (AGA) guidelines, whereas the risk of HBVr with other chemotherapeutic agents (e.g. fluorouracil, platin and taxanes) has not been clearly defined.^[9] Anthracyclines (doxorubicin, daunorubicin, epirubicin and idarubicin) are chemo-therapeutic agents that inhibit the enzyme topoisomerase 2 by interrupting cell division and causing the death of cancer cells. In solid organ tumors, particularly breast cancer, doxorubicin and epirubicin are preferred. Doxorubicin induces apoptosis of peripheral human lymphocytes in vitro and depletion of mouse T- and B-cells in vivo.^[10] In addition to their immunosuppressant effects, doxorubicin and epirubicin stimulate HBV replication in hepatocyte cells.^[11] Anthracycline group drugs are included in the intermediate risk group in HBsAg-negative/Anti-HBcIgG positive patients in current guidelines.^[9] Studies involving anthracyclines are mostly in patients with hematologic malignancies and bone marrow transplantation, and studies in solid organ cancers are scant. Even though anthracyclines are used in solid organ cancers, HBVr is extremely rare in studies.^[12]

In our study, we aimed to investigate the prevalence of HBVr in HBsAg-negative/Anti-HBcIgG-positive patients with solid organ malignancy receiving anthracyclines.

Methods

Characteristics of the Patients

Our study was performed retrospectively by examining the medical records of patients diagnosed with breast cancer or soft tissue sarcoma between 01.01.2015 and 01.06.2020 from three centers. HBsAg-negative/Anti-HBcIgG positive patients treated with adjuvant and neoadjuvant anthracycline-based chemotherapeutics were included. Laboratory values of those who were followed up for at least 12 months during and after treatment were recorded. Exclusion criteria included patients with metastases at the beginning of treatment (excluded due to difficulties in monitoring liver function tests and in HBVr differentiation), receiving immunosuppressants, having an additional hematologic malignancy, being tested positive for HBsAg, Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV).

Patients' age, gender, cancer type, cancer stage, cancer subtype, type of adjuvant-neoadjuvant therapy, chemotherapy regimen, HBV-DNA level, antiviral use for prophylaxis and its duration, number of chemotherapy administrations, medications taken with chemotherapy or during the follow-up period were recorded. Serum levels of glutamic oxaloacetic transaminase (SGOT or AST), serum glutamate pyruvate transaminase (SGPT or ALT) and international normalized ratio (INR) were examined as liver function tests. Laboratory tests (HbsAg positive/negative, HBV-DNA level), radiological imaging studies (metastasis status and diagnostic ultrasound-guided liver biopsy in non-metastatic patients), use of antiviral therapy, other medications, and herbal products were recorded in patients with elevated liver enzymes.

Definition of HBV Reactivation

Liver damage may result from HBVr and range from asymptomatic increase in the levels of other liver enzymes, particularly alanine aminotransferase (ALT), to acute liver failure.^[13]

HBV reactivation in laboratory; HBsAg or HBeAg positivity is defined as a detectable increase in HBV DNA and serum ALT levels by three times or more which exceeds 100 IU/l in patients with no other cause of liver damage.^[15]

Chemotherapy Protocols

Patients receiving CA (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²), FAC (fluorouracil 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m² every 3

weeks), TAC (doxorubicin 50 mg/m², cyclophosphamide 500 mg/m², cyclophosphamide 500 mg/m² every 3 weeks), IMA (doxorubicin 30 mg/m² on days 1 and 2, ifosfamide 2000 mg/m² on days 1 to 5, mesna 400 mg/m² ×3 on days 1 to 5 every 3 weeks) and single-agent adriamycin (doxorubicin 75 mg/m² every 3 weeks) treatment protocols were included.

Statistical Analysis

The study data were analyzed using SPSS (Statistical Package for Social Sciences) 22.0 package program. For descriptive analyses, frequency data were expressed as number (n) and percentage (%). Survival rates were examined by Kaplan-Meier analysis.

Results

A total of 3147 patients receiving anthracyclines which were registered in our hospital's database were examined. Of the patients, 151 (4.8%) were found to be HBsAg-positive and 196 HBsAg-negative/Anti-HBc IgG-positive. All patients had used doxorubicin. There were 180 (91.8%) breast cancer and 16 (8.2%) sarcoma patients in the study. The median age was 53.1 years, with 5.1% being male and 94.9% female. The median follow-up duration was 30.9 months. The characteristic features of the patients are given in Table 1. The number of patients with negative Anti-HBs was 2 (1%), that of those with positive Anti-HBs 194 (99%). Only 59 (30.2%) patients had been checked for HBV-DNA levels before chemotherapy. HBV-DNA levels were found to be negative in all of these patients. It was determined that 39 (19.9%) of the patients in our study received antiviral prophylaxis. No hepatitis exacerbation was found in patients receiving prophylaxis.

The mean duration of post-treatment liver enzyme follow-up was 16 months. Liver enzyme elevation was found to be more than 3 times higher than the upper limit of normal in 45 (23%) patients during chemotherapy and follow-up. The characteristics of the 45 patients with elevated liver enzymes are given in Table 2. Liver biopsy was performed in 15 patients with elevated liver enzymes; liver metastasis was detected in 11 patients, toxic hepatitis due to herbal treatment in 3 patients, and hepatitis B-induced fibrosis in 1 patient (biopsy performed in a patient with systemic lupus erythematosus). Of 45 patients with elevated liver enzymes, liver dysfunction due to HBVr and HbsAg positivity was found in 2 (1%).

Both patients with HBVr had received high-dose steroids due to rheumatologic/inflammatory diseases in addition to cancer. In the first patient, steroid use due to hand joint involvement of rheumatoid arthritis (RA) was detected

Table 1. General characteristics of patients

	Breast, n (%)	Sarcoma, n (%)
Number of patients (total n:196)	180 (91.8)	16 (8.2)
Age (years)	47.8	60.5
BMI (kg/m ²)	26.1	23.8
Gender		
Female	178 (90.8)	8 (4.1)
Male	2 (1)	8 (4.1)
Comorbidity		
Yes	32 (16.3)	11 (5.6)
None	148 (75.5)	5 (2.6)
ECOG PS		
ECOG 0	177 (90.3)	15 (7.6)
ECOG 1	3 (1.5)	1 (0.6)
Sarcoma subtypes		
Liposarcoma	6 (37.5)	
Leiomyosarcoma	5 (31.3)	
Alveolar Rhabdomyosarcoma	2 (12.5)	
Angiosarcoma	2 (12.5)	
Sarkomatoid Renal cell carcinoma	1 (6.2)	
Breast cancer subtypes		
Luminal A	70 (38.9)	
Luminal B, Her-2-negative	42 (23.3)	
Luminal B, Her-2-positive	19 (10.5)	
Her-2 overexpression	25 (14)	
Triple Negative	24 (13.3)	
Cancer stage	Breast Cancer n (%)	Sarcoma n (%)
Stage		
1	10 (5.5)	-
2	64 (35.6)	4 (25)
3	106 (58.9)	12 (75)
Treatment status	Breast Cancer n (%)	Sarcoma n (%)
Adjuvant	107 (59.4)	14 (87.5)
Neoadjuvant	73 (40.6)	2 (12.5)
Chemotherapy regimens	Breast Cancer n (%)	Sarcoma n (%)
CA	177 (90.3)	-
Adriamycin	-	2 (1)
FAC	2 (1)	-
IMA	-	14 (7.2)
TAC	1 (0.5)	-

Body Mass Index (BMI); Eastern Cooperative Oncology Group Performance Status (ECOG); Adriamycin and Cyclophosphamide (CA); Cyclophosphamide, Adriamycin and Fluorouracil (FAC); Ifosfamide, Adriamycin and Mesna (IMA); Docetaxel, Adriamycin and Cyclophosphamide (TAC).

Table 2. Elevated liver function tests and etiology		
	Breast cancer n (%)	Sarcoma n (%)
Liver function test (LFT) abnormality		
Times the normal		
3-10	34 (17.3)	2 (1)
10-20	8 (4)	-
Over 20	1 (0.5)	-
Etiology of elevated LFT		
Adverse effect of chemotherapeutics	16 (8.1)	2 (1)
Cancer progression (liver metastases)	8 (4)	3 (1.5)
Use of antibiotics/analgesics	7 (3.6)	-
Herbal medicine	6 (3)	1 (0.5)
Hepatic flare	2 (1)	-
Liver function test (LFT).		

during the 4th cycle of CA (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²) chemotherapy (treatment was initiated 3 months before due to RA and he was receiving methylprednisolone treatment at a dose of 32 mg/day). In the other patient, steroid use due to lupus nephritis was detected 1 month after the completion of CA chemotherapy (1 g/day methylprednisolone for 3 days, using 64 mg/day methylprednisolone in maintenance treatment, on the 50th day of steroid treatment).

HBV-DNA level was checked in 32 of 45 patients with elevated liver enzymes and HBV DNA level was found to be elevated in 2 patients (HBV-DNA copy of 20.000IU/ml in RA patient and 36.000 IU/ml in SLE patient). Tenofovir disoproxil (245 mg/day) was started for these two patients who had hepatitis exacerbation. Liver function tests of the RA patient improved with palliative treatment and tenofovir disoproxil (with a treatment duration of 45 days) and the treatment regimen was switched (paclitaxel and carboplatin). The SLE patient underwent plasmapheresis and dialysis with tenofovir disoproxil, but deceased (7-month survival after initiation of anthracycline therapy).

Discussion

Hepatitis B reactivation is a potentially life-threatening risk for those with hematologic malignancies who will receive chemotherapy, with rates ranging from 14-72% between studies.^[8] However, HBVr reported for solid organ cancers is much rarer. However, although it depends on the chemotherapy regimens administered, it is reported that HBVr in HBsAg-negative/Anti-HBcIgG positive patients is not as high as that seen in HBsAg-positive patients. Therefore, screening for HBV is important for patients who will receive systemic chemotherapy. In addition, most of the high HBVr

rates reported in the literature belong to studies carried out with patients with hematologic malignancies or HBsAg seropositive cancer patients.^[15] The frequency and risk factors of HBVr in patients receiving chemotherapy for solid organ cancer are not well defined. Specific studies evaluating HBVr in anthracycline use in HBsAg-negative/Anti-HBc IgG-positive solid organ cancers are scant with limited number of patients. There are no multicenter studies with a large number of patients regarding the effect of anthracyclines in neoadjuvant and adjuvant periods in solid organ cancers. In our study, only breast and sarcoma cancer patients receiving adjuvant and neoadjuvant anthracycline treatment were included.

In our study, HBVr was extremely rare in the HBsAg-negative/Anti-HBc IgG-positive patient group with anthracycline use. Both patients who developed reactivation had concomitant rheumatologic diseases and steroid use. There were no significant differences in terms of disease stage, adjuvant/neoadjuvant use, age, gender, ECOG performance status, sarcoma subtype, hormone receptor (ER, PR) status, and Her2 receptor status for HBVr.

In current guidelines, there are two different suggestions for HBsAg-negative/Anti-HBc IgG-positive patients. Some of the important global reference guidelines recommend prophylaxis,^[9,16-17] while others do not recommend prophylaxis, follow-up and/or prophylaxis in case of hepatic exacerbation.^[5,18,19,20] Guidelines recommending prophylaxis suggest starting prophylaxis before treatment and continuing by 6-12 months after treatment.^[9,16-17] Guidelines recommending follow-up without prophylaxis recommend monitoring patients with ALT, HBsAg and HBVDNA levels every 1-3 months.^[5,18-20]

In the American Gastroenterological Association Institute (AGA) guidelines, HBsAg-negative/Anti-HBc IgG-positive patients are included in the intermediate risk group. It recommends the use of antiviral prophylaxis (up to 6 months after treatment discontinuation) instead of monitoring for intermediate-risk patients to be treated with anthracycline-based regimens.^[9]

Preclinical studies have reported direct stimulation of HBV replication and gene expression by steroids.^[21] It is known that 2 of our patients with HBVr were also receiving steroids. Our data suggested that steroid dose is a more important factor than chemotherapy regimen in HBV reactivation in patients with solid tumors. The results of the study by Kotake et al. evaluating the risk of HBVr in solid cancer patients are similar to those of our study.^[22] In the aforementioned study, HBVr rate was 2.1% and low anti-HBs antibody titer (<10.0 mIU/mL) and daily high-dose corticosteroid treatment (>1.0 mg/kg/day) were revealed

to be important high-risk factors. Furthermore, it was observed that the patients included in the study were comprising a heterogeneous study group with various cancer types (respiratory, gastrointestinal, gynecological tumors) and different cancer treatments (anthracycline- and platinum-based).

American Association for the Study of Liver Diseases (AASLD) guideline reported that HBsAg-negative/Anti-HBcIgG-positive patients (excluding patients receiving anti-CD20 antibody therapy or stem cell transplantation in whom anti-HBV prophylaxis is recommended) can be carefully monitored with optional ALT, HBV DNA and HBsAg.^[5] In The American Society of Clinical Oncology (ASCO) guideline recommends follow-up with HBsAg and ALT tests every 3 months in solid organ cancers and initiation of antiviral treatment only if HBsAg becomes positive or HBV DNA exceeds 1,000IU/mL in hepatitis exacerbation.^[18] In the Asian Pacific Association for the study of the liver (APASL) guidelines, the use of anthracyclines in HBsAg-negative and antiHBc-positive solid cancer patients is included in the intermediate risk group and prophylaxis is recommended in this group.^[16]

Day et al. reported that pre-chemotherapy HBV screening in all patients was not cost-effective for patients with solid tumors according to current guidelines.^[23] Nevertheless, HBV reactivations have been reported in patients with low anti-HBs titers and those receiving high-dose steroid therapy. Although HBVr is rare in patients with solid tumors, studies have reported that appropriate screening and follow-up for HBV prevent the development and reduce the severity of hepatitis.

In a review by Cholongitas et al. analyzing 55 studies, 3640 HBsAg-negative/Anti-HBc IgG-positive patients were included and the HBVr rate was found to be 10.9% in patients with hematologic malignancies and 3.6% in non-hematologic patients.^[6] In this study, non-hematologic diseases included rheumatic diseases (975 patients), solid cancers (114 patients), gastrointestinal diseases (ulcerative colitis and chron's disease) (105 patients), dermatologic diseases (88 patients) and miscellaneous diseases (67 patients). Solid cancer patients constitute a small proportion of the total population (<10%). In our study, the number of patients with solid cancer was 196 and our patient group was comprised of a more homogeneous population including breast cancer and sarcomas. In the study by Cholongitas et al. HBVr was detected in 3.6% of non-hematologic patients, whereas it was 1% in our study. Cholongitas et al. do not recommend prophylaxis in non-hematologic patients and in patients with solid organ cancer excluding rituximab treatment; they recommend prophylaxis in case of hepatic

exacerbation or when HbsAg becomes positive and HBVDNA level is detectable. Our study results suggest that it is important to start antiviral prophylaxis early in solid cancer patients receiving anthracycline chemotherapy in the presence of autoimmune-rheumatologic diseases or in cases where high-dose steroids are required for any reason.

In the study by Araz et al., 38 HBsAg-negative/Anti-HBc IgG-positive breast cancer patients receiving anthracycline therapy were included and no reactivation was detected during follow-up, without any antiviral prophylaxis given.^[12] In a study by Kim et al. involving a larger patient group, 675 HBsAg-negative/Anti-HBc IgG-positive patients were included, 321 (47.6%) of whom had solid organ cancer. All chemotherapeutics were included in the study and HBV reactivation was reported in 1 (0.3%) patient with solid organ cancer.^[24] In the study by Ling et al. 1149 patients without HBV screening in solid organ cancers were included, CA/FAC chemotherapy was administered to 434 patients, 363 patients received as adjuvant treatment, with no patient receiving neoadjuvant treatment. In this study, 220 patients were screened for HBV, 6 of which were found to be HbsAg-positive and started prophylaxis, and 214 patients were not screened for HBV. While no reactivation was observed in the screened group, 3 patients (1.4%) in the unscreened group developed HBVr, 1 of which deceased.^[25] In our study, adjuvant and neoadjuvant patients who were HBsAg-negative/Anti-HBc IgG-positive were included as a separate group. Of our patients, 75 (38.2%) received neoadjuvant CA treatment, and 73 (37.2%) of them, especially those received for breast cancer, were included in our study. Similarly, HBVr rate was 1% in our study.

In the study by Takahashi et al. HBVr was detected in hematologic malignancies by the 12th month and within first 12 months in solid organ malignancies.^[26] In our study, two of our patients with HBVr (RA patient at month 3 and SLE patient at month 6) were diagnosed within first 12 months. The relatively small patient population and retrospective design are the most important limitations of our study. In addition, the lack of baseline HBV-DNA levels in a significant proportion of patients is another limitation.

Considering the low HBVr rates found in our study, we are in thought of that prophylactic antiviral treatment in patients with solid tumors receiving anthracycline may increase additional costs and side effects, and that patients can be followed up with appropriate screening tests without prophylaxis. We also think that in the presence of conditions that may increase the risk of HBVr, including autoimmune diseases, high-dose or long-term steroid use, antiviral prophylaxis should be given if anthracycline-based chemotherapy is to be administered. In order to determine the groups to

receive hepatitis B prophylaxis in HBsAg-negative/Anti-HBc IgG-positive solid tumor patients; larger, comparative and prospective multicenter studies with additional risk factors and chemotherapy type-specific guidelines are required.

Disclosures

Ethics Committee Approval: This study was approved by the Necmettin Erbakan University Research Ethics Committee [protocol number: 2021/3003, permission date: January 8, 2021].

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