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Reactivation risk of Hepatitis B Virus in both HBsAg negative and HBcIgG positive patients with solid malignancy. Is antiviral prophylaxis really necessary?

Murat Araz[1], Ismail Beypinar[2], Tarik Demir[3], Hacer Demir[2], Mukremin Uysal[2]

[1]Necmettin Erbakan University, Faculty of Medicine, Department of Medical Oncology, Konya, Turkey
[2]Afyon Health Sciences University, Faculty of Medicine, Department of Medical Oncology, Afyonkarahisar, Turkey
[3]Bezmialem Vakif University, Department of Medical Oncology, Istanbul, Turkey

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Abstract

Prophylactic antiviral treatment is controversial due to a lack of studies in both HBsAg negative/HBcIgG positive patients who treated conventional chemotherapy with solid malignancy, unlike HBsAg positive. In this cross-sectional and retrospective study, we analyzed that the reactivation risk of Hepatitis B Virus (HBVr) of totally 457 HBcIgG positive patients with solid cancer in archives records between 2011 and 2018 years of two different centers. Totally 217 HBcIgG positive patients with solid cancer were included in the study. Anti-HBs positive and negative patients were 119 (54.8%) and 98 (45.2%), respectively. Frequent diagnosis of the patients was lung (28.1%), colorectal (19.4%), breast (17.5%) and hepatobiliary tract cancers (8.3%), respectively. Most of the study population had stage 4 disease (48.8%) and received palliative chemotherapy. When the patients were stratified due to American Gastroenterological Association Institute (AGA) guideline, HBVr risk of chemo regimen was moderate in 21 patients (17.5%), low in 8 patients (3.7%). The majority of the patients were undefined risk group (78.8%). We did not determine any HBVr in the patients who have received different conventional chemotherapy regimens and have different primer tumor site despite all the patients did not receive the prophylactic antiviral drug.

Keywords: Antiviral prophylaxis, Hepatitis B virus, reactivation risk, solid malignancy

Introduction

Hepatitis B Virus (HBV) related clinical pictures are one of the most important public health problems due to one-third of the World population had an interaction with it [1]. Reactivation of HBV (HBVr) under treatment with immunosuppressive or chemotherapy is well known in HBsAg positive patients. The HBVr may result in the discontinuation of treatment and can cause increased morbidity and mortality related to the primary disease and liver damage [2].

The HBVr risk is closely associated with viral serology, baseline serum HBV DNA level, kind of drug and treatment intensity, and underlying malignancy, inflammatory, and autoimmune diseases [3]. While HBsAg positive patients with hematopoietic stem cell and organ recipients, and hematological malignancies have a higher risk, HBsAg positive patients with solid malignancy are accepted as moderate HBVr risk. The reactivation risk of HBsAg positive patients is known as approximately eight times higher than in HBsAg negative/HBcIgG positive [2,3]. Although HBsAg positive patients have a higher risk to have an HBVr, HbsAg negative/HBcIgG positive patients more likely to be seen in the population [4].

The HBVr risk in solid tumor quite varies by the administered systemic chemotherapy agents [5]. Although there is a high risk (>10%) in HBsAg negative patients who are treated with T and B cell depleting agents like rituximab and anthracycline derivates, the risk of reactivation decreases to a moderate level (1-10%) in HBsAg negative/HBcIgG positive patients with solid malignancy for anthracycline derivates. However, HBVr risk of conventional chemotherapy agents such as taxans, platins, fluorouracil which frequently used for the treatment of solid malignancies have not been well defined in American Gastroenterological Association Institute (AGA) guideline drug list, unlike anthracycline derivatives [6].

***Coresponding Author:** Murat Araz, Necmettin Erbakan University, Faculty of Medicine, Department of Medical Oncology, Konya, Turkey
E-mail: zaratarum@yahoo.com

Recently published two metanalyses [7,8] have shown that antiviral prophylaxis treatment provides a statistically significant reduction of HBV reactivation risk in HBsAg positive patients with a solid tumor. Therefore, this patient population is indicated to have HBV prophylaxis with anti-viral drugs. However, prophylactic antiviral treatment is controversial due to a lack of studies in both HBsAg negative/HBcIgG positive patients who treated conventional chemotherapy with solid malignancy [2].

In this study, we aimed to analyze the HBV reactivation risk in the HBsAg negative and HBcIgG positive patients who received conventional chemotherapy for the treatment of solid malignancy.

Material and Methods

Patient Selection

In this cross-sectional study, 4651 patient's records in archives of two different centers between 2011 and 2018 were retrospectively scanned. HBcIgG positive 457 patients were found. When the patients who were HBsAg positive or not received chemotherapy or lost follow-up were excluded, the rest of 217 patients were enrolled in the study. The patient characteristics, the HBVr risk of chemotherapy regimens, the number of cycles patients received were recorded. The HBVr ratio of chemotherapy regimens was evaluated according to the recommendations of AGA Guideline in 2015. Also the baseline International Normalized Ratio (INR), aminotransferase level, albumin levels analyzed for an unknown hepatic disease. The aminotransferase levels of the patients were recorded at baseline before the initiation of chemotherapy, at the third cycle and sixth cycle of the chemo and the control times after the complete treatment. The aminotransferase levels during chemotherapy and observation recorded as numbers and categorized as normal, between two to five, five to ten and above the tenfold from the normal range. The duration of the observation period, antiviral prophylaxis status, and reactivation status for each patient were recorded.

Statistical analysis

The SPPS 22.0 programme was used for the statistical analysis. The parameters tested for normal distribution with Kolmogorov-Smirnov and Shapiro-Wilk tests. The descriptive statistics were analyzed.

Results

The majority of 217 patients including the study were male (138 patients). The mean age of male patients was 63 years, and female patients were 58 years. The most frequent diagnosis of the patients was lung (28.1%), then colorectal (19.4%), breast (17.5%) and hepatobiliary tract cancers (8.3%), respectively. Most of the study population had stage 4 disease (48.8%) and had received palliative chemotherapy. The median chemotherapy cycles were 6. Doublet chemotherapeutic combinations have been administered primarily for the treatment of colorectal and lung cancer patients. When the chemotherapy regimens compared, most of the patients received platinum-based treatment (42%). The rates of other combined chemo regimen with anthracycline, taxane, and anti-metabolites were 18%, 20.7%, and 22.6%, respectively. Most of the patients had received only one line chemotherapy, and only the minority of the patients had received third or fourth line chemotherapy. Anti-HBs positive and negative patients were 119 (54.8%) and 98 (45.2%), respectively.

When the patients were stratified due to AGA guideline, HBVr risk of chemo regimen was moderate in 21 patients (17.5%), low in 8 patients (3.7%). The majority of the remain patients were undefined risk group (78.8%). Moderate risk group patients had received mostly as adjuvant anthracycline-containing chemo regimen for breast cancer treatment — the median observation time after chemotherapy was four months which differed from 0 to 36 months. Any patients had received antiviral prophylactic medication. All the patient's characteristics were shown in the Table 1.

Table 1. The Characteristics of The Patients

Age		**Female**	**Male**			
	n:217	58t	63.7t			
Gender						
	n:217	79	138			
Stage		**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	
	n:217	3 (1.4%)	20 (9.2%)	88 (40.6%)	106 (48.8%)	
Diagnosis		**Lung**	**Colorectal**	**Breast**	**Pankreatobilier**	**Others**
	n:217	61 (28.1%)	42 (19.4%)	38 (17.5%)	18 (8.3%)	58 (26.7%)
Anti-HBs		**Positive**	**Negative**			
	n:217	119 (54.8%)	98 (45.2%)			
Aim of Chemother-apy		**Neoadjuvant**	**Adjuvant**	**Palliative**	**Chemoradiotherapy**	
	n:217	8 (3.7%)	84 (38.7%)	116 (53.5%)	9 (4.1%)	
Risk of Reactivation		**High**	**Moderate**	**Low**	**Undefined**	
	n:217	0	38 (17.5%)	8 (3.7%)	171 (78.8%)	
Chemotherapy type		**Monotherapy**	**Doublet Triplet**			
	n:217	40 (18.4%)	177 (81.6%)			
Parameters at Diag-nosis		**Albumin**	**INR**			
	n:217	4.07*	1.02*			
ALT levels (U/L)		**Diagnosis**	**3th Cycle**	**6thCycle**	**After Chemo**	
		n: 217	n:212	n:158	n:158	
		18*	18*	20*	19*	
Combination Chemo regimens Based on.. n (%)		**Platinum**	**Taxane**	**5-FU**	**Anthracycline**	
		92 (42%)	45 (20.7%)	49 (22.6%)	39 (18%)	
Line of Treatments n (%)		**First line**	**Second line**	**Third line**	**Fourth line**	
		159 (73.3%)	55 (25.3%)	2 (0.9%)	1 (0.5%)	

t: Mean *: Median

We did not detect any HBVr in the HBsAg negative and HBcIgG positive patients with solid malignancy who treated with conventional chemotherapy. Whether HBsAb positive or negative did not affect this result.

Discussion

In the study, we aimed to evaluate the HBVr status of solid organ malignancy patients who have HBcIgG positive. We did not determine any HBVr in the patients who have received different conventional chemotherapy regimens and have different primer tumor site despite all the patients did not receive the prophylactic antiviral drug.

While the HBVr in solid tumor treatment is thought much lower than stem cell/organ transplantation and hematologic cancer, the absolute risk with conventional chemotherapeutic agents using for solid cancer treatment is still unclear. In a meta-analysis, the reactivation rates in HBsAg positive and HBsAg negative/HBc IgG positive patients with solid malignancy were median 25% (ranged from 4-68%) and 3%(ranged from 0.3-9%), respectively [7].

Recently, in a systematic comparativesystematic review [4] including 55 studies with a total of 3640 HBsAg negative/HBcIgG positive patients who received immunosuppressive therapy, Cholongitas et al. showed that HBVr rate was detected as 10.9% in patients with hematological diseases and 3.6% in patients with non-hematological diseases. However, the majority of patients with non-hematological diseases were constituting with rheumatic disease (975 patients) in the study. The other non-hematological diseases were including gastrointestinal diseases (105 patients), dermatological diseases (88 patients), various diseases (67 patients), and solid cancer (114). Solid cancer patients were only a small part of the study population (<10%). Also, patients with rheumatic, dermatologic, gastrointestinal, and various non-hematological disease had been received tumor necrosis factor alfa inhibitors (anti-TNF) or rituximab containing treatment. Rituximab and anti-TNF inhibitors are two essential immunosuppressive drugs that well known associated with HBVr in isolated HBc IgG positive patients [9]. In a multicentre and prospective study, Fukuda et al. [10]. found that the incidence of HBVr in patients with HBsAg negative/HBcIgG positive under immunosuppressive therapy for the rheumatic disease was 1.9%. Although anti-TNF agents-associated HBVr risk which accepted with moderate risk is well known, conventional chemotherapy agents have quite variable HBVr risk, and data is limited with heterogenous small case series [2]. Therefore, HBVr risk levels of these drugs, unlike anthracycline derivates, could not be classified in the guidelines [6]. While anthracyclines derivates and cyclophosphamide may cause HBVr in HBsAg positive patients via inducing lymphodepletion, there is very limited data with topoisomerase inhibitors and an antimetabolite agents fluorouracil [5].

When comparing patients regarding detectable and undetectable serum baseline HBV DNA in the study of Cholongiatis et al. [4], HBVr rate was significantly higher in non-hematological diseases (14.2% vs. 2.0%, P=0.001; respectively), but, this difference was not significant in the sensitivity analysis (p=0.090). Although detectable serum baseline HBV DNA had numerically higher reactivation than undetectable HBV DNA (21.9% vs. 11.3%, P=0.173; respectively), there was no statistically meaningful difference in patients with hematological disease (P=0.938). HBVr rate was numerically higher in patients treated with rituximab-containing (9.7% vs. 4.1 %, P=0.056) and significantly higher in patients with detectable baseline serum HBV DNA treated with rituximab-free regimens (14.0% vs. 2.6%, P=0.003; respectively). However, no such difference was seen in patients treated with rituximab-containing regimens (11.7% vs. 11.6 %, P=0.997; respectively). Also, they showed that anti-HBs seropositivity is protective for HBVr in all studies (5.2% vs. 17%, p<0.001) regardless of underlying disease and rituximab treatment. However, the protective effect on HBVr of anti-HBs is very controversial in the literature [11]. However, HBsAb positivity had not affected our results and also, baseline HBV DNA levels of the patients were not available in our study.

A relationship between the intensity or multi-line of conventional chemotherapy administration and HBVr is not clearly defined. In both studies of Paul et al. [7] and our, doublet or triplet chemo regimens or increased lines of therapies were not correlated with HBVr. Also, Patullo et al. suggest that some mutation of HBV gene in patients with HBsAg nega¬tive/HBcIgG positive may be related to increased HBVr risk. However, this issue is not clearly determined [3]. Consequently, this issue has still so many restricted factors for the quality of the study results from such as incomplete data from retrospective trials, heterogeneity of study populations, and heterogeneity of chemotherapy drugs.

From their results, Cholongitas et al. suggest that antiviral prophylaxis should be given in HBsAg negative, HBcIgG positive patients with non-hematological diseases including solid malignancies who have detectable baseline HBV DNA [4]. However, AGA [6] and recently published Turkish Consensus Report [2] do not recommend the routinely using antiviral prophylaxis before the initiate conventional chemo regimen which has low HBVr risk regardless baseline HBV DNA level. If we use routinely prophylactic antiviral drugs in this low-risk group, it will cause an increased economic burden and treatment-related adverse events, especially in HBV endemic countries [7].

Retrospective design, unknown basal HBV DNA level, and short observation duration after chemotherapy of patients were study limitations of our study. Notably, in metastatic patients, cancer-related high mortality rates in short time after disease progression were related to low observation periods.

Conclusion

Reactivation risk of hepatitis B virus in both HBsAg negative and HBcIgG positive patients with solid malignancy is very rarely under treatment with conventional chemotherapy regimens. Therefore, we think that antiviral prophylaxis is usually unnecessary. However, in this area have still need comparative and prospective trials.

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Competing interests
The authors declare that they have no competing interest.

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Ethical approval
The study was approved by the local ethics committee of Afyon Kocatepe University and was conducted by fo llowing the Helsinki Declaration principles.

Murat Araz ORCID:0000-0002-4632-9501
Ismail Beypinar ORCID:0000-0002-0853-4096
Tarik Demir ORCID:0000-0001-6334-4079
Hacer Demir ORCID:0000-0003-1235-9363
Mukremin Uysal ORCID:0000-0002-8524-0665

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