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Hepatitis B Reactivation During Cancer Chemotherapy: An International Survey of the Membership of the American Association for the Study of Liver Diseases

Jessica P. Hwang[1], **Andrea G. Barbo**[2], and **Robert P. Perrillo**[3]

[1]Departments of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, and the Hepatology Division, Baylor University Medical Center, Dallas, Texas

[2]Departments of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, and the Hepatology Division, Baylor University Medical Center, Dallas, Texas

Abstract

Background—Hepatitis B virus reactivation (HBVr) can be a serious complication of cancer chemotherapy. However, underutilization of HBV screening and secondary underutilization of antiviral prophylaxis have been frequently reported.

Methods—The authors electronically distributed a 30-point questionnaire to members of the American Association for the Study of Liver Diseases to capture experiences with HBVr during cancer chemotherapy. The questionnaire specified diagnostic criteria and collected information on HBV screening, antiviral prophylaxis, and clinical outcomes.

Results—Ninety-nine respondents reported 188 patients who met the criteria for HBV reactivation. Fortyone practiced outside the United States, and most were hepatologists (n = 71) or gastroenterologists (n = 12). One hundred twenty-six patients had hematologic malignancies, of which 88 (70%) had lymphoma. Seventy-five patients (40%) had screening for both hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti/HBc) and an additional 24 patients (13%) had HBsAg screening alone. Prophylactic antiviral therapy was reported in only 18 patients (10%). Chemotherapy was interrupted in 52 patients (41%) with hematologic malignancies and 26 of 41 patients (63%) with solid tumors (P = 0.01). Rituximab-treated patients (n = 66) required hospitalization more frequently (P = 0.04), but their overall survival did not differ from individuals not treated with rituximab. Death due to liver failure was reported in 43 patients overall (23%).

Conclusions—Underutilization of prophylactic antiviral therapy occured in a substantial number of patients who were found to be HBV-infected prior to the initiation of cancer

Corresponding author: Robert Perrillo, roberper@baylorhealth.edu, (214) 820-2956 (tel), (214) 820-3565 (fax), 3410 Worth Street, Suite 953, Dallas, Texas 75246.

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chemotherapy. The reasons for this need further exploration because reactivation results in serious yet preventable outcomes.

Keywords

Hepatitis B; antiviral prophylaxis; HBV screening; cancer chemotherapy

Introduction

Hepatitis B virus (HBV) reactivation is a common and potentially serious complication of treatment with immunosuppressive drugs (1). Reactivation is a virologic phenomenon and it may occur without any change in liver chemistries. However, in many cases it is associated with an increase in serum aminotransferase levels due to an exacerbation of hepatitis, and in severe cases, there may be marked elevations of serum aminotransferase levels, acute-on-chronic liver failure, and death. Prophylactic antiviral therapy has been shown to significantly reduce the frequency of reactivation in HBsAg carriers and in patients who are HBsAg negative but positive for anti-HBc (2-4).

Despite recommendations by the Centers for Disease Control and several international liver disease organizations to screen for HBV in all patients who will undergo chronic immunosuppressive drug therapy (5-8), it has been shown that oncologists, dermatologists, and rheumatologists do this infrequently (9-11). This may reflect a lack of awareness of the above recommendations and/or absence of specific screening recommendations in their individual specialty practice guidelines (12). The frequency of HBV screening by gastroenterologists and hepatologists has not been defined but is anticipated to be higher.

Much of the published data on HBV reactivation during cancer chemotherapy comes from large cancer centers or other types of institutions outside the United States (13-15). These studies describe clinical outcomes such as the rate of severe hepatitis, liver failure, and death. Relatively little information, however, is available on other significant outcomes, such as the need for hospitalization, intensive care management, or alteration of chemotherapy.

Here, we present the results of a recently completed questionnaire in which we asked all AASLD members about their experience with HBV reactivation during cancer chemotherapy. We envisioned that this study might provide a unique data set on screening and treatment practices and also capture information on reactivation-related outcomes that had not been emphasized previously.

Methods

A 30-question questionnaire was developed by 2 of the authors (JPH and RPP) and reviewed and approved by members of the AASLD Hepatitis B Special Interest Group. Respondents were allowed to present more than 1 case.

The AASLD announced the purpose of the questionnaire to all members in 3 separate electronic communications in which potential respondents were encouraged to have hard-copy or electronic medical records available to facilitate accurate data entry.

Virologic criteria for HBV reactivation required 1 or more of the following: (a) serum HBV DNA level > 5 log IU/mL; (b) > 1 log IU/mL increase in serum HBV DNA level compared to the value before chemotherapy; and (c) appearance of HBV DNA in serum when it was previously undetectable. Biochemical criteria for HBV reactivation were an alanine aminotransferase (ALT) level > 100 IU/mL and at least twice the prechemotherapy level. Recipients of the questionnaire were asked if HBV screening was done before chemotherapy, if antiviral therapy was used, and if so, whether this was given prophylactically or therapeutically. Recipients were also queried about several possible clinical outcomes of HBV reactivation, including interruption of chemotherapy (defined as early discontinuation or delay in initiation), need for hospitalization, and liver-related mortality.

We used chi-square test or Fisher's exact test (where appropriate) to test the association of cancer type, HBV screening, and prophylactic antiviral therapy with clinical outcomes. For the clinical outcomes analysis, we grouped patients with unknown outcomes with patients who did not have the reported outcome. The chi-square test was used to compare screening rates between patients with solid and hematologic cancers and between patients who received rituximab with those who did not All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). This study was approved by the institutional review boards of the Baylor Health Care System Research Institute and The University of Texas MD Anderson Cancer Center.

Results

Provider characteristics

There were 128 survey respondents. Twenty-nine either indicated that they had never seen a case of HBV reactivation (n = 17) or provided inadequate data (n = 12). The remaining 99 respondents (77%) reported at least 1 patient and completed the survey. The data acquired from these 99 individuals were used for all analyses.

The majority of the 99 respondents (n = 83, 84%) were either hepatologists or gastroenterologists. Forty one percent indicated that they practiced outside of the United States. [See supplementary Table for more information]. Sixty-three respondents reported caring for 1 patient with HBV reactivation, 22 reported caring for 2 patients, and 14 reported caring for 3 or more patients. Two respondents each reported having cared for more than 10 patients with HBV reactivation.

Patient characteristics and HBV screening

A total of 188 reactivation cases were reported by the 99 respondents. Patient characteristics are listed in Table 1. The majority of the patients were from Asia (n = 69,37%) or Europe (n = 54, 29%). Hematologic malignancies predominated (n = 126, 67%), and the majority of patients in this group (66, 52%) received rituximab as part of the chemotherapy regimen.

HBV testing and antiviral therapy are described in Table 2. HBV screening before chemotherapy was done in 100 patients (53%). Screening was more frequent among patients with hematologic malignancies than among those with solid tumors (79/126 [63%] vs. 12/41

[29%], P ≤ 0.001). The HBV screening rate was also higher among patients who received rituximab than among those who did not, although this difference was not significant (73% vs. 56%, P = 0.06).

Only 17 of the 100 screened patients had antiviral therapy initiated before chemotherapy: 15 of the 79 (19%) with hematologic malignancies, none of the 12 with solid tumors, 1 of the 2 with hepatocellular cancer, and 1 of the 7 with an unknown type of cancer. Antiviral therapy was initiated before chemotherapy in 11 of the 66 patients (17%) treated with rituximab compared to 5 of the 55 patients (9%) not treated with this agent (P = 0.22).

Reactivation criteria

Each of the 188 patients met at least one of the virologic criteria for reactivation in the following distribution: One hundred fifty patients (80%) had an absolute increase in HBV DNA level > 5 log IU/mL after chemotherapy (see blue bars); 82 patients (44%) had a > 1 log IU/mL increase in HBV DNA level compared to the value before chemotherapy (see red bars); and 78 patients (41%) had appearance of HBV DNA when it was previously undetectable (see green bars) [see Figure in supplementary information]. One hundred and sixty-three patients (87%) had a postchemotherapy ALT level > 100 IU/mL and at least twice the prechemotherapy baseline value.

Clinical outcomes

Table 3 depicts the clinical outcomes of the patients with reactivation. Eighty four patients (45%) experienced interruption in chemotherapy and 41 (22%) had dose reduction after reactivation became apparent. Chemotherapy interruption was more common among patients with solid tumors than among patients with hematologic malignancies (63% vs. 41 %, P = 0.01). Interruptions in chemotherapy also were more common among patients who did not undergo prechemotherapy HBV screening (52% vs. 38%, P = 0.05). Among the 41 patients who had a reduction in chemotherapy dose, 19 had been screened for HBV, but none had been given antiviral prophylaxis.

One hundred eight patients (57 %) were hospitalized for reactivation, and among these, 40 patients (37%) required care in the intensive care unit. Forty-three patients (23%) died of liver failure: 10 with solid tumors, 31 with hematologic malignancies, and 2 with an unknown cancer type. Among the 43 patients who died of liver failure, 23 (53%) were screened for HBV prior to chemotherapy, but only 4 (17%) received prophylactic antiviral therapy.

Outcomes were generally similar in rituximab-treated patients when compared to those not treated with this agent [see supplementary information]. The only difference was in the rate of hospitalization, which was more frequent in rituximab-treated patients (P = 0.04). There was no difference in the frequency of liver failure-related mortality between the 2 groups.

Discussion

The current study differs from previous studies of HBV reactivation following cancer chemotherapy in several respects. First, we surveyed the membership of the AASLD; as a

result, the data collected were from US and non-US providers who were primarily hepatologists and gastroenterologists. Second, the questionnaire provided details on outcomes that often have not been included in other case series, such as the requirement for hospitalization, intensive care management, or interruption in chemotherapy after HBVr becomes evident. Third, the questionnaire allowed assessment of HBV screening practice and the subsequent use of antiviral prophylaxis before chemotherapy.

The overall frequency of prechemotherapy HBV screening observed in this study (53%) was substantially higher than rates previously reported in a study from a US cancer center (9) and other surveys of medical oncologists in the United States (13%-18%) and Australia (19%) (16,17). However, in comparing the HBV screening rate in our study and previous studies, it is important to consider that our study was limited to patients with HBV reactivation whereas the other studies were not. Another potentially important factor is that a large number of patients with hematologic malignancies were included in this study which could have heightened the awareness of the need to screen for HBV. This may be especially relevant in patients with lymphoma (47% of the patients in our study), whose treatment regimens often include rituximab, a B- cell- depleting agent frequently linked to reactivation (18-20). The American Society for Clinical Oncology Provisional Clinical Opinion statement advises that HBV screening be considered when rituximab or bone marrow transplantation is planned (21). Given this endorsement, therefore, it is not surprising that HBV screening was more frequently reported in patients with hematologic malignancies versus those with solid tumors ($P \leq 0.001$), and there was a trend for an increased frequency of HBV screening in rituximab- treated patients (73% vs. 56%, $P = 0.06$).

The apparent lack of association between prechemotherapy HBV screening and prophylactic antiviral therapy in the current study is more difficult to understand. This was even evident in the cases of hematologic malignancy treated with rituximab of which 73% were screened and yet only 17% were given antiviral prophylaxis. The survey did not collect information on the HBV serologic status of the reactivation cases. However, it is likely that the majority of patients with reactivated hepatitis B were HBsAg positive, a group for which prophylactic antiviral treatment has been strongly recommended (6-8,12). The low overall rate of prophylactic antiviral therapy in our study seems to imply either a lack of awareness of current recommendations to treat HBsAg positive patients, a preference for a observation-and-treat approach, or a combination of both factors.

Serial monitoring of HBV DNA and ALT with delayed antiviral therapy as needed has been explored in clinical trials as a means of reducing reactivation-associated hepatitis in HBV-infected patients (2,3,22). A driving force for these clinical trials is the added cost associated with routine antiviral prophylaxis, a factor that is particularly relevant in areas where hepatitis B is endemic and a large proportion of the population may have the inactive HBsAg carrier state or serologic evidence for resolved infection. However, it must be emphasized that several small randomized, controlled clinical trials and a large systematic analysis have demonstrated reduced rates of reactivation and improved clinical outcomes when prophylactic treatment (either started before or at the time chemotherapy is initiated) is compared to delayed treatment (started when the diagnosis of HBVr is established) in HBsAg-positive patients (2-4). Some of these studies have shown that the benefit of early

therapy also applies to lymphoma patients who are HBsAg negative but anti-HBc –positive (3,23).

Previous studies of clinical outcomes in patients with HBV reactivation during cancer chemotherapy have largely focused on short-term indicators of severe disease, including elevated aminotransferase levels, jaundice, and liver-related deaths. The current study provides additional information about outcomes. More than 50% of the patients with reactivation in the current study required hospitalization, 20% required care in the intensive care unit, and 23% died of liver failure. We also found that interruptions in chemotherapy occurred in many patients (Table 3) and were particularly common in patients with solid tumors and those who were not screened before cancer chemotherapy. The proportion of patients with chemotherapy interruptions (45%) exceeded that reported in an Australian survey of 54 patients with HBV reactivation, in which 30% of patients had premature discontinuation of chemotherapy (17). The lack of a chemotherapy-treated control group in the current study limits the level of confidence with which one may assume that the increased rate of treatment interruptions was due to HBV reactivation as opposed to cytopenias and septic complications of chemotherapy. However, observational studies in lymphoma and breast cancer patients have reported an increased frequency of chemotherapy interruption in HBV infected patients which were considered to be attributable to reactivation (24). A further compelling statistic from the current study is that none of the 41 patients with a reduction in chemotherapy dose received prophylactic antiviral therapy. The current study did not address the response rate to chemotherapy in these patients or the rate of cancer-free survival, but it may be reasonable to assume that both would be adversely affected in patients having interruption of therapy, particulary premature discontinuation of treatment.

It is worth mentioning that our study had several limitations. Physicians were asked to recall their clinical experiences of patients with reactivation, and this may have biased the results. Also, we surveyed liver specialists about their patterns over the span of their practice, and thus we were not able to follow any trends over time or account for the impact of changes in medical practice or national recommendations. Despite these limitations, however, to our knowledge this is the first survey of international liver specialists, and the results of this study underscore the fact that missed opportunities to prevent HBV reactivation during cancer chemotherapy is an important national and international health problem.

In conclusion, we found that antiviral prophylaxis was infrequently administered to cancer patients given chemotherapy, even those who were screened and found to have HBV infection prior to initiation of chemotherapy. These data indicate that it is not only urgent to educate all providers who prescribe potent immunosuppressive drugs about the importance of HBV screening, but also on the need to take effective action based on the results of such screening. Perhaps nowhere else are the stakes from hepatitis B reactivation quite as high as in patients given cancer chemotherapy because liver transplantation is generally not an option for such patients and while further study is needed, survivors of HBV reactivation may be faced with a lower rate of response to cancer chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AASLD	American Association for the Study of Liver Diseases
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

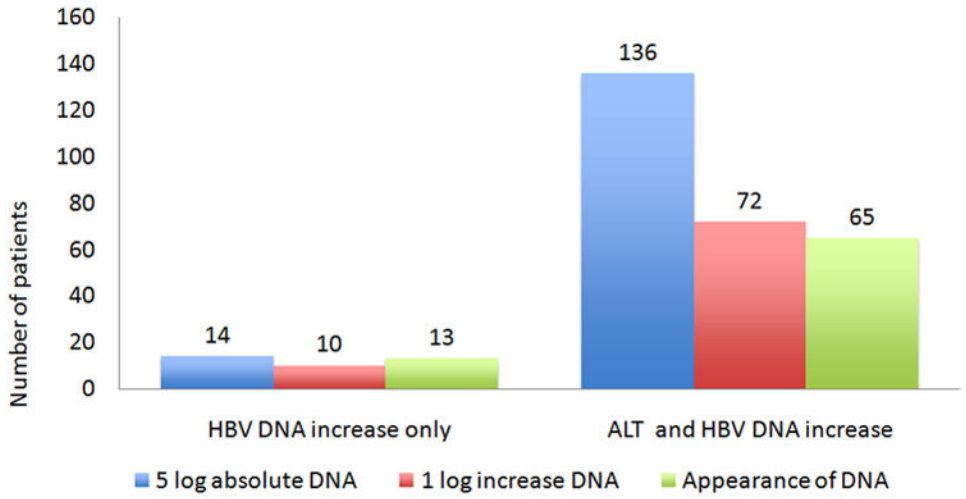

Figure 1. Distribution of HBV DNA and ALT change in the total population

ALT increase: twice the baseline level and value >100 IU; serum HBV DNA change: 1) > 5 log absolute value (IU/ml); 2) > 1 log increase compared to baseline before chemotherapy; 3) appearance of HBV DNA when previously undetectable. HBV DNA increase only: patients who had HBV DNA increase but not ALT increase. ALT and HBV DNA increase: patients who had both ALT and HBV DNA increase. Note: Total count of patients in this figure does not add to total number of study patients because patients may have met more than one reactivation definition.

Table 1

Characteristics of Reactivation Cases

Feature	N = 188 n (%)
Gender	
Male	114 (60.6)
Female	58 (30.9)
Unknown	16 (8.5)
Age at reactivation, years	
≤ 40	17 (9.0)
41-50	31 (16.5)
51-65	76 (40.4)
>65	44 (23.4)
Unknown	20 (10.6)
Race/ethnicity	
White	81 (43.1)
Asian	68 (36.2)
Black	15 (8.0)
Hispanic	5 (2.7)
Unknown	19 (10.1)
Geographic origin	
Asia	69 (36.7)
Europe	54 (28.7)
North America	30 (16.0)
Africa	4 (2.1)
South America	4 (2.1)
Unknown	27 (14.4)
Cancer type	
Solid tumor	
Breast	17 (9.0)
Lung	4 (2.1)
Colon	2 (1.1)
Other[1]	13 (6.9)
Unknown	5 (2.7)
Hematologic malignancy	
Lymphoma	88 (46.8)
Received rituximab	56 (63.6)
Leukemia	30 (16.0)
Received Rituximab	10 (33.3)
Other	8 (4.3)
Hepatocellular cancer	4 (2.1)
Unknown	17 (9.0)

[1]Other solid tumors (one in each cancer type except where indicated) included bone, brain, esophagus (n =2), gallbladder, head and neck, jejunum, pancreas (n=2), retinoblastoma, round cell, sarcoma, and teratoma.

Table 2
HBV Screening and Timing of Antiviral Therapy

Feature	N = 188 n (%)
HBV screening before chemotherapy	
Both tests	75 (39.9)
HBsAg only	24 (12.8)
Anti-HBc only	1 (0.5)
Not screened	60 (31.9)
Unknown	28 (14.9)
Antiviral therapy	
Yes	
After chemotherapy	137 (72.9)
Before chemotherapy	18 (9.6) *
Unknown	6 (3.2)
No	11 (5.9)
Unknown	16 (8.5)

*Includes one patient in whom pre-chemotherapy screening could not be documented

Table 3

Clinical Outcomes of Patients with Reactivation

		Cancer type			Screening[1]			Prophylactic antiviral[2]		
Clinical Outcome	Total N = 188 n (%)	Hematologic malignancy N = 126 n (%)	Solid tumor N = 41 n (%)	p value[3]	Yes N = 100 n (%)	No N = 88 n (%)	p value[3]	Yes N = 18 n (%)	No N = 170 n (%)	p value[3]
Chemotherapy interruption										
Yes	84 (44.7)	52 (41.3)	26 (63.4)	0.01	38 (38.0)	46 (52.3)	0.05	5 (27.8)	79 (46.5)	0.13
No	81 (43.1)	64 (50.8)	9 (22.0)		60 (60.0)	21 (23.9)		13 (72.2)	68 (40.0)	
Unknown	23 (12.2)	10 (7.9)	6 (14.6)		2 (2.0)	21 (23.9)		0 (0.0)	23 (13.5)	
Chemotherapydose decreased										
Yes	41 (21.8)	27 (21.4)	12 (29.3)	0.30	19 (19.0)	22 (25.0)	0.32	0 (0.0)	41 (24.1)	0.01
No	113 (60.1)	83 (65.9)	18 (43.9)		78 (78.0)	35 (39.8)		18 (100.0)	95 (55.9)	
Unknown	34 (18.1)	16 (12.7)	11 (26.8)		3 (3.0)	31 (35.2)		0 (0.0)	34 (20.0)	
Jaundice										
Yes	105 (55.9)	72 (57.1)	27 (65.9)	0.32	57 (57.0)	48 (54.5)	0.74	7 (38.9)	98 (57.6)	0.13
No	65 (34.6)	46 (36.5)	9 (22.0)		42 (42.0)	23 (26.1)		11 (61.1)	54 (31.8)	
Unknown	18 (9.6)	8 (6.3)	5 (12.2)		1 (1.0)	17 (19.3)		0 (0.0)	18 (10.6)	
Hospitalization										
Yes	108 (57.4)	77 (61.1)	26 (63.4)	0.79	58 (58.0)	50 (56.8)	0.87	9 (50.0)	99 (58.2)	0.50
No	62 (33.0)	42 (33.3)	10 (24.4)		40 (40.0)	22 (25.0)		9 (50.0)	53 (31.2)	
Unknown	18 (9.6)	7 (5.6)	5 (12.2)		2 (2.0)	16 (18.2)		0 (0.0)	18 (10.6)	
Intensive careunit admission										
Yes	40 (21.3)	30 (23.8)	8 (19.5)	0.57	18 (18.0)	22 (25.0)	0.24	4 (22.2)	36 (21.2)	>0.99
No	121 (64.4)	86 (68.3)	23 (56.1)		79 (79.0)	42 (47.7)		14 (77.8)	107 (62.9)	
Unknown	27 (14.4)	10 (7.9)	10 (24.4)		3 (3.0)	24 (27.3)		0 (0.0)	27 (15.9)	
Mortality related to liver failure										
Yes	43 (22.9)	31 (24.6)	10 (24.4)	0.98	23 (23.0)	20 (22.7)	0.96	4 (22.2)	39 (22.9)	>0.99
No	123 (65.4)	87 (69.0)	23 (56.1)		74 (74.0)	49 (55.7)		14 (77.8)	109 (64.1)	
Unknown	22 (11.7)	8 (6.3)	8 (19.5)		3 (3.0)	19 (21.6)		0 (0.0)	22 (12.9)	

[1]Yes: patient was screened with HBsAg and/or anti-HBc tests before chemotherapy. No: patient was not screened or was not known to have had HBV screening.

[2]Yes: patient received antiviral therapy before chemotherapy. No: patient did not receive antiviral therapy, was not known to have antiviral therapy before chemotherapy, or received antiviral therapy after chemotherapy.

[3]For the association between clinical outcome (Yes vs. No/Unknown) and cancer type, screening, and prophylactic antiviral.