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Evaluation of the clinical practices and awareness of hematologists related to hepatitis B reactivation

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Abstract

Aim: This study aimed to evaluate the awareness and knowledge of hematologists about hepatitis B virus reactivation (HBVr) to draw attention to this subject's importance.
Material and Methods: Sixty-six hematologists included in Turkey. A 13-item questionnaire was administered to the study group to evaluate awareness, knowledge, and experience of HBVr.
Results: It was thought by 97% of the participants that all patients who were to receive immunosuppressive treatment (IST) should be screened in respect of HBV. While 98.5% of the hematologists thought HBsAg should be examined in the screening, 89.4% thought anti-HBcIgG should be examined. A total of 89.4% of the hematologists stated that prophylaxis should be started before IST. HBV prophylaxis had been previously administered to patients receiving IST by 97% of the hematologists, and 44% had encountered HBVr at least once in patients. Training related to HBVr after IST had been received following graduation by 75.8% of the hematologists.
Conclusions: Awareness about HBVr was found to be high in the hematologists in this study. However, it is worrying that there are clinicians not using anti-HBcIgG test in screening, and the screening rate before treatment with tyrosine kinase inhibitors was low. There was seen to be no standard follow-up protocol either for patients who had started or had not started prophylaxis. This study can be considered to be a stimulus on the subjects of preventing patients with isolated anti-HBcIgG positivity being overlooked, determining the HBVr risk associated with IST, and optimizing the follow-up of patients.

Introduction

Approximately 350 million people worldwide are infected with chronic hepatitis B virus (HBV) (1), and approximately 30% of the global populations have encountered HBV (2). Patients with a hematological malignancy are at risk of HBV reactivation (HBVr) following immunosuppressive treatment (IST) and high-dose chemotherapy. This reactivation can result in increased serum aminotransferase levels, fulminating hepatic failure and death (3). It can also lead to termination of the IST and a delay in the treatment of the underlying disease. Therefore, it is important that antiviral treatmentis started by the risk identification according to HBV screening before chemotherapy and the chemotherapy protocols to be applied (4, 5).

The HBVr risk of the patient is related to the HBV serology, viral replication markers and the immunosuppressive agent used. The HBVr risk is greater in HBsAg positive patients than in HBsAg negative and anti-HBcIgG positive patients (6). This risk can be greatly reduced by screening patients in respect of HBV before IST and starting antiviral treatment in patients requiring prophylaxis (7).

Various studies have reported that HBVr developed in 20%-50% of HBV infected patients or chronic HBV patients receiving IST (3, 8). The European Association for the Study of the Liver (EASL), the Asian-Pacific Association for the Study of the Liver (APASL), and the Center for Disease Control and Prevention (CDC) recommend anti-HBcIgG and anti-HBs screening before IST in countries where HBsAg prevalence is > 2% (1, 3, 8). The determination of anti-HBc alone without other serological markers of HBV infection is named anti-HBc positivity, and indicates an encounter with HBV infection (9).

Despite the screening recommendations of the guidelines, real-life data show the HBV screening rates to be low. Studies in literature that have evaluated the clinical awareness and practices on the subject of HBVr of physicians administering IST have usually included oncologists as the study group. Previous studies have reported that HBV screening is not performed at extremely high rates in oncology clinics (10-12). When the literature is evaluated, it is noteworthy that there are insufficient studies on this subject in hematology clinics.

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Table 1. Questionnaire and Responses

		Yes	No	Not sure
1	Is there a guideline/literature that you have followed on the subject of HBV screening of patients receiving immunosuppressive treatment?	39	27	-
2	Which of the drugs listed below would you consider requesting for HBV serology before starting immunosuppressive treatment?			
	Rituximab andofatumumab	66		
	Tyrosine kinase inhibitors (imatinib, nilotinib, etc)	29		
	≥10mg prednisolone and equivalents for longer than 4 weeks	60		
	<10mg prednisolone and equivalents for longer than 4 weeks	15		
	Azathioprine, methotrexate, 6 mercaptopurine	42		
3	Before starting treatment with which of the following drugs do you routinely HBV screen all patients? Rituximab and ofatumumab			
	Rituximab and ofatumumab	66		
	Tyrosine kinase inhibitors (imatinib, nilotinib, etc)	38		
	≥10mg prednisolone and equivalents for longer than 4 weeks	57		
	<10mg prednisolone and equivalents for longer than 4 weeks	26		
	Azathioprine, methotrexate, 6 mercaptopurine	46		
4	In the presence of which of the following in patients for whom you are going to start immunosuppressive treatment, do you think it is necessary to screen for HBV infection?			
	All patients who are to receive any immunosuppressive treatment	64		
	Elevated results in liver function tests	2		
	Family history of hepatitis	2		
	Personal history of jaundice	2		
	Use of IV drugs	2		
	Homosexual males	2		
	Healthcare workers	2		
	History of blood transfusion	2		
	Receiving hemodialysis	2		
	No HBV vaccination	2		
	Living in an endemic region	2		
5	Which tests do you routinely perform for the screening of HBV and related infections?			
	HBsAg	65		
	Anti-HBs	61		
	Anti-HBcIgG	59		
	HBV DNA	4		
	Anti-HCV	36		
	Anti-HIV	38		
6	When should HBV prophylaxis be started?			
	Before starting IST	59		
	Together with immunosuppressive treatment	7		
	After starting immunosuppressive treatment	-		
	If reactivation develops during follow-up	-		
7	How often do you follow up patients who have started HBV prophylaxis?			
	Once a month	18		
	Once every 3 months	30		
	Once every 6 months	5		
	Once a year	-		
	I determine follow up according to symptoms and findings	12		
	I do not follow up these patients	1		
8	Do you follow up patients who are HBV serology positive but have not been recommended prophylactic treatment in respect of reactivation?			
	Once a month	18		
	Once every 3 months	21		
	Once every 6 months	9		
	Once a year	2		
	I determine follow up according to symptoms and findings	14		
	I do not follow up these patients	2		
9	Has HBV prophylaxis been given to your patients receiving immunosuppressive treatment?	64	2	
	Which treatment(s) are used if prophylaxis is started?			
	Lamivudine	20		
	Entecavir	49		
	Tenofovir disoproxil fumarate	51		
	Tenofovir alafenamide	20		
	Adefovir	4		
	Telbivudine	-		
11	Has HBV reactivation developed in your patients who are receiving immunosuppressive treatment?	29	36	1
12	If HBV reactivation has been determined, how was the follow-up of the patients terminated?			
	There was no need to suspend the hematological treatment	23		
	It was necessary to suspend the hematological treatment	36		
	Liver transplantation was performed	1		
	Ex	6		
13	What postgraduate training have you received related to HBV reactivation in immunosuppressive patients?			
	Textbooks/Guidelines	50	16	
	Congress/Symposium	38		
	Training seminars organized by the pharmaceutical industry	25		
	Internet sources	16		
	Other	-		

Therefore, the aim of this study was to evaluate the awareness and levels of knowledge of hematologists on the subject of HBVr, and to draw attention to the importance of this subject through this evaluation.

Material and Methods

This study was conducted between 01.01.2020 and 31.05.2020 and included 66 hematologists working in healthcare institutions in Turkey. Before starting the study, the participants were informed about the study and consent was obtained for voluntary participation. A 13-item questionnaire was applied to the study group to investigate the awareness, level of knowledge, and experience of HBVr with IST (Table 1).

The questionnaire was prepared by a team comprising two hematologists and an infectious diseases specialist, each experienced in their field. While preparing the questionnaire, the current literature related to HBVr in patients receiving IST was scanned and current guidelines were examined (AGA, EASL, APASL, AASLD, NCNN). The comprehensibility of the questionnaire and the reliability of the questions and responses were evaluated by this team. The questionnaire was delivered to the study participants using the Google forms website (http://www.google.com/forms). The questions were in the form of multiple-choice, and more than one option could be selected for some questions. Approval for the study was granted by the Local Ethics Committee (decision no:02.01.2020/34-09) and the study has been conducted according to the Declaration of Helsinki 1975.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 20.0 software (IBM SPSS Statistics). Continuous variables were stated as median (minimum-maximum) and mean ± standard deviation (SD) values, and categorical variables as number (n) and percentage (%).

Results

Study Group

Evaluation was made of 66 hematologists who completed the questionnaire. The study participants comprised 60 (91%) hematologists working in a university hospital or training and research hospital, and 6 (9%) in a second-level healthcare institution. The mean duration of professional experience was 9.1 years (range, 1-38 years). The demographic data of the study participants are shown in Table 2.

Table 2. Demographic data of the hematologists participating in the study (n = 66)

Characteristic	Number (%)
Age (years)	
32-40	46 (69.7)
41-50	16 (24.3)
51+	4 (6)
Gender	
Female	32 (48.5)
Male	34 (51.5)
Academic title	
Fellowship	15 (22.8)
Specialist	40 (60.6)
Assistant professor	7 (10.6)
Professor	4 (6)
Duration of working (years)	
0-5	31 (47)
6-10	9 (13.7)
11-20	21 (31.8)
21+	5 (7.5)
Institution where employed	
University hospital	32 (48.5)
Training and Research hospital	28 (42.5)
Second-level healthcare institution	6 (9)

HBVr Awareness and Screening Guidelines

Of the total hematologists participating in the study, 39 (59%) stated that they followed at least one guideline and 27 (41%) that they did not follow any guideline. The three guidelines followed most by the hematologists were the AGA, NCNN and AASLD guidelines, respectively. While 64 (97%) hematologists thought it was necessary to perform HBV screening on all patients to be given IST, 2 (3%) stated that it should only be applied to high-risk patients. In the screening, 65 (98.5%) hematologists thought HBsAg should be examined, 61 (92.4%) anti-HBs, and 59 (89.4%) anti-HBcIgG. HBV DNA test was thought to be neccessary for screening by 4 (6%) of the study participants (Figure 1).

Screening was thought to be necessary for anti-HCV by 36 (54.5%) of the hematologists, and for anti-HIV by 38 (57.6%).

Immunosuppressive Drugs and HBV Screening

All the hematologists in the study stated that HBV screening was necessary before treatment with rituximab and ofatumumab, and 29 (43.9%) thought it was necessary before tyrosine kinase inhibitors, 60 (90.9%) before ≥10mg prednisolone and equivalents for longer than 4 weeks, 15 (22.7%) before < 10mg prednisolone and equivalents for longer than 4 weeks, and 42 (63.6%) before azathioprine, methotrexate, and 6 mercaptopurine. All the participants stated that in clinical practice they performed routine HBV screening before treatment with rituximab and ofatumumab. HBV screening before the other treatments was performed by 57 (86.4%) before ≥ 10mg prednisolone and equivalents for longer than 4 weeks, by 46 (69.7%) before azathioprine, methotrexate, and 6 mercaptopurine, by 38 (57.6%) before tyrosine kinase inhibitors, and by 26 (39.4%)

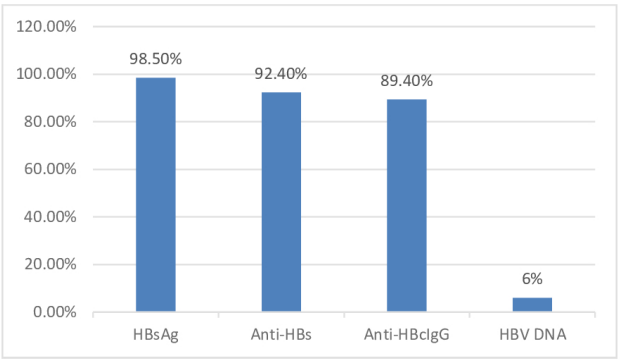

Figure 1. The tests used by the hematologists for HBV screening

before < 10mg prednisolone and equivalents for longer than 4 weeks. The theoretical knowledge and the clinical practice of the participants on the subject of HBV screening were seen to be similar.

The Timing and Follow Up of Prophylaxis

The vast majority (89.4%) of the hematologists in the study thought prophylaxis should be started before IST, and very few (10.6%) thought it should be started together with the IST. None of the study participants thought prophylaxis should be started after the IST. Follow up of patients who had started prophylaxis was made once every 3 months by 30 (45.4%) hematologists, once a month by 18 (27.3%) according to symptoms and findings by 12 (18.2%) and once every 6 months by 5 (7.6%). One hematologist stated that follow up was not necessary. When the frequency of follow up in respect of reactivation was questioned for patients who were HBV serology positive but for whom prophylaxis was not recommended, this was stated to be once every 3 months by 21 (31.9%), once a month by 18 (27.3%) according to symptoms and findings by 14 (21.2%), once every 6 months by 9 (13.6%), once a year by 2 (3%), and 2 hematologists did not recommend follow up.

Prophylaxis Experience and Reactivation

While 64 (97%) of the hematologists in the study stated that they had previously administered HBV prophylaxis to patients receiving IST, 2 (3%) had not. The agents most preferred in prophylaxis were tenofovir disoproxil fumarate (77.3%) and entecavir (74.2%), followed by lamivudine (30.3%) tenofovir alafenamide (30.3%) and adefovir (6%). A total of 29 (44%) hematologists reported that they had encountered HBVr at least once in patients receiving IST, 36 (54.5%) stated that HBVr had not developed, and 1 (1.5%) was not sure. When patients developed HBVr, 36 (54.4%) hematologists reported that hematological treatment had to be suspended, and 23 (35%) stated that hematological treatment continued without a break. Patient mortality because of HBVr was reported by 6 (9%) hematologists, and 1 (1.5%) stated that liver transplantation had been performed.

Training Related to HBV Reactivation

Training related to HBVr following IST had been received after graduation by 50 (75.8%) of the hematologists in the current study. The most common sources of information were textbooks and guidelines, and congresses or symposia. The participants reported to have received less benefit from internet sources and training seminars organized by drug companies.

Discussion

The field of IST has broadened in recent years and because of the risk of liver failure with these treatments in patients who are HBV carriers, HBV screening before IST is recommended in all the current guidelines related to this subject. The hematologists in this study had a very high level of awareness of the subject of performing this screening, which was higher than rates reported in previous studies that have evaluated the HBV screening rates of physicians administering IST (11-15). This finding shows that there has been an increase in awareness of HBV screening in recent years, and is extremely pleasing.

If patients with serological evidence of HBV infection (HBsAg or anti-HBcIgG positivity) receive IST, they are at risk of HBVr. The risk of reactivation is higher in HBsAg positive patients than in HBsAg negative patients. HBsAg positive patients are the highest risk group if there is HBeAg positivity and/or high HBV DNA levels (HBV DNA > 104 IU/mL). If HBsAg negative, anti-HBcIgG positive patients receive IST because cccDNA has remained in the hepatocyte nucleus, there is a risk of reactivation. In anti-HBcIgG positive patients, even if they are anti-HBs positive, reactivation may occur but the risk is lower (16).

In a retrospective study from the MD Anderson Cancer Centre, 8% of multiple myeloma patients who were planned to undergo transplantation were determined to have had HBV infection and the HBVr rate of these patients was reported as 6.5% (16). In another prospective study of lymphoma patients treated with various chemotherapy regimens, the majority of which were CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), HBVr was determined as 48% in HBsAg positive patients and 4% in anti-HBc and/or anti-HBs positive patients (17). In literature it has been reported that in patients with immunity from having had HBsAg negative and anti-HBc positive infection, HBVr may have a fatal course after the use of rituximab (18). In guidelines related to HBVr, it is recommended that HBsAg and anti-HBcIgG are tested together for HBV screening (1, 4, 8, 19-21). In the current study, the number of hematologists using the HBsAg test in screening was extremely high but the number requesting Anti-HBcIgG was lower.

The reactivation risk is calculated on the basis of the the combination of the serological status of the patient and the IST given to the patient. If the reactivation frequency of drugs is taken into consideration, the screening rate in the current study was not seen to be proportional with the reactivation power of the agents. There are very few articles related to HBV screening by hematologists before IST. A study conducted in Canada reported that in hematology and oncology practice, 58% of clinicians screened patients in respect of HBV before chemotherapy administered for solid and hematological malignancies (22). In the current study, all the hematologists reported that HBV screening was necessary before treatment with rituximab and ofatumumab, but the screening rates before treatment with tyrosine kinase inhibitors were very low.

In a study which evaluated the awareness of HBVr of physicians administering chemotherapy, including hematologists, it was reported that 45.8% of the participants considered it necessary to start prophylactic antivirals one month before chemotherapy, 42.2% at one week before chemotherapy and 12% at the same time as chemotherapy (23). Studies that have compared two strategies have shown that antiviral prophylaxis is more effective than protective precautions (24). The time of starting prophylaxis and the antiviral agent to be used depend on the duration of IST, the risk of reactivation, HBV serology and HBV DNA levels, and previous antiviral treatment (25). HBsAg positive patients should start anti-viral treatment before chemotherapy. Antiviral treatment should be started several weeks before chemotherapy and should be continued throughout the whole chemotherapy (11). It is appropriate to start prophylactic antiviral treatment a few weeks before IST in patients with HBV DNA levels > 104 IU/ml, and for other patients the two treatments can be started at the same time (4, 8). Proportional with guideline recommendations, the vast majority of the hematologists in the current study agreed that prophylaxis

should start before IST.

More recent nucleoside/nucleotide analogs, such as tenofovir and entecavir, have a more rapid and stronger effect, and a high resistance barrier. Therefore, most authorities recommend the use of tenofovir and entecavir in HBV prophylaxis. The EASL Clinical Practices Guideline in particular presents a recommendation at A1 level for entecavir or tenofovir prophylaxis for patients with high HBV DNA levels (4). Similarly in the current study, the two most preferred antiviral agents in prophylaxis were tenofovir disoproxil fumarate and entecavir.

Patients starting prophylactic treatment should be followed up in respect of liver enzymes and HBV DNA at 3-6 month intervals (4, 26). The prophylaxis recommendations for HBsAg negative, anti-HBcIgG positive (anti-HBs negative or positive) and HBV DNA negative patients vary according to international guidelines. If prophylaxis is not started, these patients should be followed up with liver function tests at 1-3 months and with HBV DNA in the 3rd month (4, 7). In the current study, there were seen to be very different approaches on the subject of follow up for patients who had started or not started prophylaxis. It was therefore concluded that there is a need for a standard follow-up approach to be established on this subject.

In various studies investigating the frequency of viral reactivation in HBV carriers receiving IST, viral reactivation has been reported to vary between 14% and 50%, and mortality related to viral reactivation at rates varying from 3.7% to 60% (27). Approximately half of the hematologists in the current study stated that they had encountered reactivation at least once. Of those, half reported that hematological treatment had to be suspended, and within these were patients with a mortal course.

It is extremely important that clinicians receive training on the subjects of the prevention of HBVr, and the investigation and management of HBV infection in patients who are to be administered IST. HBVr awareness can be increased with symposia and conferences, case meetings and seminars, and brochures and educational documents. The facilitation of consultations with infectious diseases and gastroenterology departments and improving communication between clinicians will reduce delays in prophylactic treatment and incorrect practices. More than half of the hematologists in the current study reported that they had received training related to HBVr after graduation.

There were some limitations to this study, primarily that the study questionnaire was only completed by 66 hematologists. A second limitation was that the vast majority of the hematologists participating in the study were working as academicians in university or other tertiary level hospitals. A sufficient number of hematologists working in state hospitals or second-level hospitals could not be reached. As the study population was comprised in this way, this could explain the high rate of awareness of the hematologists of HBVr risk. Further more comprehensive studies could eliminate these limitations.

Conclusion

The study group of this research comprised academic and non-academic hematologists, with a wide range of professional experience from 1 to 38 years, from various regions in Turkey. HBVr awareness was found to be at a high level in this group of hematologists, although it is concerning that there were physicians who did not use the anti-HBcIgG test in screening. Moreover, the rate of screening before treatment with tyrosine kinase inhibitors was low. There was seen to be no standard protocol for the follow up of patients who had or had not started prophylaxis. In conclusion, this study can be considered to be a stimulus on the subjects of preventing patients with isolated anti-HBcIgG positivity being overlooked, determining the HBVr risk associated with immunosuppressive drugs, and optimizing the follow up of patients.

Ethical Approval

Approval for the study was granted by the Local Ethics Committee (decision no:02.01.2020/34-09) and the study has been conducted according to the Declaration of Helsinki 1975.

Conflict of Interest

The authors declare that they do not have any interests that could constitute a real, potential or apparent conflict of interest with respect to their involvement in the publication.

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