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The compliance of our practice of hepatitis B virus screening with the current guidelines in patients undergoing chemotherapy for hematological malignancies

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Ethics Committee Approval
This study was approved by 'Non-Invasive Research Ethics Committee of Cukurova University Medical Faculty' on November 6, 2020 (document number 105/66).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The reactivation of Hepatitis B virus (HBV) among cancer patients is a critical issue which is preventable by precise detection of risky cases prior to the administration of chemotherapy drugs. This study aimed to investigate whether the evaluated serological tests for HBV screening before chemotherapy in adults with newly diagnosed hematological malignancies follow the guidelines.
Methods: In this retrospective cohort study, all patients with hematological malignancies who visited our hematology clinic between January 01, 2018-January 01, 2020, were examined and adult patients referred to the outpatient clinic for combined chemotherapy were included. All clinical data and laboratory results were obtained from the electronic hospital information system. Serological tests performed for HBV screening and their results were noted. The compliance of our clinical practice with the current guidelines was analyzed assuming that there are three mandatory serological tests for screening, HBsAg, anti-HBs and anti-HBc, recommended in the guidelines.
Results: A total of 91 newly diagnosed cases were included for analysis. HBV screening completely lacked in 10% of the patients and it did not follow the current guidelines in 30%. The most neglected serological test was anti-HBc. Regarding different hematological malignancies, the results were best in lymphoma patients (76% compliance with guidelines) and worst in MM (only 40% compliance with guidelines). The serological test results of eighty-two cases were also examined and the seropositivity rates for HBsAg and anti-HBc were 2%, and 41%, respectively.
Conclusion: We observed that the risk of reactivation was not adequately evaluated by serological screenings for HBV in adult patients receiving chemotherapy for hematological malignancy. To protect patients from this mostly preventable complication, it is necessary to increase the awareness on the subject and encourage more compliance with the related guidelines.

Keywords: Hepatitis B virus, Hematological malignancies, Reactivation

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Introduction

Hepatitis B virus (HBV) is an important health problem. According to the World Health Organization (WHO) data, our country is located where it is considered moderately endemic for HBV. One out of every three adults in Turkey is exposed to HBV [1,2]. Although the HBV vaccine is in the routine immunization program for children since 1998 and the vaccination of adults in the risk group is encouraged, epidemiological studies still reveal high rates of seropositivity in adults. One of the most important studies on HBV epidemiology in Turkey was conducted by the 'Turkish Association for the Study of the Liver' in 23 provinces that screened a total of 5460 individuals between 2009 and 2010. According to this study, 4% hepatitis B surface antigen (HBsAg) positivity and 30.6% total hepatitis B core antigen-antibody (anti-HBc) positivity were detected in individuals over 18 years of age [2].

On the other hand, the risk of treatment-related viral reactivation in cancer patients during chemotherapy is a well-known complication [3]. Serologically, HBsAg positivity is an indicator of chronic carriage, while anti-HBc positivity indicates previous exposure to HBV. Viral reactivation should be considered not only for HBsAg-positive cases, but also for HBsAg-negative/anti-HBc-positive patients [4]. Therefore, current guidelines recommend that HBsAg, anti-bodies against HBsAg (anti-HBs) and anti-HBc should be evaluated together in serological screenings before chemotherapy [5-8].

During the follow-up of cancer patients, the severity of the primary disease and the urgency of chemotherapy may cause missing or incomplete HBV screening practices. In our study, we aimed to investigate whether the evaluated serological tests for HBV screening before chemotherapy in newly diagnosed hematological malignancies were in accordance with the guidelines.

Materials and methods

In this retrospective cohort study, all adult patients with hematological malignancies who were referred to our hematology clinic between January 01, 2018-January 01, 2020, were examined. The patients aged 18 years and over who were referred to the outpatient unit to receive combined chemotherapy with a diagnosis of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia (CLL) or multiple myeloma (MM) were included in the study. The cases treated solely with steroids, those receiving chemotherapy due to recurrence or refractory disease, and patients with missing information on treatment or follow-up were excluded from the study. Patients whose treatment was continuing in our clinic but whose first treatment was started in another center were excluded as well.

All clinical data and laboratory results were obtained from the electronic information system used in our center for patient follow-up. Laboratory tests, which were conducted up to 3 months before the first day of chemotherapy were examined. Serological tests performed for HBV screening and their results were noted. To avoid bias during data collection, laboratory results were gathered from the system by an independent health worker who was blinded to the study details. Then, the compliance of our clinical practice with current guidelines was analyzed, assuming that there are three mandatory serological tests for screening: HBsAg, anti-HBs and anti-HBc, since these tests were recommended in both the national and international literature [5-8].

Ethical issues

This study was approved by the Non-Invasive Research Ethics Committee of Cukurova University Medical Faculty on November 6, 2020 (document number 105/66) and performed per the Helsinki Declaration guidelines.

Statistical analysis

Statistical analyses were performed by a biostatistician using SPSS Statistics version 17.0 (IBM). The normality of data was analyzed using the Kolmogorov-Smirnov test. For categorical values, p-values were calculated using the Chi-square test. All comparative tests were 2-tailed, and a *P*-value of less than 0.05 was considered statistically significant.

Results

In our study, 113 patients who were referred to our hematology clinic between January 01, 2018-January 01, 2020 and received combined chemotherapy in the outpatient unit were examined. Then, 91 newly diagnosed cases meeting the inclusion criteria were included for further analysis. The diagnoses of the cases were lymphoma in 56% (n = 51), CLL in 22% (n=20) and MM in 22% (n = 20). Among lymphoma patients, 80% (n = 41) were NHL and 20% (n = 10) were HL. The average age of study patients was 61 (20-81) years and 36% (n = 33) were female, while 64% (n = 58) were male.

Our HBV screening practice before chemotherapy is summarized in Table 1. It was observed that 90% (n=46) of lymphoma patients were screened with HBsAg, while 78% (n=40) were screened with anti-HBc. Similarly, 95% of CLL patients were screened for HBsAg (n=19), and 85% (n=17), for anti-HBc. Patients with MM were screened for HBsAg at a rate of 85% (n=17), while only 45% (n=9) were screened for anti-HBc. Compared to lymphoma and CLL, it seems that the ordering of appropriate serological tests was most often neglected in MM patients ($P<0.05$).

Table 1: Serological test ratios for HBV screening before chemotherapy

	Total (n=91)	Lymphoma (n=51)	CLL (n=20)	MM (n=20)	*P*-value*
Serological test					
HBs Ag, % (n)	90 (82)	90 (46)	95 (19)	85 (17)	0.570
anti-HBs, % (n)	88 (80)	88 (45)	95 (19)	80 (16)	0.345
anti-HBc, % (n)	72 (66)	78 (40)	85 (17)	45 (9)	0.027

*Chi-square test, HBV: Hepatitis B virus, CLL: Chronic Lymphocytic Leukemia, MM: Multiple Myeloma, HBsAg: Hepatitis B Surface Antigen, anti-HBs: Anti-Hepatitis B Surface Antigen Antibody, anti-HBc: Anti-Hepatitis B Core Antigen Antibody

Regarding all cases, HBV screening completely lacked in 10% (n=9) and it was not in accordance with the current guidelines in 30% (n=27). Concerning different hematological malignancies, the results of analysis about the compliance of our screening with the guidelines are summarized in Figure 1. It was best in lymphoma, since 76% was in accordance. The worst was in MM, because in 60% of the patients, the guidelines were not followed.

The evaluation of patients who received rituximab as a part of a combined chemotherapy protocol in a separate group revealed that 56 patients (n=40 NHL and n=16 CLL) were screened. The serological tests in 23% (n=13) were not in

accordance with the guidelines, and in 9% (n=5), screening was not performed at all.

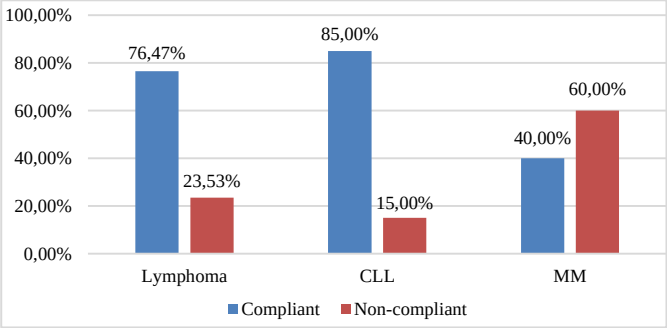
The results of serological tests in 82 cases who were screened for HBV were also examined. The rate of seropositivity for HBsAg was 2%, whereas it was 41% for anti-HBc. The rate of patients found to have anti-HBs positivity was 41% (Table 2).

Table 2: Serological test results in patients screened for HBV, n=82

	Total % (n*)	Lymphoma % (n*)	CLL % (n*)	MM % (n*)	*P*-value **
Rate of HBsAg seropositivity	2 (2/82)	4 (2/46)	0 (0/19)	0 (0/17)	0.448
Rate of anti-HBs seropositivity	41 (33/80)	47 (21/45)	42 (8/19)	25 (4/16)	0.318
Rate of anti-HBc seropositivity	41 (27/66)	30 (12/40)	65 (11/17)	44 (4/9)	0.050

* Number of seropositive patients divided by the number of screened patients, **Chi-square test, HBV: Hepatitis B virus, CLL: Chronic Lymphocytic Leukemia, MM: Multiple Myeloma, HBsAg: Hepatitis B Surface Antigen, anti-HBs: Anti-Hepatitis B Surface Antigen Antibody, anti-HBc: Anti-Hepatitis B Core Antigen Antibody

Figure 1: Compliance of our HBV screening practice with current guidelines (CLL: chronic lymphocytic leukemia; MM: multiple myeloma)



Discussion

HBV reactivation is preventable, provided that the risky cases are detected before the onset of chemotherapy and anti-viral agents are given prophylactically. On the other hand, if patients are not managed appropriately, past HBV exposure may result in asymptomatic hepatitis or sometimes life-threatening severe fulminant liver failure and death during chemotherapy [9].

In our study, routine screening for HBV was not performed before chemotherapy in 10% of the outpatients with hematological malignancies, and the serological evaluations were not in accordance with the current guidelines in about one third of the screened patients.

The most neglected serological test in our screening practice was anti-HBc. However, the exposure to the virus is recognized by the seropositivity of anti-HBc, while persistent HBsAg positivity indicates the presence of chronic infection. Following exposure, when the virus is eliminated from the blood, HBsAg becomes negative, but since viral DNA remains in the nuclei of infected hepatocytes, anti-HBc continues to be positive. Therefore, in individuals with a history of HBV exposure, even if HBsAg is negative, viral reactivation may occur in the case of immunosuppression [10].

When the cases were evaluated according to disease subgroups, our serological screening was found to be insufficient in about one fourth of the patients who received chemotherapy for lymphoma. When the literature on viral reactivation in patients with hematological malignancies undergoing chemotherapy is examined, it is seen that lymphoma patients are mainly included in the studies on the subject. In these patients, the reactivation rate can reach up to 50% and the risk is much higher for patients whose treatment protocol includes rituximab [3, 11].

Although the number of studies examining hematological malignancies other than lymphoma is less in the literature, there are also studies involving patients with MM [12]. In a retrospective study recently published from Turkey, a reactivation risk of 8% was reported for MM cases treated with new agents [13]. In our study, 60% of MM patients were insufficiently screened for Hepatitis B.

Regarding CLL, the ratio of insufficiently screened patients was 15%. Although the literature on CLL patients is scarce, these patients are also regarded to have increased risk for HBV reactivation, at least because of rituximab being the backbone of chemotherapy for CLL. The association of anti-CD20 monoclonal antibody ‘rituximab’ with viral reactivation is a well-known complication that has been the subject of many studies [14-16]. Rituximab usually exists in the treatment protocols for non-Hodgkin lymphoma and CLL. When our lymphoma and CLL patients who have rituximab in their treatment protocol were evaluated together, the ratio of patients whose serological screening was not performed per the guidelines was 23%, which is high.

In another study from Turkey, the rate of correct screening with serological tests in a different center was much lower than that recommended in the literature [17]. In the same study, the rate of patients who were positive for only HBsAg was 4%, while the rate of patients who were positive for anti-HBc was 16%. Similarly, our seropositivity rate for HBsAg was 4%, whereas it was 41% for anti-HBc in screened patients.

In a recent study involving 37 centers from our country, the awareness and clinical practice of physicians, 21% of which were hematologists, about HBV reactivation was investigated. While 88% of the total 430 physicians included in this study stated that they performed screening before immunosuppressive treatment in all patients, the rate of use of HBsAg as a screening test was 97%, while the rate of screening with anti-HBc was only 63% [18]. Our results are in parallel with these findings, as we mentioned that anti-HBc was the most neglected serological test.

The literature published from other countries reveals that the awareness deficit on the subject is a problem in many countries, including developed ones [19-21]. However, the fact that our country is in a region that is considered moderately endemic for HBV increases the importance of the issue.

The most important limitations of our study are its retrospective and single-center design. However, it is obvious that awareness on the subject should be increased, and our research may contribute to the future, larger scale studies.

Conclusion

We found that serological screening for HBV in adult patients with hematological malignancies receiving chemotherapy were not adequately ordered to assess the risk of reactivation during the treatment process and encouraging greater compliance with relevant guidelines is necessary to protect patients from this, often preventable, complication.

References

1. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Report No: CC BY-NC-SA 3.0 IGO.

2. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21:1020-6. doi: 10.1016/j.cmi.2015.06.028.
3. Lubel JS, Angus PW. Hepatitis B reactivation in patients receiving cytotoxic chemotherapy: diagnosis and management. J Gastroenterol Hepatol. 2010;25:864-71. doi: 10.1111/j.1440-1746.2010.06243.x.
4. Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol. 2016;22:219-37. doi: 10.3350/cmh.2016.0024.
5. Aygen B, Demir AM, Gümüş M, Karabay O, Kaymakoğlu S, Köksal AŞ, et al. Immunosuppressive therapy and the risk of hepatitis B reactivation: Consensus report. Turk J Gastroenterol . 2018;29:259-69. doi: 10.5152/tjg.2018.18263.
6. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98. doi: 10.1016/j.jhep.2017.03.021.
7. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1-98. doi: 10.1007/s12072-015-9675-4.
8. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57:1-20.
9. Hoofnagle JH. Reactivation of hepatitis B. Hepatology. 2009;49:156-65. doi: 10.1002/hep.22945.
10. Pattullo V. Hepatitis B reactivation in the setting of chemotherapy and immunosuppression - prevention is better than cure. World J Hepatol. 2015;7:954-67. doi: 10.4254/wjh.v7.i7.954.
11. Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, et al. Taiwan Cooperative Oncology Group. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. Hepatology. 2014;59:2092-100. doi: 10.1002/hep.26718.
12. Gentile G, Andreoni M, Antonelli G, Sarmati L. Screening, monitoring, prevention, prophylaxis and therapy for hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation: a systematic review. Clin Microbiol Infect. 2017;23:916-23. doi: 10.1016/j.cmi.2017.06.024.
13. Ataca Atilla P, Yalçıner M, Atilla E, İdilman R, Beksaç M. Hepatitis B Reactivation Rate and Fate Among Multiple Myeloma Patients Receiving Regimens Containing Lenalidomide and/or Bortezomib. Turk J Haematol. 2019;36:266-73. doi: 10.4274/tjh.galenos.2019.2019.0103.
14. Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol. 2011;22:1170-80. doi: 10.1093/annonc/mdq583.
15. Tsutsumi Y, Yamamoto Y, Ito S, Ohigashi H, Shiratori S, Naruse H, et al. Hepatitis B virus reactivation with a rituximab-containing regimen. World J Hepatol. 2015;7:2344-51. doi: 10.4254/wjh.v7.i21.2344.
16. Drößler L, Lehmann C, Töpelt K, Nierhoff D, Vehreschild JJ, Rybniker J, et al. HBsAg-negative/anti-HBc-positive patients treated with rituximab: prophylaxis or monitoring to prevent hepatitis B reactivation? Infection. 2019;47:293-300. doi: 10.1007/s15010-019-01271-z.
17. Sarı NG, Yıldırım Aİ, Doğu H, Yörük G. Hematolojik Maligniteli Hastalarda Hepatit B Virüs Serolojileri, Antiviral Profilaksi ve Reaktivasyon Hepatit Oranlarının Değerlendirilmesi. Turkiye Klinikleri J Med Sci. 2020;40(1):74-8. doi: 10.5336/medsci.2019-71432.
18. Korkmaz P, Demirtürk N, Aydın G, Ceken S, Aygen B, Toka O, et al. Awareness of hepatitis B virus reactivation among physicians administering immunosuppressive treatment and related clinical practices. Klimik Derg. 2019;32:146-53. doi: 10.5152/kd.2019.33.
19. Kawsar HI, Shahnewaz J, Gopalakrishna KV, Spiro TP, Daw HA. Hepatitis B reactivation in cancer patients: role of prechemotherapy screening and antiviral prophylaxis. Clin Adv Hematol Oncol. 2012;10:370-8.
20. Marignani M, Marzano A, Begini P, Vitolo U, Luminari S, Levis A, et al. Perception of hepatitis B virus infection reactivation-related issues among specialists managing hematologic malignancies: result of an Italian survey. Leuk Lymphoma. 2014;55:2564-71. doi: 10.3109/10428194.2013.879712.
21. Yuen MF. Need to improve awareness and management of hepatitis B reactivation in patients receiving immunosuppressive therapy. Hepatol Int. 2016;10:102-5. doi: 10.1007/s12072-015-9694-1.

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