

Original Article



Hepatitis B Virus Screening and Real Life Data in Patients with Solid Tumor Receiving Chemotherapy

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Abstract

Background: Reactivation of the hepatitis B virus (HBV) either during or after chemotherapy may cause serious and sometimes fatal hepatitis. All patients undergoing chemotherapy should therefore be screened in terms of HBV before chemotherapy. The purpose of this research was to identify HBV screening rates in patients with solid cancer undergoing parenteral chemotherapy and to determine the outcomes of patients undergoing HBV screening.

Methods: Data for patients undergoing parenteral chemotherapy for solid cancer from January 1, 2012 to December 30, 2018 were retrieved from our electronic health record patient files in this retrospective study. Screening was defined as hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (HBcAb) tests carried out within six months prior the first chemotherapy session.

Results: Four thousand fifty-eight (63%) of the 6440 patients who underwent parenteral chemotherapy were screened for HBsAg and/or HBcAb. The proportions of patients screened for HBsAg and HBcAb improved from 38.8% (2012) to 76.3% (2018), and from 0.2% (2012) to 43% (2018), respectively ($P < 0.001$). The HBsAg and HBcAb positivity rates were 2.9% and 36.5%, respectively. Antiviral prophylaxis was started in 11.8% of HBsAg-negative/HBcAb-positive patients and 40.5% of HBsAg-positive patients. HBV reactivation did not occur in patients receiving antiviral prophylaxis, but was identified in 7.2% of HBsAg-positive patients and 0.6% of HBsAg-negative/HBcAb-positive patients without antiviral prophylaxis.

Conclusion: Although HBV screening rates before chemotherapy are increasing among solid cancer patients, the rate of initiation of antiviral prophylaxis is still low. It is therefore important to raise awareness regarding HBV reactivation during/after chemotherapy.

Keywords: Chemotherapy, Hepatitis B virus, Malignancy, Reactivation, Solid tumours

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Introduction

The hepatitis B virus (HBV) infection is an important global health problem. According to the World Health Organization data, approximately 257 million people are chronically infected with HBV.¹ Since the viral genomic structure persists in the hepatocyte nucleus in individuals infected with HBV (hepatitis B surface antigen [HBsAg]-positive and/or hepatitis B core antibody [HBcAb]-positive), these patients are at risk of HBV reactivation when undergoing chemotherapy or immunosuppressive therapy.²⁻⁴ HBV reactivation rates in chemotherapy patients depend on HBV infection status and host factors, in addition to the chemotherapy regimen.^{5,6} Although chemotherapy-induced HBV reactivation is more common in patients with positive HBsAg, reactivation may also occur in HBsAg-negative/HBcAb-positive individuals.⁷ HBV reactivation presents in a wide spectrum, from an asymptomatic clinical course to severe hepatitis, and sometimes even death due to fulminant hepatic failure.^{4,8} HBV reactivation in cancer patients may also result in delayed or termination of curative oncological treatment,

potentially increasing the risk of morbidity and mortality.⁹ HBV screening prior to commencement of chemotherapy and prophylactic antiviral therapy in appropriate patients constitute one of the best ways to prevent HBV reactivation.¹⁰ Prophylactic antiviral therapies have been shown to be more effective than pre-emptive strategies in preventing HBV reactivation.^{11,12} The ideal approach for preventing HBV reactivation is therefore to start HBV prophylaxis in appropriate patients before chemotherapy.

Current gastroenterology guidelines recommend that all patients should be evaluated for HBsAg, hepatitis B surface antibody (HBsAb) and HBcAb before chemotherapy, and that all HBsAg-positive patients should be checked for antiviral therapy or prophylaxis. In addition, if the patient is HBsAg-negative but HBcAb-positive, and at high risk of HBV reactivation, prophylaxis should be also administered.¹³⁻¹⁵ However, it is still unclear whether patients receiving chemotherapy receive proper screening for HBV as recommended by the guidelines. We report the results of a retrospective observational study of HBV screening rates in patients with solid cancer undergoing

parenteral chemotherapy in a large university hospital. We also evaluated the rates of onset of antiviral prophylaxis and HBV reactivation among patients receiving chemotherapy who underwent HBV testing.

Materials and Methods

Study Populations and Data Sources

Solid cancer patients undergoing parenteral chemotherapy at the Karadeniz Technical University Medical Faculty Hospital, Turkey, between January 1, 2012 and December 30, 2018 were included in the study. Data were retrieved from our electronic health records using search terms (keywords and ICD codes), patient files, and the laboratory recording system. Patients diagnosed with solid cancer were first identified using ICD codes (C.00-C.75) from our hospital's electronic database. These patients' file numbers, age at time of diagnosis, gender, and dates of initial parenteral chemotherapy and hepatitis B serology tests were then determined. Patients who received intra-peritoneal, intra-pleural, intra-bladder, etc. chemotherapy, or receiving only targeted or hormonal therapy without immunosuppressive effects, or not receiving chemotherapy for any reason were excluded.^{5,16,17} Patients with primary liver cancer were excluded due to the etiological relationship between HBV and hepatocellular carcinoma.¹⁸ We also excluded patients who received antiviral treatment for HBV infection prior to chemotherapy, and those who were under 18 years of age. A flow chart of the study participants is shown in Figure 1.

Methods and Definitions

Screening was defined as HBsAg and/or HBcAb tests ordered within six months before the first chemotherapy session.^{4,19} HBsAb screening rates were also investigated. Positive findings on both HBsAg and HBcAb tests were regarded as chronic HBV infection, while HBsAg-negative and HBcAb-positive cases were regarded as occult HBV infection or resolved HBV infection.¹⁹ HBV reactivation

was defined as an abrupt increase in HBV DNA replication (10-fold or more) from baseline values or the reappearance of HBV DNA in serum, or reverse seroconversion from HBsAg-negative to HBsAg-positive, with or without increased hepatic enzymes.^{20,21} We evaluated whether antiviral prophylaxis was initiated based on the HBV test results. During the study period, serological markers, including HBsAg, HBsAb and HBcAb levels, were measured using electrochemiluminescence immunoassay on a Roche Cobas E601 device (Japan). Serum HBV DNA levels were determined using the real-time PCR method on a Roche Cobas AmpliPrep device (Japan) (lower limit of detection, 12 IU/mL). Routine biochemical parameters were assayed on a Roche Hitachi Cobas 8000 autoanalyzer (Roch, Germany).

Statistical Analysis

Statistical Program for Social Sciences software (SPSS 23.0 for Windows; SPSS Inc., Chicago, IL, USA) was employed for all statistical analyses. Descriptive statistics were expressed as number and percentage for categorical variables and as mean \pm standard deviation for numerical variables. Confidence intervals were calculated by Wilson method with continuity correction. Normal distribution of numerical variables was analyzed using the Kolmogorov-Smirnov test and Q-Q plot. The Mann-Whitney U test was employed in the comparison of numerical variables between two independent groups. Pearson's chi-square test was applied to evaluate the relationship between HBV screening status and gender, and the linear-by-linear association test (chi-square for trend) to evaluate HBV screening rates and antiviral prophylaxis initiation rates before chemotherapy by years. The screening rates for each cancer type were compared according to the screening rate of the gastrointestinal cancer group. The test requirement for Pearson chi-square test, the number of expected counts below five, was checked before performing the Pearson chi-square test. Statistical significance was set at $P < 0.05$.

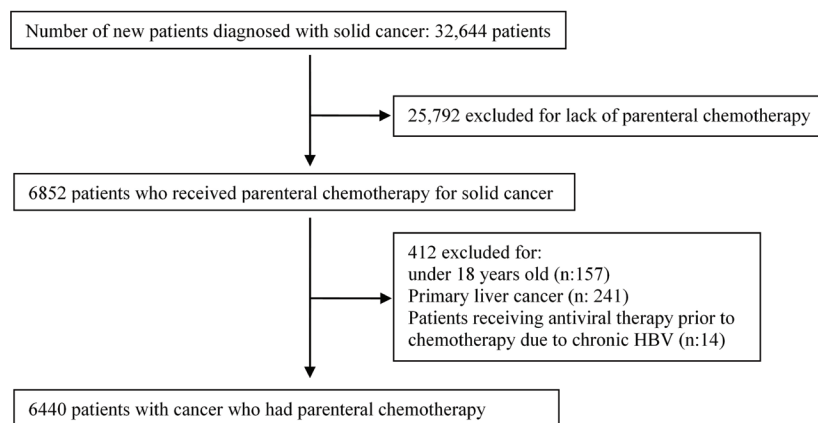


Figure 1. Flow Chart of Patients Enrolled in This Analysis.

Results

A total of 6440 adult patients received parenteral chemotherapy for solid cancer between January 1, 2012 and December 30, 2018. The average age of the patient group at the time of chemotherapy was 58 years, and the majority were men (54.1%; $n = 3482$). The most common malignancies were gastrointestinal (28.9%), respiratory (25.1%) and breast cancers (22.4%). HBV screening rates differed according to cancer types (Pearson chi-square, $p: 0.03$). HBV Screening rate was highest in soft tissue tumors (70.1%) followed by gastrointestinal (65.3%) and respiratory system (64.6%) tumors. The distribution of the solid tumors and characteristics of these patients are given in Table 1. Of the 6440 patients who received chemotherapy, 4058 (63%) underwent screening for HBsAg and/or HBcAb before the first chemotherapy session. Overall, 62.9% of patients ($n = 4050$) underwent screening for HBsAg, 52.5% ($n = 3379$) for HBsAb, and 18.9% ($n = 1218$) for HBcAb before chemotherapy. The screening rates for HBsAg, HBsAb and HBcAb improved from 38.8% (2012) to 76.3% (2018), from 31.2% (2012) to 67.6% (2018), and from 0.2% (2012) to 43% (2018), respectively (chi-square for trend, $P < 0.001$) (Figure 2). HBsAg, HBsAb and HBcAb positivity rates among the patients screened for HBV serological markers were 2.9% (116/4050), 31.5% (1066/3379), and 36.5% (445/1218), respectively. The prevalence of a positive HBcAb result with a negative HBsAg test was 33.9% (396/1169). HBV DNA was tested in only 25 (21.5%) of the 116 patients with HBsAg positivity, and five were identified as HBV-

DNA-positive. HBV-DNA was tested in only 5 (1.3%) of the 396 patients identified as HBsAg-negative/HBcAb-positive, none of whom were HBV-DNA-positive. Forty-seven (40.5%) of the 116 patients who tested positive for HBsAg before chemotherapy received prophylactic antiviral treatment, and none exhibited HBV reactivation, whereas five (7.2%) of the 69 patients with no antiviral prophylaxis had HBV reactivation. Four of the patients exhibiting reactivation were treated with pre-emptive antiviral therapy, while one was not. Two of these patients exhibited no deterioration in clinical and laboratory tests, while three had elevated transaminases. No mortality was seen in any of the patients with reactivation. Forty-seven (11.8%) of the 396 patients identified as HBsAg-negative/HBcAb-positive before chemotherapy received prophylactic antiviral treatment, and no HBV reactivation was detected in any of these, whereas two (0.6%) of the 349 patients with no antiviral prophylaxis exhibited HBV reactivation (Table 2). Two patients exhibiting reactivation received pre-emptive antiviral therapy. One of the patients who developed reactivation was successfully treated with rescue therapy, while the second died due to liver failure. A marked time-dependent increase was observed in rates of initiation of antiviral prophylaxis in patients identified as HBsAg-positive before chemotherapy (chi-square for trend, $P = 0.04$). None of the HBsAg-negative/HBcAb-positive patients was started on prophylaxis before 2015. Although the rates of patients started on prophylaxis rose after 2015, the increase was not statistically significant (chi-square for trend, $P = 0.240$) (Figure 3).

Table 1. Characteristics and HBV Screening Pattern of the Study Population Before Chemotherapy

Characteristics	All patients 6440 (%100) n [% ^a (95% CI)]	Screened patients ^b 4058 (%63) n [% ^c (95% CI)]	Unscreened patients ^d 2382 (%37) n [% ^d (95% CI)]	P value [OR (95%CI)]
Age (Mean±SD)	58.3±12.8	58.3±12.6	58.6±13	0.279*
Sex				
Male	3482 [54.1 (52.8-55.3)]	2204 [54.3 (52.8-55.8)]	1278 53.6 (51.6-55.7)]	0.588 [0.97 (0.87-1.07)]**
Female	2958 [45.9 (44.7-47.2)]	1854 [45.7 (44.2-47.2)]	1104 [46.4 (44.3-48.4)]	
Cancer type				0.003***
Gastrointestinal	1861 [28.9 (27.8-30.0)]	1216 [65.3 (63.1-67.5)]	645 [34.7 (32.5-36.9)]	—
Respiratory	1617 [25.1 (24.7-26.2)]	1044 [64.6 (62.8-66.9)]	573 [35.4 (33.1-37.8)]	0.632 [0.96 (0.84-1.11)]
Breast	1444 [22.4 (21.4-23.5)]	851 [58.9 (56.3-61.5)]	593 [41.1 (38.5-43.7)]	0.001 [0,76 (0.66-0.87)]
Genitourinary	1111 [17.3 (16.3-18.2)]	687 [61.8 (58.9-64.7)]	424 [38.2 (35.3-41.1)]	0.054 [0.85 (0.73-1.00)]
Soft tissue	117 [1.8 (1.5-2.1)]	82 [70.1 (60.8-78.0)]	35 [29.9 (22.0-39.2)]	0.295 [1.24 (0.82-1.86)]
Head and Neck	105 [1.6 (1.3-2.0)]	66 [62.9 (52.8-72.0)]	39 [37.1 (28.1-47.2)]	0.603 [0.89 (0.59-1.34)]
Others	185 [2.9 (2.5-3.3)]	112 [60 (53.1-67.6)]	73 [40 (32.4-47.0)]	0.147 [0.79 (0.58-1.08)]

HBV, hepatitis B virüs; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody.

^a The percentages represent column percentages.

^b Patients screened for HBsAg and /or HBcAb within 6 months prior to first chemotherapy.

^c The percentages represent row percentages.

^d Patients not screened for HBsAg and /or HBcAb within 6 months prior to first chemotherapy.

* The Mann Whitney U test.

** Pearson Chi-square.

***Comparison of screening rates for each cancer type according to the rate of gastrointestinal cancer screening.

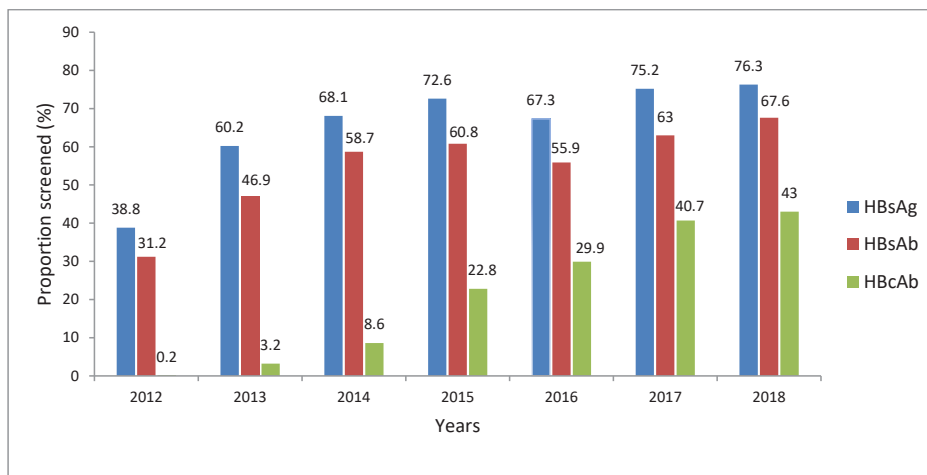


Figure 2. Series Annual Changes in HbsAg, HbsAb and HbcAb Screening Rates Before Chemotherapy.

Discussion

HBV reactivation is a potentially significant complication seen in patients with HBV infection receiving chemotherapy or other immunosuppressive agents. In one meta-analysis, the rate of HBV reactivation in patients with chronic HBV undergoing chemotherapy for solid tumors without antiviral prophylaxis ranged from 4% to 68% (median, 25%).² HBV reactivation can be largely avoided by means of prophylactic or early treatment with antiviral agents.^{2,10-12} However, initiation of antiviral treatment after chemotherapy-induced HBV reactivation is usually not effective in reducing hepatic damage and preventing progression to hepatic failure.^{11,22} Routine HBV screening in these patients before chemotherapy and the commencement of antiviral prophylaxis before developing HBV reactivation are therefore recommended by major gastroenterology guidelines.¹³⁻¹⁵

Studies have investigated HBV screening rates before chemotherapy in regions with low^{4,5,18,23,24} and high hepatitis B prevalence.^{19,20} According to the results of an epidemiological study from Turkey, the prevalence rates of HBsAg positivity and HBcAb positivity in the adult age group (≥18 years) are 4% and 30.6%, respectively.²⁵ To the

best of our knowledge, there have been no previous studies concerning pre-chemotherapy HBV screening in solid tumor cases in countries with a moderate prevalence of HBV, such as Turkey. This retrospective study investigated HBV screening rates before chemotherapy in patients undergoing chemotherapy for solid cancer in Turkey. The results showed that the overall HBV screening rate (defined as testing for HBsAg and/or HBcAb) over the period 2012–2018 was 63%, much lower than it should be. HBsAg, HBsAb and HBcAb positivity rates among patients screened for HBV serological markers were 2.9%, 31.5%, and 36.5%, respectively. The screening rates for HBsAg, HBsAb and HBcAb improved from 38.8% (2012) to 76.3% (2018), from 31.2% (2012) to 67.6% (2018), and from 0.2% (2012) to 43% (2018), respectively.

Far lower HBV screening rates have been reported in patients receiving cancer chemotherapy than those recommended by guidelines. Studies conducted in low endemic areas for HBV such as Canada and the United States have reported overall HBV screening rates below 20%. These studies have reported screening rates for solid cancers between 4% and 8.3%.^{4,5,16,19,23,24} Surveys conducted among oncologists in low-endemic areas

Table 2. HBV Screening and Treatment Rates of the Study Population Before Chemotherapy

Screening Test	Screening Test Performed Before Chemotherapy Patients/Total [% (95% CI)]	Positive Test Result Patients/Total [% (95% CI)]	Antiviral Therapy Started in Positive Test Result Patients/Total [% (95% CI)]	Antiviral Therapy Did not Start in Positive Test Result Patients/Total [% (95% CI)]	HBV Reactivation in Patients not Receiving Antiviral Prophylaxis Patients/Total [% (95% CI)]
HBsAg	4050/6440 [62.9(61.7-64.1)]	116/4050 [2.9(2.4-3.4)]	47/116 [40.5(31.6-50.1)]	69/116 [59.5(50.0-68.4)]	5/69 [7.2(2.7-16.8)]
HBcAb IgG/total	1218/6440 [18.9(18.0-19.9)]	445/1218 [36.5(33.8-39.3)]	47/396* [11.9(8.9-15.5)]	349/396 [88.1(84.4-91.1)]	2/349 [0.6(0.1-2.2)]
HBsAb	3379/6440 [52.5(51.2-53.7)]	1066/3379 [31.5(30.0-33.2)]	0/773**	773/773 [100.0(99.4-100.0)]	0/773

HBV hepatitis B virus; HBsAg hepatitis B surface antigen; HBsAb hepatitis B surface antibody; HBcAb hepatitis B core antibody.

*Out of 445 HBcAb positive patients, 49 HBsAg positive patients were excluded.

**Out of 1066 HBsAb positive patients, 293 HBsAg and / or HBcAb positive patients were excluded.

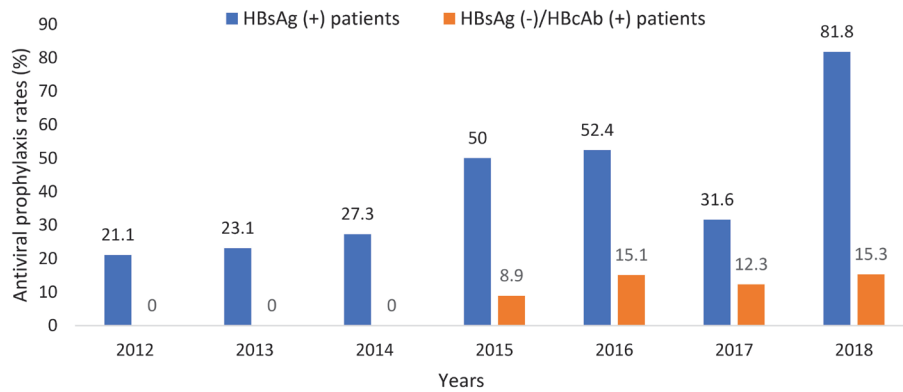


Figure 3. Antiviral Prophylaxis Rates in Hepatitis B Surface Antigen-Positive (n = 116) and HbsAg-Negative/HbcAb-Positive (n = 396) Patients Undergoing Chemotherapy for Solid Tumors.

have revealed that only a small proportion of oncologists (13–22%) report screening all patients receiving chemotherapy.^{21,26,27} The majority of oncologists generally screen for risk factors such as ethnicity or abnormal liver biochemistry. Even in high endemic areas, screening rates were low. In a study from China, only 17% of patients underwent pre-chemotherapy HBV tests.²⁰ Similar to our own research, another study from Japan reported pre-chemotherapy screening rates of 66.3% and 19.9% for HBsAg and HbcAb, respectively.¹⁹ These results indicate that the importance of HBV screening before chemotherapy is not fully understood yet. We therefore think that this may be due to various differences between oncology and gastroenterology guidelines in these patients. Although gastroenterology guidelines¹³⁻¹⁵ advise that all patients should be screened for HBV before chemotherapy, oncology guidelines^{28,29} recommend screening only patients receiving high-risk chemotherapy or those at high risk of reactivation. This leads to confusion among physicians applying chemotherapy. In addition, the fact that HBV reactivation is relatively uncommon in cases receiving chemotherapy or is ignored by physicians applying chemotherapy, and probable concerns over additional costs entailed by HBV screening, may also be responsible for low HBV screening rates.

HBV screening rates can be increased by raising the awareness regarding HBV reactivation among physicians applying chemotherapy and by using routine screening programs and/or alarm systems for HBV before chemotherapy. In a retrospective study of cancer patients in Canada, Lee et al reported an increase in pre-chemotherapy screening rates from 14% to 31% after training of principal members of the oncology team, including physicians and pharmacists.²⁴ A recent retrospective study from Holland by Leber et al reported that the pre-chemotherapy HBV screening rate of 52.9% increased to 80.7% following the application of a routine HBV screening protocol. The screening rate in patients with solid tumors in that study rose from 22–58% to 42–98%.³⁰ The use of an automated

alarm system to monitor HBV status in electronic patient records prior to chemotherapy may help improve HBV screening results. In a study of patients receiving biological therapy, Sampedro et al showed that with the use of an alarm system before treatment, screening rates for HBsAg increased from 50% to 94% and those for HbcAb from 30% to 85%.³¹ In a study from 2009, Sun et al reported that the screening rate of 26.8% for HBsAg before cytotoxic chemotherapy increased to approximately 85.5% in the same hospital with the use of an alarm system.¹⁷

In our study, only 40.5% (47/116) of patients with HBsAg-positive patients, who were at high risk of HBV reactivation, were started on antiviral prophylaxis prior to chemotherapy. However, the rates of starting antiviral prophylaxis in these patients improved significantly over the years ($P=0.04$) (Figure 3). Only 11.8% (47/396) of HBsAg-negative/HbcAb-positive patients were started on antiviral prophylaxis. In agreement with our findings, previous studies have also reported low rates of initiation of antiviral prophylaxis in patients screened and testing positive for HBV. Sun et al investigated 1053 patients receiving cytotoxic chemotherapy and reported that only 45.5% (61/134) of HBsAg-positive patients before chemotherapy were started on antiviral prophylaxis. HBV reactivation rates in that study were 1.6% in patients receiving antiviral prophylaxis but 15.1% in those not receiving it.¹⁷ Chung et al performed a retrospective study of 8005 patients receiving chemotherapy in the Mayo Clinic in the USA and reported that eight (61.5%) of the 13 patients identified as positive for HBV were started on antiviral prophylaxis and that no HBV reactivation occurred in them, while reactivation was identified in two of the five patients not started on antiviral prophylaxis.¹⁶ The best means of preventing HBV reactivation among patients testing positive for HBV is antiviral prophylaxis prior to chemotherapy. In the present study, no HBV reactivation was observed in patients started on antiviral prophylaxis, while reactivation was identified in 7.2% of the HBsAg-positive patients not started on antiviral

prophylaxis and in 0.6% of the HBsAg-negative/HBcAb-positive patients.

Our current study yielded important findings concerning both HBV screening rates and antiviral prophylaxis initiation rates in solid cancer patients undergoing chemotherapy. The principal limitations of our study are associated with its retrospective nature. No specific protocol was employed to detect all cases of HBV reactivation, and most patients had no HBV DNA data available at baseline or during chemotherapy. In addition, due to the retrospective nature of the present study, confounding factors which might have affected the outcome of the study could not be included in the analysis because of lack of information about possible confounders within the data, and the according adjustments could not therefore be made.

In conclusion, the overall rate of HBV screening before chemotherapy among patients with solid cancer undergoing parenteral chemotherapy during 2012–2018 was 63%, but it increased over time. Additionally, we found that even among patients identified as HBsAg-positive before chemotherapy, fewer than half of patients were started on antiviral prophylaxis. More advances strategies are therefore needed both in order to improve levels of awareness regarding HBV reactivation among physicians applying chemotherapy and also to increase antiviral prophylaxis rates among appropriate patients.

Authors' Contribution

SF and EF contributed equally to the working concept and design. The critical revision of the article was made by EF, AMC, and ME. All authors have made significant contributions to the analysis and interpretation of the data. SF wrote the first draft of the manuscript, and all authors read and approved the last article.

Conflict of Interest Disclosures

The authors have no conflict of interest to declare.

Ethical Statement

The study was carried out in line with the principles of the Declaration of Helsinki and was approved by the local ethical committee of Karadeniz Technical University (No. 2018 /211).


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