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A survey of clinical practices among oncologists regarding hepatitis B screening in patients with cancer

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***Background & objectives*: Screening for hepatitis B prior to the initiation of chemotherapy in patients with cancer is recommended by all major hepatology and oncology societies. This study was aimed to determine the screening practices for hepatitis B among oncologists from India and their experience with hepatitis B reactivation.**

***Methods*: A questionnaire-based survey was conducted among oncologists attending the Evidence-Based Medicine Conference at Tata Memorial Centre, Mumbai, India. The questionnaire was developed in keeping with the recent guidelines for hepatitis B reactivation on chemotherapy, with questions regarding demographics, years in practice and hepatitis B screening practices and management. There was 78 per cent response rate to the questionnaire.**

***Results*: Most respondents were <35 yr of age (69%), with <five years of experience (39%), practicing in an academic institution (81%). Seventy four per cent respondents always screened their patients with cancer for hepatitis prior to chemotherapy, whereas 19 per cent in special settings and seven per cent never screened; 96 per cent respondents used hepatitis B surface antigen (HBsAg) as a screening test, while 17 per cent also used antibody to hepatitis B core antigen. Sixty one per cent respondents used entecavir or tenofovir for prophylaxis; 70 per cent continued prophylaxis till 6-12 months after completion of chemotherapy, while 21 per cent continued only till the end of chemotherapy.**

***Interpretation & conclusions*: More than 25 per cent of the oncologists were not screening their patients with cancer for viral hepatitis prior to cancer-directed therapy, and only 17 per cent of the oncologists used the recommended tests for screening. Better training of oncologists regarding viral hepatitis screening and management is needed.**

Key words Cancer - hepatitis B virus - hepatitis B virus reactivation - hepatitis B screening - oncologists

Hepatitis B infection is a global health problem with a prevalence that varies according to geographic area. Approximately two billion people worldwide show serological evidence of prior or current hepatitis B virus (HBV) infection with 350-380 million chronic carriers[1]. India is an intermediate prevalence region (2-8%) for hepatitis B[2]. Chronic HBV infection can cause liver cirrhosis and is the leading cause of hepatocellular carcinoma in India[3].

Cancer patients with hepatitis B can develop HBV reactivation (HBVr) when started on chemotherapy without antiviral prophylaxis. The risk of reactivation is in the range of 20-50 per cent for hepatitis B surface antigen (HBsAg)-positive patients[4]. Patients with reactivation may present with acute hepatitis, acute liver failure or acute-on chronic liver failure. This may affect the dose intensity as well as compliance with chemotherapy regimens, leading to compromised oncologic outcomes. Prophylactic antivirals prior to initiating chemotherapy reduce the relative risk of reactivation by 87 per cent and lead to 84 per cent of reduction in flares[5]. HBsAg-negative, anti-HBc (hepatitis B core antibody)-total positive patients who are likely to have occult hepatitis B infection are at risk of reactivation and reverse seroconversion with certain immunosuppressive agents[6]. Hence, pre-emptive therapy after assessing HBV DNA, if not prophylaxis, based on risk is warranted in this subgroup.

The American Gastroenterology Association (AGA) guidelines and the American Society of Clinical Oncologists clinical opinion update recommend screening for all patients planned for immunosuppressive chemotherapy by testing for HBsAg and anti-HBc[5,7]. It is recommended to start antiviral prophylaxis based on the expected risk of reactivation with the need for close monitoring of patients for the same. Although clearly mentioned in guidelines and clinical opinion, there is a variable implementation of these screening practices in real life. Therefore, a questionnaire-based survey of oncologists attending an evidence-based medicine (EBM) meeting in oncology was conducted to study the current clinical patterns of HBV screening and management of hepatitis B in patients with cancer.

Material & Methods

This was a cross-sectional, questionnaire-based survey, granted an exemption from review by the Institutional Ethics Committee of the Tata Memorial Hospital, Mumbai, India. The questionnaire was developed in a multiple-choice format by the investigators after reviewing the current literature and guidelines regarding HBVr. A two-page questionnaire with 13 multiple-choice questions pertaining to demographic data of the participant, HBV screening practices and treatment plan was developed. This questionnaire was used to determine the knowledge and clinical practices towards hepatitis B screening among oncologists attending the annual EBM conference, 2018, held at Tata Memorial Centre, Mumbai, between February 23-25, 2018. Medical and radiation oncologists in particular were approached for participation and voluntarily answered the questionnaire, which took 5-7 min to complete. Surgical oncologists and doctors from other specialities were not included in the survey. Anonymity of the participants was ensured.

Statistical analysis: Data were collated from the survey forms and analyzed. Frequencies were used to describe the demographic data. Data analysis for comparisons based on practice setting, years of practice, screening tests used and preferred antivirals was done using Chi-square or Fisher's exact test. Statistics were done using SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results & Discussion

Of the 888 participants registered for the conference, 350 were medical and radiation oncologists. A total of 204 participants were contacted and 161 responses (78%) were received. Eighty one per cent (130/161) respondents practiced in an institutional or academic setting, whereas 19 per cent (31/161) had a non-institution-based private practice. Most respondents (69%, 111/161) were <35 yr of age; 27 per cent (43/161) were between 35 and 50 yr of age and four per cent (7/161) were >50 yr of age. Based on years of practice, 39 per cent (63/161) respondents were in practice for <five years; 30 per cent (49/161) were doing their residency in oncology, 22 per cent (35/161) were in practice for 5-15 yr and nine per cent (14/161) were in practice for >15 yr.

Details on screening and treatment practices are summarized in the Table. Seventy four per cent respondents always screened patients for hepatitis B prior to initiating chemotherapy while seven per cent never screened prior to chemotherapy. Respondents practicing in an academic or institutional setting were more likely to screen patients for hepatitis B prior to chemotherapy (P<0.05), and respondents who were either doing their residency or in practice for <five years were more likely to screen for hepatitis B (P<0.001). Forty per cent (64/161) respondents had experience with hepatitis B reactivation during chemotherapy.

The preferred screening test was HBsAg in 96 per cent (154/161) respondents. Anti-HBc was advised by 17 per cent, antibody to hepatitis B surface antigen (anti-HBs) by 5.5 per cent, HBV DNA PCR by 11 per cent (18/161) and hepatitis B e antigen by

Table. Hepatitis B virus screening and treatment practices (n=161)

Parameters	n (%)
Screening of patients	
Always	120 (74)
Selected groups	30 (19)
Never	11 (7)
Tests ordered	
HBsAg	154 (96)
Anti-HBc	27 (17)
Anti-HBs	9 (5.5)
HBV DNA	18 (11)
HBeAg	5 (3)
Preferred antiviral	
Entecavir	79 (49)
Tenofovir	20 (12)
Lamivudine	37 (23)
Peg-interferon	4 (2.5)
Other	8 (5)
Duration of antiviral prophylaxis	
Till completion of chemotherapy	33 (21)
6-12 months after stopping chemotherapy	113 (70)

HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; anti-HBc, hepatitis B core antibody

three per cent (Table). Eighty nine per cent (144/161) respondents referred to a specialist if screening tests were positive, 10 per cent respondents treated patients by themselves, while one per cent monitored patients without any prophylaxis despite positive screening tests. The preferred antiviral was entecavir in 49 per cent (79/161) and tenofovir in 12 per cent (20/161). Lamivudine was preferred by 23 per cent (37/161). Of the 161 respondents, 113 (70%) believed that the duration of prophylaxis was till 6-12 months after chemotherapy completion while 33 (21%) believed that prophylaxis was to be given only till the end of chemotherapy.

In our study, 26 per cent oncologists screened only selected groups or did not screen at all prior to initiating therapy. The reasons could be lack of knowledge, additional costs of the tests and also perception of questionable benefit among oncologists. The consequences of such practice include hepatitis B reactivation leading to flare, with delay or termination of oncologic therapy resulting in increased morbidity and in severe cases, even mortality[4,5]. As India is a country with >2 per cent seroprevalence for hepatitis B[2], screening all patients prior to chemotherapy would be the right strategy. There are no guidelines laid down by the Indian societies with regard to screening for hepatitis B. Hepatitis B risk factors occur more commonly in patients with cancer[8]. Rates of HBsAg seroreactivity in a high-risk group of patients, including those receiving chemotherapy in the USA varied between 3 and 9 per cent as compared to normal population having a rate of <1 per cent[9]. Reactivity to antibody to core antigen (anti-HBc) was higher (15-46%) among oncology patients compared to normal population (5-8%). Despite this, low rates (16-17%) of screening of cancer patients for HBV infection have been reported among oncologists[9,10].

In a previous study from the USA, 76 per cent of the respondents used HBsAg as the screening test prior to chemotherapy, whereas 64 per cent used anti-HBs and 46 per cent of used anti-HBc to screen patients[11]. Hence, contrary to the recommendations from major hepatology societies, use of anti-HBc to screen patients prior to chemotherapy seems uncommon. In our study, HBsAg was used by 96 per cent participants for screening for HBV infection, whereas only 17 per cent believed in using a combination of HBsAg and anti-HBc.

The role of hepatitis B surface antibody (anti-HBs) in screening prior to cytotoxic chemotherapy is not clear. Up to 10 per cent of chronic hepatitis B patients may have anti-HBs reactivity, which may not be protective[12]. However, in a patient who is HBsAg negative, anti-HBc and anti-HBs reactive, loss of anti-HBs may be predictive of reactivation[13]. The AGA[5], American Association for the Study of Liver Diseases (AASLD)[14] and European Association for Study of Liver (EASL)[15] in their clinical practice guidelines recommend for universal testing with HBsAg and anti-HBc prior to the initiation of chemotherapy. No recommendation is made for anti-HBs testing prior to chemotherapy[5,14,15]. Although six per cent respondents in our survey chose anti-HBs as a screening test, its clinical utility is currently questionable.

Oral nucleos(t)ide analogues with high barrier to resistance (entecavir and tenofovir) are recommended as prophylaxis during ongoing chemotherapy as per the AGA recommendations[5]. Two meta-analyses recommended in favour of these drugs over lamivudine with respect to lower rates of HBVr, HBV-related hepatitis and mortality and also resistance[16,17]. Although

efficacious, the high rates of resistance encountered with the use of lamivudine pose a significant clinical challenge, when used as antiviral prophylaxis. The predictors of early resistance include pre-core mutations, higher baseline alanine transaminase and persistent viraemia at six months after treatment initiation[18]. Pre-core mutants constitute approximately 15 per cent of all chronic hepatitis B patients in India and hence are at an increased risk of resistance[19].

The ideal duration of prophylaxis recommended is up to 6-12 months after the completion of chemotherapy or immunosuppression[5,14]. There are reports of reactivation after 12 months of completion of chemotherapy, especially after bone marrow transplantation and biologic therapy[20,21]. Hence, close monitoring is required in this subset of patients, even after cessation of antiviral prophylaxis.

The limitations of our study include those associated with survey studies, wherein the population surveyed may not be truly representative of practicing physicians in the real world. In addition, as these were medical and radiation oncologists attending an EBM meeting, there was a possibility of self-selection bias as these physicians were likely to be more self-motivated and aware of the recent guidelines and to update their practice based on recent knowledge[22].

In conclusion, the study showed gaps in screening practices of oncologists screening patients with cancer inadequately for hepatitis B prior to chemotherapy and a large proportion unaware of correct options for prophylaxis and the duration for treatment. These gaps in the training and education of oncologists need to be addressed.

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***Conflicts of Interest*:** None.

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