Screening and Prevention of Hepatitis B Virus Reactivation During Chemotherapy

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The incidence of both hepatitis B virus infection and cancer is common. The use of immunosuppressive therapy in patients with hepatitis B virus can result in reactivation of hepatitis B virus, which can, in turn, lead to significant morbidity and mortality.

Introduction

Hepatitis B virus (HBV) infection is common across the world. Infection can lead to significant morbidity from cirrhosis and hepatocellular carcinoma. An estimated 240 million people have chronic (hepatitis B surface antigen [HBsAg]-positive) HBV infection.[1] As a result of increasing immigration from highly endemic areas (eg, China, Southeast Asia, Africa, Eastern Europe), the prevalence of chronic infection in the United States is rising and is estimated to be 1.5 million.[2] Across the country, the overall age-adjusted prevalence of chronic infection and evidence of exposure to infection (defined by the presence of antibody to HBV core antigen [anti-HBc] in the absence of HBsAg) have been reported to be 0.3% and 4.7%, respectively[3]; however, rates are much higher and can approach 10% to 15% in certain cities. In addition, many patients with HBV infection are unaware that they are infected.[4,5] At the same time, it is estimated that over 40% of the US population will develop some type of cancer during their lifetime,[6] and most patients will receive immunosuppressive therapy (IST) as treatment for their malignancy. This is notable because patients with chronic HBV infection or evidence of prior HBV infection who are exposed to IST are at risk for HBV reactivation.[7,8] We will discuss HBV reactivation in order to raise awareness of the problem and to detail our strategy for preventing this potentially severe complication of IST.

Why Do We Screen?

Screening patients for HBV and intervening with appropriate antiviral prophylaxis prior to IST prevents HBV reactivation and its morbid sequelae. The definition of HBV reactivation varies, but we define viral reactivation as the reappearance of detectable HBV DNA that had been previously undetectable, or a positive HBsAg and HBV DNA level > 10,000 IU/mL in a previously unscreened patient. HBV can lead to hepatitis, which is defined as a threefold increase in alanine aminotransferase from baseline value. Hepatitis may then lead to impairment of liver function, liver failure, and death.[7,9] HBV reactivation can result in delay or termination of curative oncologic treatment, which may increase a patient's risk of mortality.[10]

Who Do We Screen?

There is variability in the approach to HBV screening before cancer therapy. Some national guidelines[5,11] encourage universal screening of patients receiving cytotoxic therapy or IST, whereas others[12,13] support risk-based screening. Our current approach at Memorial Sloan Kettering Cancer Center (MSKCC) is to screen all new patients who will be receiving IST. Although certain patients may have a higher pre-test probability of a positive screening result (based on country of birth, sexual history, and blood transfusion, among other factors), our past experience at MSKCC has shown that at least half of HBV reactivations occurred in patients considered to be “low risk” for HBV infection; therefore, individualized risk-based screening would have missed these patients. Although HBV reactivation was initially described in lymphoma patients and best documented in HBsAg-positive patients treated with IST for hematologic malignancies,[14,15] the risk is not confined to this group; patients with solid tumors have also had documented HBV reactivation.[10,16,17] B-cell–depleting therapies and hematopoietic stem cell transplant (HSCT) are associated with higher risk of HBV reactivation.[8,18-21] For example, patients with previous
exposure to HBV can also experience HBV reactivation when receiving rituximab-based therapy.[22-24] HBV reactivation can occur anytime during and for at least 12 months after completion of IST in certain patient populations.[25,26]

How Do We Screen?

After a thorough review of the literature and society guidelines,[12,13] our approach is to screen by testing for HBsAg and anti-HBc, with reflexive testing of HBV DNA by polymerase chain reaction (PCR) in patients with positive results on either test. A small proportion of patients with exposure to HBV alone can have circulating DNA, and they appear to be at higher risk for HBV reactivation than patients who are anti-HBc–positive with negative PCR results. Patients who are HBsAg-positive or have detectable hepatitis B (HB) viral load (VL) receive oral entecavir 0.5 mg daily through the course of chemotherapy and for at least 6 months after the completion of cancer treatment. In addition, patients who are HBsAg-negative/anti-HBc–positive with undetectable HB VL are given entecavir prophylaxis prior to anti-CD20 therapy or before undergoing HSCT. Otherwise, patients positive for anti-HBc alone undergo monitoring of HB VL every 3 months, with prompt administration of entecavir if the VL becomes detectable.

For patients who are HBsAg-positive/anti-HBc–positive, there is a well-documented role for antiviral prophylaxis during treatment of hematologic and solid tumor malignancies.[27-31] Although lamivudine is inexpensive and well-studied in the prophylactic setting, breakthrough treatment resistance is a problem, both with short- and long-term use.[32-34] Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance and are therefore first-line agents. A recent randomized controlled trial found that when compared with lamivudine, entecavir significantly reduced the rate of HBV reactivation (6.6% vs 30%; P = .001) and HBV-related hepatitis (0% vs 13.3%; P = .003).[35] Patients undergoing anti-CD20 therapy or HSCT who have had prior HBV exposure also benefit from antiviral prophylaxis. Huang et al conducted a randomized controlled trial that compared entecavir prophylaxis—starting before, during, and for 3 months after completion of chemotherapy—with deferred treatment (control group). During a mean 18-month follow-up period, 1 (2.4%) of 41 patients taking entecavir prophylaxis developed HBV reactivation compared with 7 (17.9%) of 39 control patients (P = .027). No patients developed HBV-related liver decompensation or mortality in this study.[36]

Prophylaxis is maintained for at least 6 months after the completion of chemotherapy. Some guidelines recommend continuation for at least 12 months in patients receiving anti-CD20 therapy and HSCT.[12,13] The longer duration recommendation is a result of the discovery of HBV flares occurring up to 12 to 17 months after the last anti-CD20 dose.[36,37] This is certainly an area for further study.

Conclusion

The incidence of both HBV infection and cancer is common. The use of IST in patients with HBV can result in reactivation of HBV, which can, in turn, lead to significant morbidity and mortality. Although rates of HBV infection vary among populations, we feel that selective screening can miss a significant number of patients. We believe that our strategy of universal screening with HBsAg and anti-HBc prior to IST, followed by entecavir prophylaxis in all HBsAg-positive patients and selected HBsAg-negative/anti-HBc–positive patients, is effective and reasonable. Areas of uncertainty that require further investigation include evaluating the cost-effectiveness of universal pre-IST HBV screening, management of patients with solid tumors who are positive for anti-HBc only, and optimal duration of antiviral prophylaxis following completion of IST.

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