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When Treating Cancer, Please Don't Forget Hepatitis B

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INTRODUCTION

Carriers of hepatitis B virus (HBV) can experience reactivation of HBV during chemotherapy, leading to asymptomatic elevation in serum aminotransferases or fulminant hepatic failure and death. Current guidelines mandate screening for the presence of HBV infection and pre-emptive management with antiviral therapy in chronically infected persons who are about to undergo cancer chemotherapy. However, the penetration of these recommendations into clinical practice has been limited, with occasionally dramatic consequences. We present four cases highlighting the reactivation of HBV during chemotherapy and review the current data and guidelines for pre-emptive management.

CASE 1

A 38-year-old woman was admitted with acute liver failure. She was a known carrier of HBV who, 4 months earlier, noted a breast mass on self-examination. A breast ultrasound showed a $2.6 \times 2.1 \times 1.4$ cm mass in the upper, outer quadrant of the left breast. A core biopsy revealed poorly differentiated infiltrating ductal carcinoma, which was estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2/neu negative. A sentinel biopsy showed no disease in four lymph nodes. A bone scan, chest, abdominal, and pelvic computed tomography scan, and bilateral breast magnetic resonance imaging revealed no evidence of metastasis. Neoadjuvant chemotherapy with doxorubicin and cyclophosphamide was recommended prior to surgical resection. Prior to initiation of chemotherapy, her serum aminotransferases were within normal limits. After the fourth cycle, she developed persistent nausea and vomiting. Laboratory workup revealed aspartate aminotransferase (AST) of 3,831 U/l, alanine aminotransferase (ALT) of 928 U/l, and total bilirubin of 1.7 mg/dl. She was admitted to the hospital for evaluation. She had been diagnosed with hepatitis B surface antigen positivity at 24 years of age, when she emigrated from Shanghai, China. Three years prior, her HBV DNA was $<$300 copies/ml. On examination, she had no stigmata of chronic liver disease. Her breast mass was no longer palpable. Her abdomen was nontender, with no evidence of hepatosplenomegaly. Laboratory evaluation included: hepatitis B surface antigen positive, hepatitis B e antigen positive, hepatitis B surface antibody negative, hepatitis C antibody negative, hepatitis A antibody negative, and HBV

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DNA of 4.0×10^{10} IU/ml. She was started on entecavir (1 mg daily). Her aminotransferases declined but her international normalized ratio (INR) rose to 5 and her total bilirubin increased to 20 mg/dl. She developed severe coagulopathy and stage II hepatic encephalopathy and was transferred to our institution. The oncology team estimated her relapse-free survival probability over the next 10 years to be 70% and her overall survival probability to be >80% given her response to neoadjuvant chemotherapy. She was listed as status I for liver transplant and underwent orthotopic liver transplantation. After her transplant, she underwent left simple mastectomy and pathology showed a residual 0.8-cm tumor with clear margins. Two years later, she continues on antiviral prophylaxis and immunoprophylaxis and has had no recurrence of her breast carcinoma.

Case 2

A 71-year-old woman, originally from China, presented to the hepatology clinic with abnormal aminotransferases. She had been diagnosed with endometrial cancer approximately 5 months prior. At that time, her aminotransferases were within normal limits. She underwent surgical resection of the tumor followed by chemotherapy with paclitaxel and carboplatin. Following completion of cycle 3 of chemotherapy, her aminotransferases were noted to be elevated on routine laboratory testing. She was referred to our clinic. Her AST was 170 U/l and her ALT was 400 U/l. Her total bilirubin and INR time were within normal limits. Hepatitis serologies were obtained and revealed: hepatitis B surface antigen positive, hepatitis B core antibody positive, hepatitis B e antigen negative, and hepatitis B e antibody positive. Her HBV DNA was elevated at 48,000 IU/ml. She did not carry a diagnosis of HBV prior to chemotherapy. However, she did report that she was not given the HBV vaccine prior to traveling to China 4 years ago, because her laboratory tests revealed that she had already been infected with HBV, and the virus was inactive. Given her reactivation of HBV, chemotherapy was stopped prematurely. She was started on entecavir (1 mg daily) and was able to complete her chemotherapy course. At present, her aminotransferase levels have normalized and her HBV DNA is undetectable.

Case 3

A 51-year-old gentleman, originally from Haiti, presented to his primary care doctor with a chief complaint of abdominal fullness. He was diagnosed with diffuse large B cell lymphoma. He completed eight cycles of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone. Approximately 1 month after the last cycle, he presented to the hepatology clinic with jaundice, dark urine, and pale loose stools. Laboratory testing was notable for an ALT of 662 U/l, AST of 494 U/l, and total bilirubin of 7.3 mg/dl. Hepatitis serologies revealed: hepatitis B surface antigen positive, hepatitis B core antibody positive, hepatitis B e antigen negative, and hepatitis B e antibody positive. His HBV DNA was 17,900 IU/ml. He did not carry a prior diagnosis of HBV, but his sister was known to have HBV. He was diagnosed with reactivation of HBV secondary to chemotherapy and started on entecavir (0.5 mg daily). His aminotransferases and bilirubin have normalized, and his HBV DNA is undetectable.

Case 4

A 78-year-old woman, who immigrated to the U.S. from Cape Verde, presented to the emergency department with left neck swelling. She was diagnosed with diffuse large B cell lymphoma. Her aminotransferases were within normal limits prior to the start of chemotherapy. She completed six cycles of rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone. One month after completion of chemotherapy, she presented to the hepatology clinic for asymptomatic elevation of her aminotransferases: AST, 998 IU/ml; ALT, 1,397 IU/ml. Her total bilirubin and INR time were within normal limits. Hepatitis serologies revealed: hepatitis B surface antigen positive, hepatitis B core antibody positive, hepatitis B e antigen negative, and hepatitis B e antibody positive. Her HBV DNA was 22,900 IU/ml. She carried no prior diagnosis of HBV. However, she had likely acquired HBV perinatally and had been a chronic inactive carrier until she began chemotherapy. She was started on entecavir (0.5 mg daily), with normalization of her aminotransferases.

Discussion

More than 2 billion people worldwide have been infected with HBV, and, of these, approximately 350 million persons have chronic HBV infection. The prevalence of HBV infection varies in different geographic areas of the world, with the highest prevalence in Asia, the Pacific, and sub-Saharan Africa, where the disease is acquired perinatally or in childhood [1, 2]. In the U.S., the number of newly acquired HBV infections has declined but the prevalence of chronic HBV infection remains high, with 800,000 to 1.4 million persons living with chronic HBV infection. Approximately 47%–70% of these persons were born in other countries [3]. Carriers of HBV receiving chemotherapy are at risk for viral reactivation. Immunosuppressive therapy enhances viral replication, leading to an increase in the serum level of HBV DNA and hepatitis B e antigen. With recovery of immune function after withdrawal of immunosuppressive therapy, rapid immune-mediated destruction of

infected hepatocytes occurs [4]. Hepatitis flares can be asymptomatic, but icteric hepatitis and hepatic failure leading to death or liver transplantation can occur, as demonstrated in case 1 [5, 6]. Most reported cases of HBV reactivation are documented in patients with hematological malignancies. However, HBV reactivation also occurs in patients with solid tumors [7]. In a study of HBV seropositive patients undergoing chemotherapy for breast cancer, Yeo et al. [8] demonstrated that reactivation of HBV occurred in 41% of those patients and resulted in a delay in chemotherapy or premature termination of therapy in the majority of the patients. Risk factors for HBV reactivation include chemotherapy regimens containing glucocorticoids and anthracyclines as well as elevated levels of HBV DNA prior to chemotherapy administration [9–12]. Because of the risk for viral reactivation, the American Association for the Study of Liver Diseases (AASLD) recommends screening all persons at risk for HBV infection who require immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic and gastroenterological disorders, for chronic HBV infection.

Because HBV reactivation can lead to hepatic failure and cancer treatment delays, and viral replication precedes clinical evidence of hepatitis, studies have been designed to evaluate the use of lamivudine, a nucleoside analog, for the prevention of reactivation during chemotherapy [13]. Rossi et al. [14] performed a pilot study in 1999 to test the efficacy of lamivudine as a primary prophylaxis of HBV reactivation in 20 patients treated for hematological malignancies. Two patients developed transient hepatitis, and 18 patients had no reactivation of HBV after a median follow-up of 6 months. Subsequent studies using historical control groups support the use of prophylactic lamivudine in preventing HBV reactivation in patients with hematological and solid malignancies and in patients undergoing allogeneic hematopoietic cell transplantation [15–18].

The role of pre-emptive lamivudine administration has been studied in a limited number of randomized controlled trials. Lau et al. [19] and Hsu et al. [20] performed randomized controlled trials evaluating pre-emptive versus deferred lamivudine administration in HBV carriers undergoing chemotherapy for lymphoma. Lau et al. [19] showed the efficacy of early lamivudine therapy, compared with deferred therapy, when there was serological evidence of HBV reactivation, whereas Hsu et al. [20] showed that the rate of HBV reactivation was significantly lower in patients administered pre-emptive therapy than in patients administered therapy once their serum ALT level increased to >1.5-fold the upper limit of normal.

Loomba et al. [21] and Katz et al. [22] performed reviews of the literature. Loomba et al. [21] found that, with preventive lamivudine, the relative risk for HBV reactivation and HBV-related hepatitis was in the range of 0.00–0.21. None of the patients who received lamivudine developed HBV-related hepatic failure, and lamivudine was well tolerated. Katz et al. [22] found that three patients needed to be treated to prevent one clinical reactivation, and 11 patients needed to be treated to prevent one death.

In light of these data, the AASLD issued practice guidelines recommending antiviral prophylaxis for HBV carriers who receive chemotherapy. Similarly, the National Institutes of Health Consensus Development Conference on the management of hepatitis B recently issued recommendations for initiation of prophylactic antiviral therapy at the onset of chemotherapy [23]. Patients with a baseline HBV DNA <2,000 IU/ml should continue treatment for 6 months after completion of chemotherapy. Because patients with high baseline HBV DNA (>2,000 IU/ml) have a higher risk for HBV reactivation after lamivudine withdrawal, the AASLD recommends continuing treatment in these patients until they reach treatment endpoints as in immunocompetent patients. Lamivudine is recommended if the anticipated duration of treatment is <12 months, whereas tenofovir or entecavir is preferred if a longer duration of treatment is anticipated [24].

Our cases represent a failure of percolation of these recommendations to the oncologic community. The patient in case 1 was a known carrier of HBV. Rather than receiving pre-emptive therapy, she was monitored closely during chemotherapy. The development of acute liver failure requiring liver transplantation even in the face of prospective surveillance underscores the inability of this approach to prevent severe clinical outcomes. This case, which, only because of an excellent chemotherapy response, allowed listing for life-saving transplantation, strongly suggests that the recommended practice, pre-emptive therapy for HBV carriers, has not found its way into everyday oncologic practice. Furthermore, we would strongly urge that all patients about to undergo chemotherapy, particularly those from areas of high HBV prevalence and those receiving high-dose steroids or doxorubicin-based regimens, be screened for HBV infection, which did not occur in cases 2–4. In the event that HBV infection is identified, pre-emptive antiviral therapy should be initiated in close consultation with an experienced treater of HBV. Patients appropriately undergo aggressive chemotherapy to save lives. As part of this aggressive approach, careful steps to prevent complications of chemotherapy would appear to be every bit as important in maximizing clinical outcomes as the delivery of chemotherapy itself. With ever-increasing

numbers of chronically HBV-infected persons immigrating to the U.S. and effective antiviral therapy widely available, we would argue that HBV assessment and pre-emption should become a reflexive practice among oncologists, and that fulminant HBV reactivation should now be fully preventable.

Author Contributions

Conception/Design: Raymond T. Chung
Provision of study material or patients: Raymond T. Chung
Collection and/or assembly of data: Lindsay Y. King
Data analysis and interpretation: Raymond T. Chung, Lindsay Y. King
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Final approval of manuscript: Raymond T. Chung

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