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Case Report

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Hepatitis B Reactivation: A Potentially Serious Complication of Chemotherapy for Solid Tumors

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Abstract

We present a case of hepatitis B reactivation in a patient receiving adjuvant chemotherapy for early breast cancer. This is a 49-year-old post-menopausal, Chinese female with history of chronic hepatitis B with inactive carrier state, and right invasive ductal carcinoma staged as cT2N1M0, pT2N1aM0, anatomic stage IIB, prognostic stage IIA, estrogen and progesterone receptor positive, and human epidermal growth factor 2 negative. The patient underwent bilateral mastectomy with implant reconstruction and right axillary lymph node dissection followed by adjuvant chemotherapy planned as dose dense doxorubicin and cyclophosphamide (ddAC), followed by dose dense paclitaxel (ddT). Two weeks after her first cycle of dose dense paclitaxel, she developed grade III HBV reactivation with hepatitis. This report highlights HBV reactivation as a potential complication of chemotherapy for solid tumors, and reviews recommended HBV screening, prevention and management of HBV reactivation in this patient population.

Keywords: Hepatitis b virus; Reactivation; Hepatitis; Solid tumors; Cancer; Chemotherapy; Antiviral; Prophylaxis; Screening; Breast cancer

Abbreviations : AALD - American Association for the Study of Liver Disease; AGA - American Gastroenterological Association Institute; ALT - alanine transferase; ASCO - American Society of Clinical Oncology; AST - aspartate aminotransferase; CDC - US Centers for Disease Control and Prevention; ddAC – Dose dense Doxorubicin Cyclophosphamide; ddT – Dose Dense Paclitaxel; ER – Estrogen Receptor; ESMO - European Society for Medical Oncology; FISH - Fluorescence in situ hybridization; HBV - Hepatitis B Virus; HBcAb – Hepatitis B Core antibody; HBeAg – Hepatitis B e antigen; HBsAb – Hepatitis B surface antibody; HBsAg – Hepatitis B surface antigen; HBV DNA – Hepatitis B Virus Deoxyribonucleic Acid; HCC - hepatocellular carcinoma; HER2 – human epidermal growth factor receptor 2; INR - International normalized ratio; NCCN - National Comprehensive Cancer Network; PR–Progesterone Receptor; TACE–transarterial chemoembolization; TNF-α - Tumor Necrosis Factor-alpha

Introduction

Chemotherapy is an important component in the management of various solid tumors. Patients with history of hepatitis B virus (HBV) or chronic HBV receiving chemotherapy for solid tumors are at risk for HBV reactivation. HBV reactivation may be associated with significant morbidity, mortality, and chemotherapy interruption. Preemptive antiviral therapy is effective in preventing HBV reactivation and associated complications in patients with chronic HBV. We present a case of HBV reactivation secondary to adjuvant immunosuppressive chemotherapy for breast cancer to illustrate the importance of appropriate screening prior to the initiation of chemotherapy to allow for HBV reactivation prevention, monitoring, and management.

Case Report

A 49-year-old post-menopausal, Chinese female presented with a palpable breast mass and was found to have a right invasive ductal carcinoma, that was positive for estrogen receptor (ER 95%) and progesterone receptor (PR 50%) and negative for human epidermal growth factor receptor 2 (HER2) by Fluorescence in situ hybridization (FISH). Her breast cancer was staged as cT2N1M0, pT2N1aM0, anatomic stage IIB, prognostic stage IIA with modified Scarff-Bloom-Richardson Score 6/9 and Nottingham Grade 2. She elected to undergo bilateral mastectomy with implant reconstruction and right axillary lymph node dissection with 3 out 18 positive lymph nodes and negative margins. The patient was subsequently started on adjuvant chemotherapy with dose dense

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doxorubicin 60mg/m^2 and cyclophosphamide 600mg/m^2 (ddAC), followed by dose dense paclitaxel 175mg/m^2 (ddT). The four cycles of anthracycline-containing chemotherapy were initially complicated by mild nausea, diarrhea, mucositis, mild anemia and grade 4 neutropenia without fever. Likely related to her prior anthracycline exposure, but two weeks during treatment with dose dense paclitaxel, the patient developed grade III hepatitis.

Her exam was benign and laboratory work-up revealed elevated transaminases (aspartate aminotransferase (AST): 2,059 U/l, ALT: 2,388 U/l), hyperbilirubinemia (total bilirubin: 1.8 mg/dl, direct bilirubin: 1.6 mg/dl), without coagulopathy (international normalized ratio [INR]:1.1). Abdominal ultrasound with doppler was negative for acute pathology, and liver and gallbladder were unremarkable. Further assessment revealed positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (Anti-HBs), hepatitis B e Ab (HBeAb), and quantitative HBV DNA of 6,990,000 IU/ml. At this point, the patient noted a history of chronic hepatitis B, inactive carrier state without history of liver disease or treatment. Chemotherapy was held and she was started on tenofovir 300mg daily. A trend of her liver function tests is demonstrated in Figure 1. After one month of antiviral therapy, HBV DNA reduced to 73.9 IU/mL. Transaminases and bilirubin normalized after two months of therapy. Although recommended to resume adjuvant chemotherapy, the patient ultimately deferred any further chemotherapy due to concern for further hepatic injury and was started on adjuvant endocrine therapy (Figure 1).

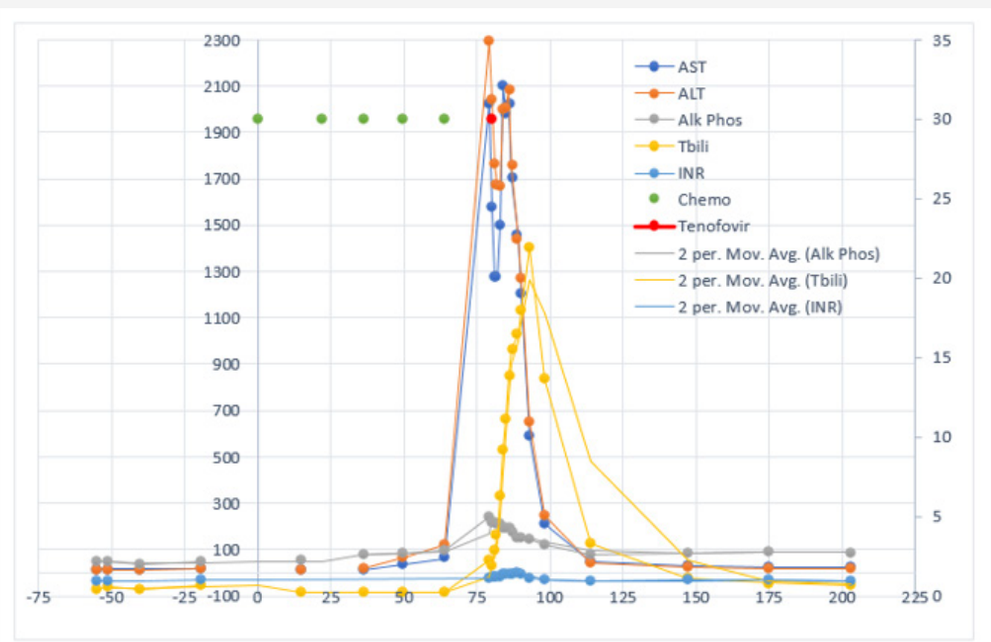

Figure 1: Liver function tests before, during and after HBV reactivation.

Discussion

It estimated that two billion people worldwide have been infected with HBV worldwide. Additionally, there are approximately 250-300 million asymptomatic chronic HBV carriers worldwide and 862,000 to 2.2 million people living with HBV in the United States, the latter including immigrants from endemic countries [1-5]. Due to the persistence of latent HBV in hepatocytes, HBV reactivation may occur after exposure to chemotherapy induced immunosuppression. While the risk of HBV reactivation for treatment of hematologic malignancies is well established, there is a paucity of literature in solid tumors. Estimates of the risk of reactivation in asymptomatic HBV carriers with solid tumors range from 3-50% depending on tumor type, chemotherapy to be administered, and HBsAg status. It is more common in patients with positive HBsAg than negative HBsAg and positive HBcAb; reported as 20% to 50% and 3 to 45%, respectively [5-20]. HBV reactivation is defined as an increase in HBV DNA by at least 10-fold in those with previously detectable HBV DNA or de novo detection of HBV DNA and HBsAg positivity. [8,21] The natural history of HBV reactivation is characterized by an asymptomatic rapid rise in HBV DNA frequently accompanied by HbsAg and HbeAg positivity, often followed by a reactivation related hepatitis with a rise in serum ALT levels and bilirubin. [22] The onset may occur as early as 2 weeks after chemotherapy initiation and up to a year after cessation of chemotherapy. HBV reactivation often results in asymptomatic self-limited hepatitis and will resolve with the cessation of chemotherapy and initiation of anti-viral therapy but can lead to acute liver failure or persistent liver injury and even death in a subset of patients [6,23]. Some suggested risk factors for HBV reactivation include male sex, older age, presence of cirrhosis, diagnosis of lymphoma, breast cancer, hepatocellular carcinoma (HCC), use of anthracyclines or steroids, high baseline HBV DNA, HBeAg positivity, chronic hepatitis B with positive HBsAg positivity, HBV genotype, and low pre-treatment white blood cell count and number of cycles for transarterial chemoembolization (TACE) in HCC. [6,8,17,18,24-26] Risk of HBV reactivation has been

stratified into high, moderate and low risk or ≥10%, 1%–10%, and <1%, respectively based on HBsAg positivity and type of chemotherapy or immunosuppressive therapy predominantly in the gastroenterology literature. [8] Immunosuppressive therapies deemed high risk for reactivation are B-cell depleting agents such as rituximab, high dose corticosteroids, anthracyclines, potent Tumor Necrosis Factor-alpha (TNF-α) inhibitors, and local therapy for HCC including TACE. [9,12-15,27-31] Therapies that have been associated with moderate risk are other systemic chemotherapies (e.g. platinum), less potent TNF- α inhibitors, cytokine-based therapies, calcineurin inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, histone deacetylase inhibitors, and moderate dose corticosteroids. Whereas, moderate and low dose prednisone and methotrexate are associated with low risk of reactivation [8].

The US Centers for Disease Control and Prevention(CDC), European Society for Medical Oncology (ESMO), European Association for the Study of the Liver (EASL), and American Association for the Study of Liver Disease (AALD) recommend universal screening of patients for hepatitis B prior to initiating cytotoxic chemotherapy.[32-40] Whereas, the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and American Gastroenterological Association Institute (AGA) recommend risk based screening. [37,41] Patients undergoing screening should be tested for HBsAg, surface antibody (HBsAb), and HBcAb with HBV DNA and HBeAg testing if either HBsAg or HBcAb are positive. About 2-41% of patients with isolated positive HBcAb have positive HBV DNA, or occult hepatitis B infection. [42] Figure 2 displays a proposed algorithm for hepatitis B screening for patients receiving chemotherapy for solid tumors based on available guidelines. Inconsistent guidelines may contribute to low rates of HBV screening often less than 20% for patients undergoing chemotherapy. [1,43,44] Low screening rates have also been attributed to underestimation of the risk of HBV reactivation, perception that there is inadequate evidence to support universal screening and of low rates of HBV infection. [45,46] There are concerns that universal screening may lead to unnecessary costs and over-treatment. Studies of the cost-effectiveness of universal HBV screening in patients with solid tumors undergoing cytotoxic chemotherapy have been conflicting. [47-49] However, risk-based approaches may be more time consuming and require oncologist knowledge of HBV reactivation risk factors and chemotherapy agents associated with increased risk (Figure 2).

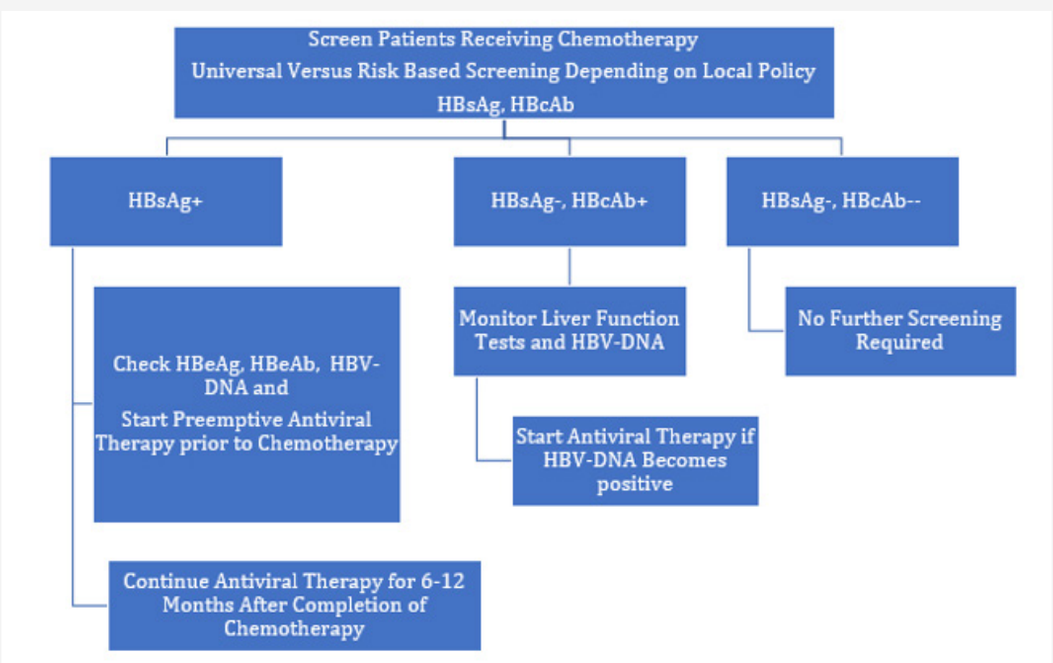

Figure 2: Proposed Hepatitis B screening algorithm prior to cytotoxic chemotherapy for solid tumors.

Preemptive antiviral therapy significantly reduces HBV reactivation, hepatic failure, mortality and chemotherapy disruption. [1,5,12,15,17,29,32,50-56] Therefore, it is recommended that HBsAg positive patients receive preemptive treatment with nucleoside reverse transcription inhibitors. Antivirals should be initiated prior to chemotherapy administration and continued for 6 to 12 months after completion of chemotherapy. Further studies are necessary to guide the optimal duration of antiviral prophylaxis after completion of chemotherapy. While lamivudine has historically been used for most trials of HBV reactivation prophylaxis, potent HBV antivirals with a high barrier to resistance, such as entecavir or tenofovir, are generally first line. Moreover, a randomized controlled trial of lamivudine versus entecavir prophylaxis for patients receiving chemotherapy for lymphoma revealed significantly lower rates of HBV reaction, HBV related hepatitis, and chemotherapy disruption in the entecavir group. [57] For HBsAg-negative/HbcAb–positive patients, on-demand antiviral therapy is recommended. The most recent ASCO provisional clinical opinion update suggests monitoring HBV DNA and ALT every 3 months for patients with HBsAg-negative/HBcAB-positive patients while receiving chemotherapy and initiating antiviral therapy if HBV reactivation occurs. [37] It is important to work with

local laboratories to ensure that sensitive diagnostic methods for HBV DNA monitoring are utilized. However, there is no standard monitoring practices and limited data available to guide practice.

Conclusion

HBV reactivation is a potentially serious, even life-threatening complication of immunosuppressive chemotherapy for solid tumors in patients with history of HBV infection or occult hepatitis B infections. As this complication can be prevented and effectively managed with antiviral therapy, screening and monitoring patients imperative. More randomized controlled trials are required to help guide safe and cost-effective screening practices and duration of antiviral therapy. Additionally, quality improvement initiatives are needed to optimize screening practices for patients at high risk.

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All authors contributed to manuscript writing and editing.

Conflict of Interest

Dr. Algaze and Dr. Donovan have no conflicts of interest to report. Dr. Kang has accepted speaker and consulting fees from Puma Biotechnology and consulting fees from Bristol Myers Squibb.

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