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Hepatitis B Reactivation After Ifosfamide Therapy for Retroperitoneal Sarcoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: **Male, 61**
Final Diagnosis: **Ifosfamide induced reactivation of hepatitis B**
Symptoms: —
Medication: **Ifosfamide**
Clinical Procedure: **DC ifosfamide and added Tenofovir**
Specialty: **Oncology**

Objective: **Unusual clinical course**

Background: Patients receiving cancer treatment are at risk for hepatitis B virus (HBV) reactivation. Ifosfamide is an alkylating agent and is considered to be one of the important drugs for the treatment of metastatic sarcoma. No association of ifosfamide and HBV reactivation has been reported so far.

Case Report: We report a case of a 61-year-old Asian man with metastatic retroperitoneal liposarcoma who was HBcAb positive and was treated with ifosfamide and dacarbazine, developed HBV reactivation secondary to ifosfamide requiring treatment with tenofovir. To the best of our knowledge, this is the first report describing HBV reactivation in a patient with positive HBcAb who was treated with ifosfamide.

Conclusions: We recommend close surveillance of possible HBV reactivation while employing ifosfamide chemotherapy.

MeSH Keywords: **Antineoplastic Agents • Hepatitis B Surface Antigens • Ifosfamide**

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Background

Patients receiving cancer treatment are at risk for hepatitis B virus (HBV) reactivation. According to National Comprehensive Cancer Network (NCCN), approximately 20% to 50% of patients with positive HBsAg and 3% to 45% of patients with positive HBcAb develop HBV reactivation after receiving chemotherapy [1]. A higher risk has been reported among patients with hematologic malignancies, stem cell transplantation [2], or receiving immunosuppressive treatment such as TNF-alpha inhibitors or monoclonal antibodies to B (e.g., anti-CD20) or T cells (e.g., anti-CD11) [3,4]. The risk of HBV reactivation among patients with solid tumor also varies among different chemotherapy regimens. Ifosfamide is an alkylating agent and is considered to be one of the important drugs for metastatic sarcoma treatment. No association of ifosfamide and HBV reactivation has been reported so far. Here, we report a case of a patient with positive HBcAb at baseline who developed HBV reactivation while being treated with ifosfamide for retroperitoneal sarcoma.

Case Report

A 61-year-old Asian man was diagnosed in June 2000 with retroperitoneal liposarcoma with surgical resection of a 30 cm sized mass with the residual mass encasing the mesenteric artery. He received six cycles of Adriamycin (doxorubicin) and dacarbazine with an excellent clinical response confirmed on CT scan. In July 2009, the patient was found to have recurrent retroperitoneal nodes, and mesenteric and peritoneal masses, which were progressively enlarging, complicated by bile obstruction. PET-CT scan showed high standardized uptake values (SUV) in masses in the mid-abdominal mesenteric and superior mesenteric artery. Both endoscopic retrograde cholangiopancreatography (ERCP) ultrasound guided biopsy and external biopsy showed strong suspicion for the recurrence of liposarcoma. The patient was treated with ifosfamide 2.5 g/m² for three days every three weeks and dacarbazine 100 mg/m² along with mesna daily for three days for eight cycles from December 2010. He was having a good response to ifosfamide, with marked improvement on CT Scan. However, substantial elevation of aspartate aminotransferase (AST) (272 IU/L) and alanine aminotransferase (ALT) (632 IU/L) were observed in September 2011. He was therefore tested for HBV markers and found to be positive for HBsAg, HBcAb, and HBeAg, and his HBV DNA titer was 10⁵ copies/mL. At his baseline in 2008 after completion of chemotherapy with Adriamycin (doxorubicin) and dacarbazine, HBV screening showed positive HBcAb only with undetectable HBV DNA titer; anti-hepatitis C virus (HCV) and anti-hepatitis E virus (HEV) were both negative; and he had normal AST and ALT (below 40 IU/L). Therefore, a diagnosis was made of reactivation of HBV secondary to chemotherapy most

likely due to ifosfamide treatment. Dacarbazine was deemed to be an unlikely cause, since he received dacarbazine therapy previously with no reactivation of hepatitis B. Chemotherapy was held and he received tenofovir therapy. His transaminases returned to normal (AST, ALT <40 IU/L) in three months. Two years after starting tenofovir, follow-up tests showed that HBsAg, HBsAb, and HBeAg were negative, and HBeAb and HBcAb were positive. HBV DNA was undetectable by real-time PCR. The patient remained well until lately, when he was found to have progression of retroperitoneal mass necessitating another set of chemotherapy with ifosfamide and tenofovir. He developed renal failure. Tenofovir was withheld, and he is currently being observed with plans to give chemotherapy regimen using eribulin.

Discussion

HBV reactivation in patients receiving cancer treatment is commonly observed. The definition of HBV reactivation varies, one of the most widely used is that of the reappearance of detectable HBV DNA that had been previously undetectable, or a positive HBsAg and HBV DNA level more than 10,000 IU/mL in a previously unscreened patient [5]. Reactivation of HBV virus can lead to hepatitis, which is defined by a 3-fold or more increase in ALT above the upper limit of normal range and has been associated with significant morbidity [6,7] and mortality [8]. Clinically, the symptom of HBV reactivation varies from asymptomatic elevation of ALT to acute liver failure or even death [8].

Many chemotherapeutic agents are associated with HBV reactivation. They act by direct cytotoxic effect on proliferative cells and cause immunosuppression, which is a well-recognized risk factor for HBV reactivation in patients with both hematologic and solid tumors. The imbalance between replication of the virus and the immune response of the host often are responsible for the reactivation of HBV. The risk of HBV reactivation can be as high as 88% among patients with hematologic malignancies [2], followed by patients receiving anti-CD20 therapy and hematopoietic stem cell transplantation. Our patient, who at baseline was only HBcAb positive, experienced HBV reactivation with ifosfamide treatment without antiviral prophylaxis, which represents a rare case. Ifosfamide is one of the most commonly used cytotoxic alkylating agents in soft tissue sarcoma. The exact mechanism of ifosfamide is still unclear. After biotransformation in the liver by cytochrome P450, the active metabolites of ifosfamide alkylate or bind with DNA through formation of inter and intra strand cross-links which eventually resulting in cell death. It was also found that by depleting intracellular glutathione (GSH), a major intracellular thiol reductant that protect cells from oxidative injury, ifosfamide impairs T cells, natural killer (NK) cells, and dendritic cells (DC)

function [9–11]. Dysfunction of the immune cells may lead to HBV reactivation, and enable spread of the virus, and eventually cause significant hepatotoxicity. HBV reactivation has been reported with several other alkylating agents, including cyclophosphamide [12,13], and temozolomide [14–17] when treating for multiple malignancies. However, to the best of our knowledge, no ifosfamide-induced HBV reactivation has been reported [5].

The three most commonly used screening tests for HBV are HBsAg, HBsAb, and HbCAb. Patients who are HBsAg negative, HBsAb negative, and HbCAb negative should be immediately immunized with hepatitis B vaccine prior to initiation of chemotherapy. Patients who are HBsAg positive should be checked for baseline HBV DNA level and prophylactic antiviral therapy initiated prior to chemotherapy [2,18]. However, the management for patients with HBsAg negative/HbCAb positive (resolved HBV infection) is less clear. Some of these patient with undetectable HBV DNA, while others with HBV DNA in the hepatocytes and therefore can be at risk of HBV reactivation. A retrospective analysis of lymphoma patients with isolated HbCAb positive who received chemotherapy or chemo-immune therapy with anti-CD20 showed 0.8% and 2.7% of HBV reactivation, respectively [19]. Less data is available for isolated HbCAb positive solid tumor patients. One report showed an approximate 10% risk of HBV reactivation in HBsAg negative/HbCAb positive patients with hepatocellular carcinoma. Another reported showed 2 of 27 patients with solid tumors who received platinum-based chemotherapy regimen experienced HBV reactivation [20,21]. More recently, a meta-analysis further revealed the risk for reactivation without antiviral prophylaxis ranged from 0.3% to 9% in solid tumor patients with resolved HBV infection [22]. Therefore, based on current available evidence, American Society of Clinical Oncology (ASCO) recently published an updated provisional clinical opinion on HBV screening in patients receiving cytotoxic chemotherapy for malignant diseases [23]. It recommended a risk-adaptive HBV screening strategy with HBsAg and HbCAb. All patients with an HBV risk factor should be screened for HBV infection. Independent of HBV infection risk, all patients anticipating cancer therapy with a high risk of reactivation of HBV (anti-CD 20 therapy or stem cell transplantation) should be screened for HBV infection. However, concerns have been

raised that screening for both HBsAg and HbCAb could lead to over-diagnosis of resolved HBV [24] due to endemic HBV infection in certain countries where HBsAg negative/HbCAb positive rates can be as high as 76% [25]. Therefore, some experts proposed a slightly different screening strategy that includes HbsAg testing for all patients before cancer therapy, but reserves HbCAb testing for patients with a hematological malignancy, and for those receiving anti-CD20 therapy or stem cell transplantation for other reasons [24]. When a risk factor-based HBV screening strategy is used, it is important to recognize the risk factors, the serological patterns, as well as the type of immunosuppressive therapies [23]. Multiple risk factors have been identified, including HIV positive, injection drug use, men who have sex with men, household or sexual contact with HBV positive person, parents born in high-prevalence region, and born in >2% HBV prevalence country [23]. In addition, the patient's serological profile at the time of chemotherapy is an important determinant of HBV reactivation. The highest risk is in patients who are HBsAg positive inactive carriers, followed by those who are HBsAg negative but HbCAb positive [26]. Patients with HBsAg negative, HbCAb positive, and undetectable HBV DNA level are considered to have the lowest risk [19]. According to the current ASCO guideline, in low-risk patients, closely monitoring of serum HBV level is preferred, while in high-risk patients, prophylactic therapy is recommended. Therefore, clinicians can either initiate antiviral therapy for HBsAg negative/HbCAb positive patients anticipating cancer therapies associated with a high risk of reactivation, or they can monitor HBV DNA and ALT levels and initiate on-demand antiviral therapy [23]. However, while prophylaxis remains controversial in patients with resolved HBV, close monitoring is mandatory. Large, multicenter prospective observational trials are necessary to address this issue in the future.

Conclusions

We recommend screening for past hepatitis B infection and consideration of anti-viral therapy or close surveillance for possible hepatitis B reactivation while employing ifosfamide chemotherapy. Our literature review suggests using a risk-based screening strategy that recognizes serological patterns as well as the type of immunosuppressive therapies employed.

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