Reactivation of hepatitis B virus after withdrawal of erlotinib

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ABSTRACT

Reactivation of hepatitis B virus (HBV) is a reported complication for patients undergoing chemotherapy, particularly immunochemotherapy with anti-CD20 agents such as rituximab. However, as the use of molecularly targeted agents increases, the risk of viral reactivation is less clearly defined. Here, we present the case of a 62-year-old woman with newly diagnosed EGFR-mutation–positive metastatic non-small-cell lung cancer (NSCLC).

Per interview, our patient had a remote history of HBV infection. She was started on erlotinib and developed profound diarrhea leading to renal failure that required hospital admission and temporary discontinuation of erlotinib. At 8 days after erlotinib cessation, she had a marked spike in her liver function tests, with viral serologies that were consistent with HBV reactivation. Although erlotinib and other tyrosine kinase inhibitors (TKIs) are not classically associated with HBV reactivation, HBV reactivation can occur even in the setting of TKI withdrawal. Before TKI initiation, careful patient screening in those at risk for HBV should be performed to attenuate preventable hepatotoxicity and to differentiate between other causes of hepatotoxicity (for example, drug-induced toxicity).

Key Words Non-small-cell lung cancer, erlotinib, hepatitis B reactivation, EGFR mutation

INTRODUCTION

Lung cancer is the 2nd most common malignancy in the United States and the leading cause of cancer-related deaths1. Non-small-cell lung cancer (NSCLC) is the most common subtype of lung cancer. When NSCLC is diagnosed in the metastatic stage, prognosis is dismal, with 1-year and 5-year survivals of only 15.9% and 1.5% respectively2. Recently, however, significant developments have occurred in targeting mutations, most notably the epidermal growth factor receptor (EGFR) mutation. In the first-line setting in EGFR-mutated NSCLC, tyrosine kinase inhibitors (TKIs) such as erlotinib have significantly improved progression-free survival from a median of about 5.6 months with chemotherapy to 11 months, thus establishing EGFR inhibitors as a standard of care for EGFR-mutated NSCLC3. In addition, in comparison with non-EGFR-mutant NSCLC treated with chemotherapy, the EGFR mutation appears to confer a survival advantage with targeted treatment, improving overall survival from just over 1 year to upwards of 2–3 years4.

Reactivation of the hepatitis B virus (HBV) has been well described in the literature in cancer patients receiving chemotherapy, immunosuppressive therapy, or steroids. In patients receiving standard chemotherapy, HBV reactivation occurs in about 20%–50% of patients positive for hepatitis B surface antigen (HBsAg)5–7. Although any cytotoxic chemotherapy agent can lead to HBV reactivation, the risk is even greater with anti-CD20 monoclonal antibodies such as rituximab. Reactivation of HBV has been added to the existing U.S. Food and Drug Administration black-box warning on the rituximab label. The warning recommends that, before the start of treatment with rituximab, all prospective patients be screened for HBV infection by measurement of HBsAg and hepatitis B core antibody8. A few case reports of HBV reactivation with the use of small-molecule TKIs such as sorafenib, imatinib, nilotinib, and ruxolitinib have also been noted in the literature9–11. Interestingly, HBV reactivation can also occur upon chemotherapy withdrawal and is thought to be a result of increased replication of HBV during immunosuppression and rebound hepatic damage after immune reconstitution12,13.

No published literature has described induction of HBV reactivation with erlotinib, an EGFR-targeted TKI. In the present case report, we describe a patient with HBV reactivation after withdrawal of erlotinib treatment for EGFR-mutant metastatic NSCLC.

CASE DESCRIPTION

In a 62-year-old woman with a 40 pack-year smoking history, screening chest radiography being done as part
of preoperative workup for a coronary artery bypass procedure showed increased opacification of the right middle lobe (RML). Positron-emission tomography showed a 3.9×2.6-cm thick-walled cavitary mass in the right lower lobe; a hypermetabolic lesion near the distal bronchus intermedius, occluding the RML bronchus and causing complete RML collapse; and numerous hypermetabolic mediastinal lymph nodes. Subsequent magnetic resonance imaging of the brain showed numerous (>20) brain metastases, with the largest one (12 mm) in the left inferior cerebellum being associated with mild left cerebellar tonsillar herniation. Biopsies taken from the RML lesion and the 4L lymph node showed different histologies: squamous cell carcinoma and adenocarcinoma respectively. The biopsy from the RML was positive for the EGFR exon 19 deletion. The patient’s disease was staged as an EGFR-mutated stage IV adenocarcinoma of the lung.

Given the numerous brain metastases (with one causing tonsillar herniation), the patient received whole-brain radiation therapy. She was started on concurrent erlotinib (150 mg standard daily dosing) based on the safety and favourable objective response rate noted in a recent phase II trial. The laboratory workup before therapy was unremarkable: creatinine 0.93 mg/dL (reference range: 0.4–1.2 mg/dL), blood urea nitrogen 14 mg/dL (reference range: 8–23 mg/dL), aspartate transaminase (AST) 16 IU/L (reference range: 10–30 IU/L), alanine transaminase (ALT) 13 IU/L (reference range: 11–45 IU/L), and alkaline phosphatase (ALP) 64 IU/dL (reference range: 30–130 IU/dL). Repeat laboratory values at 8 days after discontinuation of erlotinib showed a normal serum creatine at 1.03 mg/dL; however, marked transaminis was present at AST 268 IU/L and ALT 267 IU/L, and ALP was elevated at 448 IU/dL. Liver ultrasonography was normal, showing normal common and intrahepatic bile ducts, no mass lesions, and unremarkable echogenicity. Hepatitis serologies showed positivity for HBsAg, for total hepatitis B core antibody, and for hepatitis Be antibody; and negativity for hepatitis B surface antibody and for hepatitis Be antigen. Polymerase chain reaction for hepatitis B DNA was 307 IU/mL. Hepatitis A immunoglobulin M antibody and hepatitis C antibody were negative. On further questioning, the patient reported having been diagnosed with HBV in 1980 when she was in the navy, but having received no follow-up after that diagnosis. On chart review, her LFTs had never registered elevated as far back as 2003.

At the patient’s next clinic visit, her LFTs had trended down without intervention. Entecavir was started, together with dose-reduced erlotinib (100 mg). The most recent polymerase chain reaction for HBV DNA, at 4 months after initiation of therapy, was undetectable.

**DISCUSSION**

Here, we describe a case of acute renal failure because of erlotinib treatment, with subsequent HBV reactivation after erlotinib withdrawal. To the best of our knowledge, no prior case reports of erlotinib-withdrawal-induced or erlotinib-induced HBV reactivation have been published.

In the original TKI trials, no hepatitis reactivation was reported, given that chronic hepatitis B and C infections were exclusionary criteria. In post-marketing data, multiple case reports of the rare adverse event of hepatic failure, some with fatal outcomes, have been published. None of the cases of hepatic failure have been linked to hepatitis B or C reactivation.

In our patient, LFTs rose markedly within a week after erlotinib discontinuation and then improved without any intervention. It is unclear whether that pattern represents an acute reactivation of previously cleared hepatitis B or exacerbation of a chronic underlying hepatitis B, because no viral serologies to document HBsAg seroconversion had been obtained before initiation of chemotherapy. Regardless, the flare of this patient’s LFTs indicated that she had a clinically significant hepatitis B infection that necessitated antiviral treatment.

In 2010, the American Society of Clinical Oncology published a provisional clinical opinion article about screening for chronic HBV in patients receiving chemotherapy. The article concluded that the evidence for
routine screening was insufficient, but advocated for physician judgment when considering screening, especially for individuals at high risk for chronic HBV infection or those being considered for highly immunosuppressive therapies. Recently released clinical practice guidelines from the American Society of Clinical Oncology note that providers should screen patients about to receive highly immunosuppressive therapy (such as hematopoietic-cell transplantation and regimens including rituximab) and patients with risk factors for HBV infection.19

Small-molecule TKIs are not classically associated with immunosuppression because they do not directly cause leucopenia, nor do they target immune-system players such as B lymphocytes. However, as noted earlier, the literature contains case reports describing HBV reactivation with a variety of TKIs such as sorafenib, imatinib, nilotinib, and ruxolitinib.9–11. Erlotinib might have to be included in that group of TKIs, and we suggest that additional study into whether the risk of HBV reactivation is increased with erlotinib is warranted. Based on our experience, we favour HBV screening in patients at risk before treatment with erlotinib is initiated. If positivity for HBsAg or hepatitis B core antibody is found, we recommend treatment with antiviral agents in consultation with the Infectious Diseases or Hepatology service.

SUMMARY

We present a patient experiencing acute renal failure from diarrhea secondary to erlotinib initiation, and acute HBV reactivation after erlotinib withdrawal. Although TKIs are not generally associated with a risk of viral reactivation, we advocate risk stratification to identify patients with chronic HBV infection before treatment is initiated. Stratification will help both to attenuate preventable hepatotoxicity and to differentiate between other causes of hepatotoxicity (for example, drug-induced toxicity).

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES