Fulminant Hepatitis Following Crizotinib Administration for ALK-positive Non-small-cell Lung Carcinoma

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We herein report a case of fatal fulminant hepatitis secondary to crizotinib administration. The patient was 54-year-old female with a history of Hepatitis C infection (not current), dermatomyositis and steroid-induced diabetes mellitus. She was diagnosed with advanced lung adenocarcinoma with anaplastic lymphoma kinase rearrangement. We began 400 mg of crizotinib as first-line therapy. No adverse effects were seen until Day 16. On Day 29, she was admitted to hospital with elevated liver enzymes (aspartate aminotransferase 3236 IU/l, alanine aminotransferase 5201 IU/l) and coagulopathy (prothrombin time <10%), and was diagnosed with crizotinib-induced fulminant hepatitis. We started intensive care, using plasma exchange, continuous hemodiafiltration and high-dose steroid therapy. Unfortunately, she did not respond to therapies, and died on Day 36. The mechanism and risk factors of crizotinib-induced hepatotoxicity are uncertain. Physicians should be aware of possible adverse effects of crizotinib. A systemic survey is imperative to identify possible risk factors of crizotinib-related hepatotoxicity.

Key words: tyrosine kinase inhibitor – anaplastic lymphoma kinase – crizotinib – drug induced liver toxicity – fulminant hepatitis

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide. Non-small-cell lung cancer (NSCLC) accounts for ~80% of lung cancers. The majority of NSCLCs are already unresectable and metastatic upon their initial diagnosis (1).

Activation of the anaplastic lymphoma kinase (ALK) gene has been described in several human cancers, including NSCLC, inflammatory myofibroblastic tumors, neuroblastomas and diffuse large B-cell lymphomas. The ALK fusion gene has been established as a driver mutation of these tumors. ALK rearrangements are found in ~5% of NSCLC cases, and define a distinct molecular subtype of lung cancer.

Crizotinib is a type of tyrosine kinase inhibitor and targets several kinases: MET (mesenchymal–epithelial transition factor), ALK, c-ros oncogene 1 and recepteur d’origine nantais. In patients with locally advanced or metastatic ALK-positive NSCLC, crizotinib showed improved survival over conventional chemotherapy (2–4).

In two clinical trials, elevated alanine aminotransferase (ALT) was seen in 13% of patients, and elevated aspartate aminotransferase (AST) in 9%; however, most liver function impairment was reversible, and could be managed by dose adjustment alone (5). Less than 2% had to discontinue crizotinib because of hepatotoxicity (6,7). Here we report a patient with fatal fulminant hepatitis secondary to crizotinib administration.
CASE REPORT

A 54-year-old Japanese woman presented at our hospital with sudden-onset headache, blurred vision and deteriorating consciousness. She was never a smoker nor a drinker, and had no history of drug allergy. This patient had anti-hepatitis C virus (HCV) antibodies, but not the HCV virus; i.e. she did not have a current HCV infection. Heliotrope rash and myalgia had developed 4 years previously; 3 years previously, she had been diagnosed with dermatomyositis according to the Bohan and Peter criteria, for which she took prednisolone (PSL) and rabeprazole; and 2 years previously, she was diagnosed with steroid-induced diabetes mellitus and started taking sitagliptin (8). Her symptoms of dermatomyositis were stable at 10 mg of PSL; no drug adverse effect was observed.

Computed tomography (CT) scan showed intracranial hemorrhagic mass and surrounding edematous brain tissue. A craniotomy was performed. Pathological examination of resected brain tissue showed a thyroid transcription factor-1-positive adenocarcinoma with ALK rearrangement, confirmed by fluorescence in situ hybridization and immunohistochemistry. A whole-body CT found a nodule in the right lower lung lobe; positron emission tomography showed multiple mediastinum lymphadenopathy and clavicle bone metastases. She was diagnosed with advanced ALK-positive lung adenocarcinoma with multiple distant metastases (cT4M3N1b, Stage 4). Her Eastern Cooperative Oncology Group performance status was 2. She had antibodies to HCV, but other laboratory data were within normal limits, including liver enzymes (total bilirubin 26.5 μmol/l, AST 17 IU/l, ALT 11 IU/l). Her abdominal CT scan was normal, with no sign of liver cirrhosis, hemochromatosis or splenomegaly. Her body weight was rather light (height 155 cm, weight 40 kg), and she was anxious about adverse drug effects. As she wanted a lower dosage, we started on 400 mg per day of crizotinib as first-line therapy. No other drug was added or changed. Following the prescribing information for crizotinib, we checked her liver function on Days 4 and 7, the results of which were within normal limits. No adverse effects were seen, and she was discharged on Day 10. On Day 16, she was seen as a routine outpatient. Physical examination found no abnormality. Her chest X-ray showed shrinkage of the primary lung nodule. Laboratory data revealed trivial elevation of liver enzymes (total bilirubin 35.4 μmol/l, AST 33 IU/l, ALT 38 IU/l), but these values were all within normal limits. These changes did not meet the dose modification criteria in the prescribing information for crizotinib, and we therefore continued crizotinib at the same dosage.

On Day 29 evening, she was presented with epigastric pain, vomiting and general malaise that lasted for 2 days through emergency admission. She could not take crizotinib from the morning of Day 29 because of vomiting. She was alert and oriented, and her vital signs were normal. Physical examination showed mild jaundice. Laboratory data showed severe liver function impairment, coagulopathy and NH₃ accumulation (total bilirubin 46.2 μmol/l, AST 3236 IU/l, ALT 5201 IU/l, alkaline phosphatase 506 IU/l, gamma-glutamyltransferase 86 IU/l, prothrombin time <10%, NH₃ 153 μg/dl). Complete blood count, renal function, electrolytes and C-reactive protein were within normal limits. Her chest CT scan showed significant shrinkage of the primary lung nodule. Her abdominal CT scan with contrast showed periportal collar and edematous gall-bladder, which suggested acute hepatitis (Fig. 1). We saw no evidence of biliary obstruction, non-alcoholic fatty liver disease and ischemic hepatitis. The PCR testing for hepatitis B virus (HBV), HCV, cytomegalovirus, herpes simplex virus and Epstein–Barr virus was negative. Antibodies to hepatitis A virus, hepatitis E virus and anti-mitochondrial smooth muscle were also negative. Serum levels of copper and ceruloplasmin were normal, and serum ferritin level was slightly elevated. Then, crizotinib-induced acute hepatitis was strongly suspected, and crizotinib treatment was discontinued from the evening of Day 29. Epigastric pain and vomiting might have been the symptoms of the hepatitis or symptoms of gastrointestinal toxicity due to crizotinib. On Day 30, daily steroid pulse therapy (1 g once per day for 3 days), plasma exchange and continuous hemodiafiltration were started to support her liver function (Fig. 2). On Day 31, disturbance of consciousness developed, and she went comatose on Day 33. Her electroencephalograph showed typical triphasic wave, and her head CT was normal. Hepatic encephalopathy was then diagnosed. At this time, according to the Inuyama Symposium criteria, a diagnosis of fulminant hepatitis was made (9). On Day 32, refractory
generalized convulsions developed, so we stated intravenous fosphenytoin and midazolam. Although we continued these intensive therapies, her liver function gradually deteriorated, and she remained comatose. On Day 36, she died of liver failure. Autopsy could not be performed.

DISCUSSION

This report describes a case of a fatal fulminant hepatitis secondary to crizotinib administration. We first ruled out biliary abnormalities by CT scanning, and then viral hepatitis and autoimmune disease (including autoimmune hepatitis and primarily biliary cirrhosis) through serological testing. She did not drink alcohol, so we eliminated alcoholic liver disease. We excluded hemochromatosis and Wilson disease by her abdominal CT scanning before crizotinib administration and her serum ferritin and copper levels. We ruled out hemodynamic-induced liver disease as her hemodynamic status was stable. At this point, we strongly suspected drug-induced liver injury. Package inserts for sitagliptin, rabeprazole and crizotinib indicated that they could be the guilty drugs. However, as she had been taking sitagliptin and rabeprazole for >2 years without adverse effect, we excluded these two drugs. Considering international criteria and scoring systems for diagnosing drug-induced hepatitis, we concluded this fulminant hepatitis was caused by crizotinib (10–14).

Generally, symptoms of drug-induced hepatitis are unspecific, so diagnosis is likely to be delayed. Additionally, in this case, hepatitis developed abruptly after Day 16; moreover, she was completely asymptomatic until Day 27. We suppose that recognizing her liver toxicity was rather difficult. Although intensive treatments were initiated immediately after admission, she did not respond to these therapies.

The mechanism of liver toxicity owing to crizotinib is not clear. This patient’s hepatitis was a hepatocellular type injury. The crizotinib dose was not escalated, and no apparent abnormality was detected on Day 16. This dose-independent liver-toxicity suggests that the mechanism was not direct hepatotoxicity, but idiosyncratic—possibly an allergic reaction to metabolized substances of crizotinib or an inability to metabolize crizotinib owing to an individual genetic variance (14,15).

Until now, specific risk factors for crizotinib-induced liver toxicity have not been identified. General risk factors of drug-induced hepatotoxicity are reported to be older age, female sex, HIV infection, HBV or HCV infection, pregnancy, excessive alcohol intake, smoking and genetic variability (16,17).

According to the prescribing information for crizotinib, hepatotoxicity due to crizotinib generally occurs within the first 2 months of treatment. Therefore, monitoring liver function every 2 weeks during the first 2 months of treatment is needed. Consideration of the pharmacodynamic properties of crizotinib is important in regard to drug adverse effects. The
liver metabolizes crizotinib, and CYP3A plays a major role. Therefore, we have to avoid concomitant use of CYP3A inducers and inhibitors, which may increase the plasma concentrations of crizotinib (18).

The present case suggests that liver function should be monitored more frequently if the patient has trivial elevation of liver enzymes during the first 2 months of treatment. We should also take great care regarding liver function if the patient has a history of HCV infection, even if pre-treatment liver function is within normal limits. We should also be careful if the patient is on an antidiabetic drug, because unknown drug interactions may occur (in this case, sitagliptin is metabolized partially by CYP3A, but sitagliptin does not affect CYP3A). We might have to take care regarding liver function if the patient has a history of collagen disease such as dermatomyositis, although the mechanism of liver function disturbance in this setting is unclear.

Although crizotinib is generally well tolerated, physicians should be aware of the possibility of such a severe adverse reaction. Anyway, together with previous reports, a systematic survey for the identification and prevalence of risk factors for crizotinib-induced liver toxicity is warranted.

CONCLUSION

Crizotinib can cause fulminant hepatitis. Physicians should take great care in treating patients with crizotinib, especially if the patient has trivial elevation of liver enzymes during the first 2 months of treatment, if the patient is on an antidiabetic drug, or if there is a positive history of HCV infection or collagen disease.

Conflict of interest statement

None declared.

References