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Crizotinib-induced fatal fulminant liver failure

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ABSTRACT

Herein we describe a case of a 62-year-old female in good clinical condition with non-small-cell lung cancer who was treated with crizotinib. After 24 days of crizotinib therapy she presented with acute liver failure. Serum aspartate aminotransferase and alanine aminotransferase levels had increased from normal prior to crizotinib start to 2053 IU/L and 6194 IU/L, respectively. Total bilirubin and prothrombin time (PT-INR) increased up to 443 IU/L and 5.33, respectively, and symptoms of hepatic encephalopathy and hepatorenal syndrome emerged. Despite crizotinib discontinuation and intensive supportive therapy, the patient died 40 days after treatment with crizotinib was initiated due to acute liver failure with massive liver cell necrosis.

1. Introduction

Non-small cell lung cancer (NSCLC), accounting for about 85% of all lung cancer cases, is diagnosed in approximately 1.3 million new patients worldwide each year [1]. Activating rearrangements of the anaplastic lymphoma kinase (ALK), causing constitutive kinase activity, are found in 5–7% of patients with NSCLC [2,3]. Targeting ALK using the small-molecule inhibitor crizotinib significantly improved clinical outcome of patients with ALK-positive advanced NSCLC as compared to standard chemotherapy and has become the preferred first-line therapy for this patient group [4]. In the present report we describe a case of fatal acute hepatic toxicity induced by crizotinib in a patient with ALK-positive NSCLC.

2. Case-report

A 62-year-old female with stage IV ALK-positive NSCLC started crizotinib treatment (250 mg twice daily) after she progressed upon first-line chemotherapy with cisplatin/pemetrexed. Besides the primary tumor in the left lower lobe of the lung, radiological examination revealed lymphangitis carcinomatosis and metastases in the left breast, liver and right lobe of the lung. At baseline (day 1), Eastern Cooperative Oncology Group performance status was 1, no comorbidity other than yellow nail syndrome was present and clinical examination was normal except for diminished pulmonary sounds over the left lobe and deformed left mamma due to metastases. The patient was not known with any contra-indications for crizotinib, nor with any medication-related hypersensitivity and laboratory data revealed that serum liver enzymes were within normal limits (total bilirubin 5 μmol/L [normal reference <16 μmol/L], AST 26 IU/L [<31 IU/L], ALT 19 IU/L [<34 IU/L]) (fig. 1). Lactate dehydrogenase (LDH) (246 IU/L [<247 U/L]) was just under the upper limit of normal (ULN) and alkaline phosphatase (ALP) (184 IU/L [<98 U/L]) and gamma-glutamyltransferase (64 IU/L [<38 U/L]) were slightly increased. The patient was using dexamethasone for her lymphangitis carcinomatosis, but this was discontinued at day 14 according to a planned tapering regimen. On day 7 serum ALT (44 IU/L) was slightly elevated compared to baseline while total bilirubin (3 μmol/L) remained below ULN, which was within limits to continue treatment with crizotinib [5]. On day 17 she showed clinical signs of tumor regression as indicated by decreased stiffness of the left mamma. Adverse drug reactions were

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absent and laboratory blood samples were taken and evaluated at her next visit (day 24). Retrospectively, laboratory data revealed elevated ALT (2062 IU/L), but normal total bilirubin (5 μmol/L) at day 17. Although she showed no clinical abnormalities at day 24, liver function had further decreased (total bilirubin 25 μmol/L, ALT 6194 IU/L, AST 2053 IU/L, LDH 1073 IU/L, albumin 33 g/L) and crizotinib was discontinued. She did not use alcohol nor hepatotoxic co-medication in the past weeks. On day 31, the patient suffered from diarrhea and physical examination showed icteric sclera. Total bilirubin had further increased to 286 μmol/L and infection with hepatitis A, B or C virus was excluded. Her serum tested positive for Epstein-Barr virus IgG and hepatitis E virus IgG antibodies, but not for IgM antibodies. Coagulation factor V concentration was 11% [normal reference: 70–130%], serum ferritin level (10756 μg/L) was strongly elevated and prothrombin time (PT-INR 5.33) was prolonged, matching with the King's College criteria for acute liver failure with poor prognosis, together with age (>40 years), etiology (idiosyncratic drug-induced), icterus and bilirubin level (> 300 μmol/L) [6]. Nevertheless, given her poor lung cancer related prognosis she was not a candidate for liver transplantation. Abdominal ultrasound showed no evidence of biliary obstruction, portal hypertension, portal vein thrombosis or ascites. At this point her model for end-stage liver disease (MELD) score was 36, indicating an estimated 3-month mortality of 53%. As crizotinib metabolism largely depends on CYP3A, genetic variability in the gene encoding CYP3A may cause increased plasma concentrations of crizotinib. Plasma crizotinib levels in blood samples taken on days 31–36 were within the normal range of what can be expected after crizotinib discontinuation. The plasma elimination half-life ($t_{1/2}$) was estimated to be ~50 h, slightly longer than average (42 h) [5]. However, this effect may as well be a result of crizotinib-induced liver failure instead of genetic polymorphisms in CYP3A. On day 33 she was admitted to the Hospital because of acute liver failure with initial clinical signs of hepatic encephalopathy, although serum ammonia level (32 μmol/L [normal reference <50 μmol/L]) was not elevated. She was intensively treated according to the Dutch guidelines for acute hepatic failure including lactulose against encephalopathy, prophylactic antibiotics (cefotaxim, vancomycine), proton pump inhibitor and vitamin K suppletion. CT scan of the brain showed diffuse supratentorial edema and no evidence of cerebral metastases. On day 35 her consciousness deterioration persisted and she suffered from progressive edema of the lower legs, upper legs and hands. Serum creatinine had increased to 152 μmol/L despite intravascular volume expansion, with decreased micturition and <20 mmol/L urinary sodium. This indicated symptoms of hepatorenal syndrome for which terlipressine and albumin were initiated. She became progressively more dyspnoeic due to increasing pleural fluid and ascites. Although renal function seemed to improve on day 39 (serum creatinine 118 μmol/L), her liver function did not (total bilirubin 419 μmol/L) and her consciousness was rapidly deteriorating. On day 40 the patient died. Autopsy or liver biopsy could not be performed.

3. Discussion

This report describes the first case of crizotinib-induced fatal fulminant acute liver failure due to liver cell necrosis in a Caucasian patient. Other causes of acute liver failure were excluded including biliary obstruction, viral hepatitis infection, alcoholic liver disease and concomitant medication. Moreover, liver toxicity is a common adverse event in patients using crizotinib; grade 3–4 ALT elevations occurred within the first two months of crizotinib treatment in approximately 15% of patients in pivotal phase III studies [4,7]. In the majority of patients ALT elevations were reversible upon dosing interruption, but in rare cases permanent discontinuation was necessary [8,9]. Crizotinib-induced hepatotoxicity with fatal outcome occurred in 0.2% of patients [5]. Therefore, monitoring of liver function including ALT and total bilirubin is recommended every week during the first 2 months of treatment and once a month thereafter according to prescribing information [5]. Although the mechanism of crizotinib-induced hepatotoxicity is unknown, there seems to be a pathophysiologic difference between the common gradually increasing liver enzymes and the fulminant idiosyncratic liver failure in our patient. Sato and colleagues described a similar course of disease with mildly elevated liver enzymes on day 16 of crizotinib treatment and severe liver impairment two weeks later, which ultimately caused this patient to die on day 36 despite immediate crizotinib discontinuation and supportive therapy at the intensive care unit [10]. Therefore, weekly liver enzyme evaluation is not sufficient to prevent these sporadic crizotinib-induced hepatotoxic events with potential fatal outcome. The dose-independent and abrupt hepatic impairment argues for an immune-related mechanism, possibly similar to lapatinib-induced hepatotoxicity which has been associated with specific HLA polymorphisms within the major histocompatibility complex (MHC) [11]. Future research should therefore focus on elucidating the underlying mechanism of these severe cases and on identifying risk factors that may predict severe crizotinib-induced hepatitis. In the meantime, physicians

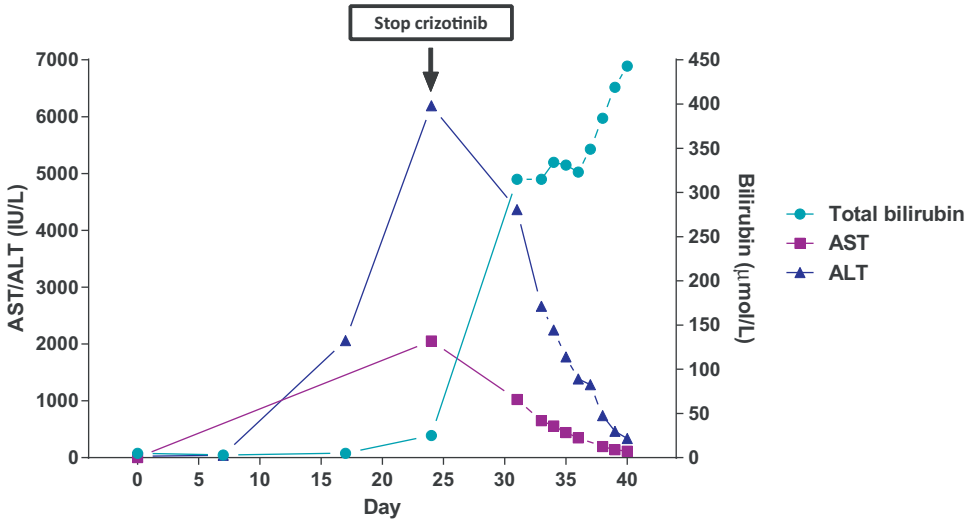

Fig. 1. Detailed overview of liver enzymes (total bilirubin, AST and ALT) during crizotinib treatment (day 0–23) and after crizotinib discontinuation (day 24–40).

should be aware of this potential fatal adverse reaction and evaluate liver function at least once a week during the first 2 months of treatment and more frequently in case of increasing liver enzymes.

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