CASE REPORT

From spotlight to shadow: ALK inhibitor-induced acute liver failure in a patient with non-small cell lung cancer

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ABSTRACT

Novel oncological therapies substantially improved the prognosis of cancer patients. Immunotherapies (immune checkpoint inhibitors) and targeted therapies (tyrosine kinase inhibitors) represent innovative strategies, which have revolutionized cancer patient's approaches. However, the new treatments may bring additional adverse effects, therefore right selection, close monitoring, and appropriate clinical decisions in the event of a complication are of upmost importance in these patients' management. We present an elderly male patient undergoing treatment with alectinib - anaplastic lymphoma kinase (ALK) inhibitor for metastatic non-small cell lung cancer, who was diagnosed with acute liver failure by drug-induced liver injury, five months after the start of the therapy. After the other possible causes of hepatocellular injury were excluded, the drug was discontinued. Using corticotherapy and supportive measures, the evolution of the patient was favorable. Up to this moment, data showed that alectinib was less associated with liver function abnormalities compared to other ALK inhibitors, however most commonly of mild or moderate grade of severity, especially in the first two months of treatment. The case we report presented acute onset liver failure, with a relatively late occurrence during alectinib therapy. Timely recognition may improve patients' prognosis, and monitoring must be carried out rigorously. Awareness and effective interdisciplinary communication among medical specialties play a pivotal role in the comprehensive care of cancer patients.

KEYWORDS: targeted therapy; ALK inhibitors; alectinib; non-small cell lung cancer; drug-induced liver injury; acute liver failure

INTRODUCTION

For many years, treatment possibilities for oncological patients were limited to conventional treatments such as surgery, radiotherapy and/or chemotherapy. Since cancer progression is not solely attributed to changes in the epithelial cells, but also closely linked to transformations in the tumor microenvironment, led to new insights into the management of these patients [1].

Over the last years, immune therapy has become a cornerstone of modern cancer treatment and improved the patient's prognosis. Studies have shown promising results in patients treated with immune therapy in which a better response was obtained compared to the classical therapy through manipulation of immune modified molecules. Recently immunotherapies have been used with adjuvants, called neo-adjuvant therapies which could stimulate the activity of the immune system, or prevent the inhibition of the immune response by tumor cells [2].

An innovation in cancer treatment is also targeted therapy. Lack of response to anti-neoplastic therapy is caused by intrinsic cellular, genetic and/or epigenetic changes due to tumor heterogeneity. Therefore, the new therapy brings a new light to the treatment of cancer, having a selective action without the side effects of systemic therapy [3]. Targeted therapy includes checkpoint inhibitors (ICIs) and anaplastic lymphoma kinase (ALK) inhibitors [4]. Currently approved ICIs target the programmed cell death receptor 1 (PD1), and the programmed cell death ligand 1 PD-L1. The synthesis of PD1 positive cells is inhibited by the PD1/PDL1 interaction and the tumor gets rid of the blockage of the immune system ending to the failure of treatment. Hence, the connection between PD1 and PDL1 has become an important value in immunotherapy. Atezolizumab was the first anti-PDL1 antibody approved for the treatment of urothelial cancer

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and metastatic NSCLC. ALK inhibitors (alectinib) also had a major impact in cancer treatment, leading to a decrease in mortality in patients with NSCLC [5].

As a result, together with the recent progress in cancer treatment, the demand for collaboration across multiple disciplines is increasing, due to various potential treatment-related side effects. Undoubtedly, the field of gastroenterology has been increasingly involved in the care of patients diagnosed with cancer, given the occurrence of gastrointestinal and liver complications associated with these novel therapies. However, when deciding the treatment approach, there must be a balance between benefits and possible side effects, and communication between medical specialties is vital in the management of cancer patients.

We present a case of an elderly male undergoing ALK inhibitors for lung cancer, addressed for acute liver failure by drug-induced liver injury, five months after the beginning of the therapy.

CASE PRESENTATION

A 73-year-old male patient, with a history of non-small cell lung cancer, with malignant pleural effusion, diagnosed 5 months ago, and treated from the beginning with alectinib, was admitted to the Institute of Gastroenterology and Hepatology for physical asthenia and jaundice, with onset ten days ago.

On physical examination, the patient had jaundice without pruritus and without fever; no abdominal pain, no acholic stools, and no clinical signs of overt hepatic encephalopathy.

Laboratory analysis showed coagulopathy (prothrombin time=19.3 s, prothrombin activity = 53%, International Normalized Ratio = 1.73), and marked syndrome of hepatic cytolysis: alanine aminotransferase (ALT) = 672 U/L, aspartate aminotransferase (AST) = 120 U/L, and icteric cholestasis: alkaline phosphatase (ALP) = 208 mg/dL, gamma-glutamyl transferase (GGT) = 73 U/L, total bilirubin = 32 mg/dL, conjugated bilirubin = 22.85 mg/dL. At the same time, blood tests showed normal serum ammonia and glucose levels, normal renal function, and absence of electrolyte abnormalities. Infectious screening was done, excluding any source of infection.

The abdominal ultrasound did not show any focal liver lesions, cholelithiasis or dilated bile ducts. A thoracic, abdominal, and pelvic computed tomography exam was also performed, showing a stationary pulmonary aspect, and no liver infiltration, no vascular thrombosis, no adenopathy, or ascites fluid.

The pattern of liver injury suggested a hepatocellular-type injury; for differential diagnosis, subsequent comprehensive investigations were performed (Table I).

On clinical and paraclinical grounds, we orientated towards the diagnosis of drug-induced liver injury (DILI), manifested by acute liver failure. Alectinib was stopped, and during hospitalization, supportive measures were applied, and treatment with N-acetylcysteine and corticosteroids, with favorable clinical evolution. The hepatotoxicity gradually improved to grade 1, and after discharge, the patient was redirected to the oncology department for appropriate treatment options.

Tabel I. The differential diagnosis of hepatocellular injury.

Possible causal conditions	Clinical/ paraclinical data
Viral Hepatitis (Acute / Flare)	Negative HAV antibodies, IgM type Negative hepatitis B surface antigen, hepatitis B core antibodies Negative HCV antibodies, undetectable RNA-HCV Negative Herpes simplex, Cytomegalovirus, Epstein-Barr antibodies
Ischemic hepatitis	No cardiac failure, no hypovolemia, no imaging findings of vascular thrombosis
Autoimmune hepatitis	Negative antinuclear antibodies (ANA), actin smooth muscle antibodies (ASMA), liver kidney microsome type 1 (LKM-1) antibodies, anti-mitochondrial (AMA) antibodies
Hemochromatosis	Normal serum ferritin level, normal transferrin saturation index
Wilson disease	No suggestive clinical signs Normal serum ceruloplasmin and urinary copper levels
Non-alcoholic fatty liver disease	No history of diabetes, high blood pressure, no signs of steatosis
Alcohol hepatitis	No history of alcohol consumption
Biliary disease (cholangitis, choledocholitiasis, primary biliary cholangitis, primary sclerosing cholangitis)	Absent antimitochondrial antibodies No imaging findings
Malignancy (hepatocellular cancer, liver metastases, pancreatobiliary malignancy)	No signs of malignancy on imaging
Herbal medicine related hepatotoxicity	No history of herbal products consumption
Drug induced liver injury	History of alectinib intake

DISCUSSIONS

DILI still represents an excited topic and remains a diagnosis of exclusion. There are two mechanisms involved in the pathogenesis of DILI: intrinsic, which depends on the administered dose and idiosyncratic, which is harder to predict [6].

In hepatocellular injury, laboratory analyses will show elevation in aminotransferases, with various degrees of bilirubin level, on the other hand, in cholestatic injury, alkaline phosphatase will be elevated [7].

Hepatotoxicity can have four degrees depending on the level of ALT and AST: grade 1 (ALT and AST are up to three times higher than the upper limit of normal (ULN)), grade 2 (ALT and AST are between three and five times higher than ULN), grade 3 (ALT and ALT are between five and twenty times higher than ULN) and grade 4 (ALT and AST are twenty times higher than ULN) [8].

The main treatment for DILI is the withdrawal of the incriminated drug. Currently, there are few specific therapies, such as N-acetylcysteine (NAC) in acetaminophen ingestion, by stimulating regeneration of glutathione, resulting in the detoxification of toxic metabolites, and L-carnitine for DILI secondary to acid valproic toxicity [8,9]. Corticosteroid therapy is given with a step-down strategy with the aim of suppressing the exaggerated inflammatory process [10].

There have been reported some cases of hepatotoxicity caused by ICIs and by ALK inhibitors. ICIs caused hepatocellular injury in up to 9% of the treated patients when administered as monotherapy [11]. The proportion of cases increases to 16% when the administered dose is high or even more, up to 18% when indicated in combination [4,12].

ALK is a tyrosine kinase that can be abnormally expressed in certain tumor types such as NSCLC (about 5%) [13].

It is important to identify gene rearrangements in recently diagnosed patients with advanced, metastatic, or recurrent NSCLC to decide the treatment. Also, that kind of tumor seem to be correlated with some specific clinical findings like younger age or never - or light smoking history but they are not mandatory for the diagnosis [14]. Advanced ALK-positive NSCLC usually is more aggressive, and patients have a higher incidence of secondary brain lesions compared with other types of NSCLC [15,16].

Crizotinib was the first ALK inhibitor used, and it has been proved that he had increased the progression-free-survival (PFS) and enhanced quality of life in comparison with chemotherapy in treatment-naïve patients [17]. Alectinib was approved as the first-line treatment for patients with ALK-positive metastatic NSCLC and for those who have progressed on crizotinib [15]. Studies have shown that alectinib considerably increased PFS compared to crizotinib [18].

Patients generally tolerate treatment with ALK inhibitors, but there are some adverse effects that can impose dose modification or treatment interruption, such as pulmonary, cardiac, visual, neurologic, musculoskeletal, metabolic, gastrointestinal, or liver toxicity.

We reported this case because as far as we know, there have not been reported many cases of acute liver failure after treatment with alectinib. Hepatotoxicity appears more often after treatment with crizotinib, and most cases of hepatotoxicity occur in the first two months of treatment. Hence, the fact that the patient developed acute liver failure relatively late and after treatment with a less incriminated drug, represented the challenges in our case.

The diagnosis was one of supposition but supported by exclusion and by the favorable evolution after stopping the drug, with supportive treatment and corticosteroids.

The ALEX study showed that in patients treated with alectinib the usual time to onset of hepatotoxicity was 1.8 months, and the majority were grade 1 or 2; grade 3 and 4 events have been reported with a much lower frequency [19].

Drug-induced hepatotoxicity is more common with crizotinib or ceritinib than alectinib [20]. In preregistration trials of alectinib, ALT elevations appear in up to 50% of patients, but there are very few cases (1-4%) in which values 5 times higher than ULN were found. Although liver injury with jaundice was rare, some cases were reported and at least 2% of alectinib treated patients suspended treatment early because of hepatotoxicity [21].

To prevent hepatotoxicity, it is important to carefully monitor the patient during treatment with ALK inhibitors. Thus, during the first three months of treatment, liver tests should be done every two weeks and then with a lower frequency once a month or when increases in ALT and bilirubin occur [22]. In case of at least grade 3 hepatotoxicity, treatment with alectinib should be temporarily interrupted until liver enzymes return to baseline or at least $<$G1 and drug could be restarted at a lower dose (450 mg twice daily). In case of increased bilirubin and ALT (bilirubin $>2\times$ ULN and ALT$\geqslant 3\times$ ULN) alectinib should be permanently stopped. A reduced dose (450 mg twice daily) is also administered to patients with severe hepatic impairment (Child-Pugh C), because increased blood levels of alectinib have been observed in such patients [23].

Moreover, there is also the major issue of reactivation in patients with chronic viral hepatitis, especially HBV, by an incompletely elucidated mechanism. Serological screening must be carried out prior to the treatment with TKIs. If the surface antigen of HBV (HBsAg)-positive, or anti-HBsAg-negative/antihepatitic B core (anti-HBc)-positive, HBV DNA level should be tested before starting ALK-TKI treatment. Antiviral therapy should be considered accordingly, with close monitoring of liver enzymes/HBV-DNA [24].

CONCLUSIONS

The innovative oncologic therapies substantially improved the prognosis of cancer patients; however, the novel therapies may bring additional adverse effects and communication between medical specialties is essential for timely recognition of these side effects and for their correct management.

This case shows a late and unexpected complication of the treatment with ALK inhibitors and emphasizes the importance of timely recognition of adverse effects. Hepatotoxicity is less common after treatment with alectinib, but it can worsen the patient's prognosis if it is not managed correctly. Moreover, depending on the severity of the hepatotoxicity, the dose of the drug can be changed, or the therapeutic agent can be temporarily interrupted and replaced with another drug. The patient must be carefully monitored during treatment with ALK inhibitors; liver tests should be constantly performed, especially in the first months of treatment.

Right indication, attentive selection and appropriate, close monitoring are mandatory in cancer patients' management. Awareness and effective interdisciplinary communication among medical specialties play a pivotal role in the comprehensive care of cancer patients.

Conflicts of interest and funding

No conflicts of interest and no funding to declare.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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