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Case Report

Alectinib-Related Hepatic Toxicity in A patient with Advanced ALK-Positive Non-Small-Cell Lung Cancer

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Abstract

Alectinib is suggested as first-line treatment for advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Nevertheless, despite being generally well-tolerated, drug-related adverse events (AEs) like hepatotoxicity and cognitive impairment are still not fully understood. We report the case of a patient affected by stage IV ALK-positive NSCLC who developed hepatic toxicity and cognitive decline during Alectinib treatment

Keywords: alectinib; hepatic toxicity; ALK-positive NSCLC

Abbreviations

ALK: Anaplastic lymphoma kinase

NSCLC: non-small cell lung cancer

CNS: central nervous system

TKI: tyrosine kinase inhibitor

BBB: blood-brain barrier

ORRs: objective response rates

AEs: adverse events

EEG: electroencephalogram

Introduction

Anaplastic lymphoma kinase (ALK) alterations occur in approximately 5% of patients with non-small cell lung cancer (NSCLC)[1]. Advanced ALK-positive NSCLC is characterized by an aggressive disease course, including a high prevalence of central nervous system (CNS) metastases, affecting approximately 30% of patients[3].

ALK-inhibitors are approved for treatment of advanced ALK-positive NSCLC, with alectinib representing a next-generation tyrosine kinase inhibitor (TKI) known for its superior systemic and CNS activity compared to crizotinib[6]. Based on the results of the phase III J-ALEX and ALESIA trials, alectinib is recommended as first-line treatment for patients with advanced ALK-positive NSCLC according to current guidelines[8, 9, 14]. Alectinib has demonstrated a high blood-brain barrier (BBB) penetration rate and powerful intracranial efficacy in several clinical trials, including both first-line and crizotinib-resistant settings, with objective response rates (ORRs) of over 75% and 60%, respectively[6, 7]. Even though patients with symptomatic or unstable CNS metastases were excluded from all clinical trials of alectinib, real-world studies showed its strong CNS effectiveness. In particular, a retrospective study conducted in China suggested that patients with symptomatic or asymptomatic BM could benefit from alectinib, both in terms of symptom reduction and its ability to postpone local treatment, which may result in some neurological issues[17, 18].

Alectinib has a tolerable and well-characterized safety profile[5]. However, undefined drug-related adverse events (AEs) have been poorly characterized.

We report the case of a young patient receiving alectinib for advanced ALK-positive NSCLC, who developed hepatic toxicity and cognitive impairment three months into the treatment.

Case Presentation:

In April 2024, a 55-year-old Caucasian woman was diagnosed with stage IV ALK-positive NSCLC due to brain metastases complicated onset with seizure. Given the extent of the disease, CNS involvement, and ALK-translocation, the patient started first-line treatment with alectinib (600 mg) twice daily[13]. Two months after initiating therapy, restaging examinations revealed a reduction in both the number and size of brain metastases as well as a substantial change in the dimensions of lung lesions (PR in RECIST 1.1).

In late August, the patient developed jaundice associated to ideomotor apraxia and memory deficits. She did not experience abdominal pain, pruritus, or fever. Laboratory analysis revealed elevated blood bilirubin (6.03 mg/dL, 5 ULN), predominantly conjugated (4.96 mg/dL), and increased levels of AST/ALT (241/261 U/L, 6 ULN, grade 3 toxicity CTCAE v5.0). Despite these abnormalities, serum ammonia levels and coagulation tests remained within normal limits.

Subsequently, the patient was admitted to the Oncology Unit. A comprehensive review of her concomitant medications, dietary habits and screening for viral hepatitis was performed, ruling out other differential causes of hepatocellular injury. Autoimmune hepatitis was also excluded with negative results from the assessment. In addition, normal ceruloplasmin and ferritin levels ruled out the possibility of concomitant Wilson disease or hemochromatosis. Restaging assessments confirmed the absence of liver metastases and revealed an additional in both the number and size of the brain lesions. A subsequent abdominal MRI uncovered delayed excretion of a contrast agent into the biliary tract, consistent with decreased liver function. Consequently, all the assessment performed ruled out any alternative cause of liver injury.

Alectinib was discontinued during hospitalization, and supportive treatment with N-acetylcysteine, corticosteroids and hydration was initiated[15]. Concurrently, the patient's neurological condition worsened progressively, though it was unrelated to hepatic encephalopathy since ammonium levels were within the normal range. An electroencephalogram (EEG) showed a pattern of left frontal distress, but no further neurological investigations were conducted. Psychiatric counseling attributed the cognitive impairment to a possible psychogenic reaction.

Following clinical improvement, with gradual but slow regression of liver toxicity, the patient was discharged with periodic liver function surveillance scheduled. Over the next two months, liver function tests gradually improved and corticosteroid doses were progressively reduced (Figure. 1). However, bilirubin levels remained elevated (> 2 ULN), leading to permanent discontinuation of alectinib (Figure. 2).

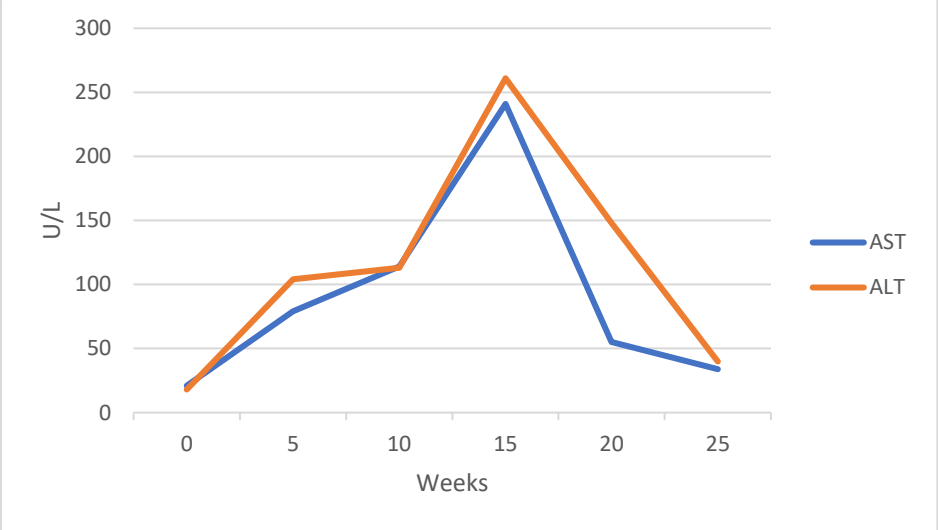

Figure 1: Plot of AST/ALT

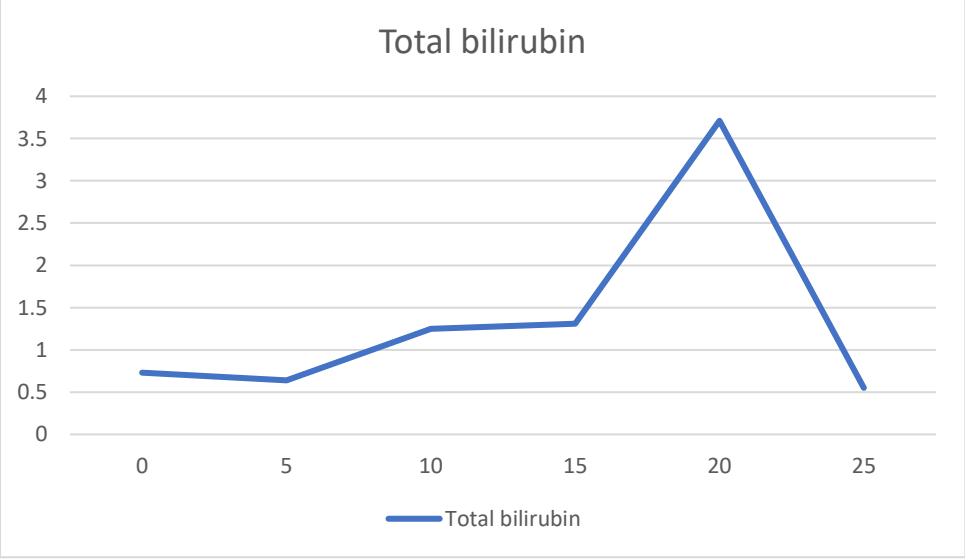

Figure 2: Trend of bilirubin levels.

In October, neurological symptoms progressively worsened, with increased ideo-motor impairment and absence seizures. A brain MRI revealed disease progression, with increased number and size of secondary localizations, as well as perilesional edema. The patient was thus readmitted to the Oncology Unit for antiedema therapy, and restaging exams were scheduled to figure out next course of treatment.

Discussion:

This case report illustrates a rare complication of treatment with Alectinib, underscoring the importance of periodic monitoring and early detection of AEs that may impair patient prognosis.

Although targeted agents are generally well tolerated, sever liver toxicities associated with TKIs have been reported. In the phase III ALEX trial, the incidence of liver function abnormalities was 34.2%, the majority of which were mild in severity (G1-2), with grade 3 or higher toxicity being uncommon. In contrast, in real world studies, the incidence of serious liver toxicity appears to be higher, affecting 8.7% of patients[4, 12]. However, the specific mechanism of alectinib-related liver toxicity remains undetermined, so further studies are needed to figure out this issue.

To our knowledge, only few cases of alectinib-related hepatotoxicity requiring hospitalization have been reported[10, 16]. Furthermore, in one case report the patient developed acute liver failure relatively late during the treatment with alectinib. Instead, in our case, the incidence of hepatotoxicity was 2 months, in accordance with that reported in ALEX study. In addition, in one case, despite a grade 3 increase in AST and ALT, Alectinib was resumed without further hepatotoxicity.

According to ESMO recommendations, the diagnosis of drug-related toxicity must be supported by the exclusion of other possible causal conditions of hepatocellular injury, as well as favorable outcomes following drugs withdrawal[4]. Furthermore, depending on the severity of drug-related liver toxicity, alectinib should be discontinued and either resumed at a lower dose or replaced with another therapeutic agent. In cases of persistent and sustained elevation of AST/ALT levels and total bilirubin >2 ULN, resumption of the drug may not be feasible, as observed in this patient. Lastly, the observed CNS progression during the alectinib-free interval, she experienced, highlights the critical need for effective monitoring and prompt intervention to mitigate treatment interruptions and optimize patient prognosis.

In our case, the possibility of subsequent treatment is limited by both the toxicity profile and the patient's clinical condition. In fact, a high frequency of neurocognitive adverse events is reported with lorlatinib, which has been approved for the treatment of advanced ALK-rearranged NSCLC in patients untreated or progressed on prior ALK TKI therapy[11]. Furthermore, the patient's unstable clinical status restricts the options of brigatinib, which also carries a moderate risk of hepatotoxicity, or radiation therapy[2].

Conclusion:

This case report highlights a rare but clinically significant presentation of alectinib-induced hepatotoxicity and cognitive impairment in a patient with advanced ALK-positive NSCLC. While alectinib remained a cornerstone of first-line therapy due to its strong systemic and intracranial activity, clinicians should be aware of the potential serious and early-onset liver toxicity and neurocognitive impairment, even if the underlying mechanism remains unknown. Prompt recognition, through differential diagnosis, and timely discontinuation are crucial to mitigating long-term effects.

Specifically, our experience underscores the need for punctual monitoring of hepatic and neurological function during therapy and raises important considerations for treatment sequencing in patients resistant or intolerable to first line ALK inhibitors. Further real-world data are needed to butter understand the pathophysiology of these adverse events in order to personalized therapeutic strategies.

Disclosure Statement of Conflict of Interest: no conflict of intertest

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