Severe Acute Hepatitis in a Patient Receiving Alectinib for *ALK*-Positive Non–Small-Cell Lung Cancer: Histologic Analysis

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Clinical Practice Points

- Alectinib may induce increased transaminases requiring dose interruption.
- Severe acute hepatitis with bridging necrosis was seen in a liver biopsy sample of an anaplastic lymphoma kinase–positive non–small-cell lung cancer patient treated with alectinib.
- Because the histologic changes were acute and no fibrosis was seen, complete recovery of liver functions might be expected, which is consistent with the outcome of our case.
- Given the expected long duration of alectinib use in the future, management of hepatotoxicity will become an essential clinical skill for oncologists to master.

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Introduction

Alectinib is a next-generation anaplastic lymphoma kinase (ALK) inhibitor that has received accelerated approval by the US Food and Drug Administration (FDA) because of its efficacy in *ALK*-positive non–small-cell lung cancer (NSCLC) from two phase 2 studies.[1] According to the FDA approval report, among 250 patients who were enrolled onto the study, 51% experienced increased aspartate aminotransferase (AST) and 34% experienced increased alanine aminotransferase (ALT) of any grade, but the incidence of grade 3 (> 5-20 times the upper limit of normal [ULN]) or higher elevation of AST and ALT was only 3.6% and 4.8%, respectively.[1] Additionally, 2 randomized trials have demonstrated significantly improved (more than doubling) median progression-free survival in *ALK*-positive NSCLC patients treated with alectinib over crizotinib.[2,3] Given the expected long duration of alectinib use in the future, management of adverse reactions such as increased transaminases is important. There is currently no published literature on the pathologic findings or the natural history of alectinib-induced hepatotoxicity.

Here we report for the first time the histologic findings from a liver biopsy sample in an *ALK*-positive NSCLC patient who experienced increased transaminases requiring 2 dose interruptions.

Case Report

A caucasian female never-smoker was diagnosed with stage IV NSCLC in February 2007 at the age of 42. She received carboplatin/pemetrexed and was subsequently enrolled onto the PROFILE 1005 clinical trial after molecular profiling had revealed *ALK* rearrangement. Crizotinib 250 mg twice daily was initiated in January 2011, which resulted in excellent extracranial response with no evidence of disease. She ultimately experienced disease progression in the central nervous system (CNS) in November 2015 but with continued excellent extracranial response, so commercial alectinib at 600 mg twice daily was initiated in December 2015. She was noted to have grade 3 increased AST and ALT with normal total bilirubin in May 2016 (Figure 1). Alectinib was held in late June, and 4 weeks later AST and ALT peaked at 337 and 331 U/L, respectively (Figure 1). She was advised to avoid any supplements, and her medication list only included lacosamide, levetiracetam, and levothyroxine. Of note, she had no known liver metastasis. Assessment for viral hepatitis revealed positive hepatitis A immunoglobulin (Ig) G but negative IgM, and negative hepatitis C IgG. For hepatitis B serology, hepatitis B surface antigen was positive, but

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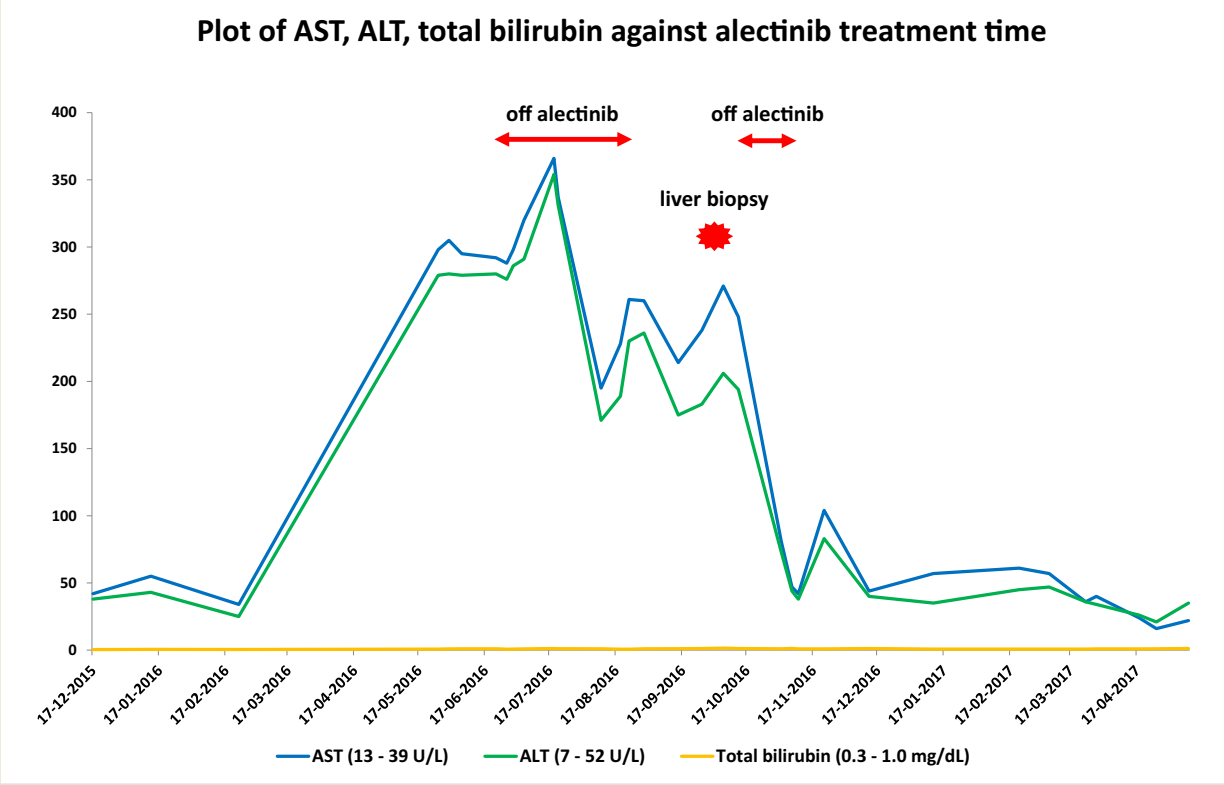
Figure 1 Plot of AST, ALT, and Total Bilirubin Against Alectinib Treatment Time. Double Arrow Indicates Period Where Alectinib was Held; Star, Date of Liver Biopsy



Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

hepatitis B surface antibody, hepatitis B e-antigen, hepatitis B e-antibody and hepatitis B core antibody (IgM and total) were all negative. The hepatitis B virus load was undetectable by quantitative PCR. In addition, cytomegalovirus IgG was positive but IgM was negative. Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgG was positive, but EBV-VCA IgM was negative, and EBV nuclear antibody IgG and early diffuse antibody IgG were both positive. Autoimmune hepatitis assessment was also unrevealing, including negative antinuclear antibody, anti-mitochondrial antibody, and anti−smooth muscle antibody. Ceruloplasmin level was normal, and ferritin level was elevated at 522 ng/mL. Liver ultrasound revealed mild increased echogenicity, likely reflecting steatosis. All these assessments failed to identify other etiologies contributing to her acute hepatitis, so alectinib was deemed the most likely culprit.

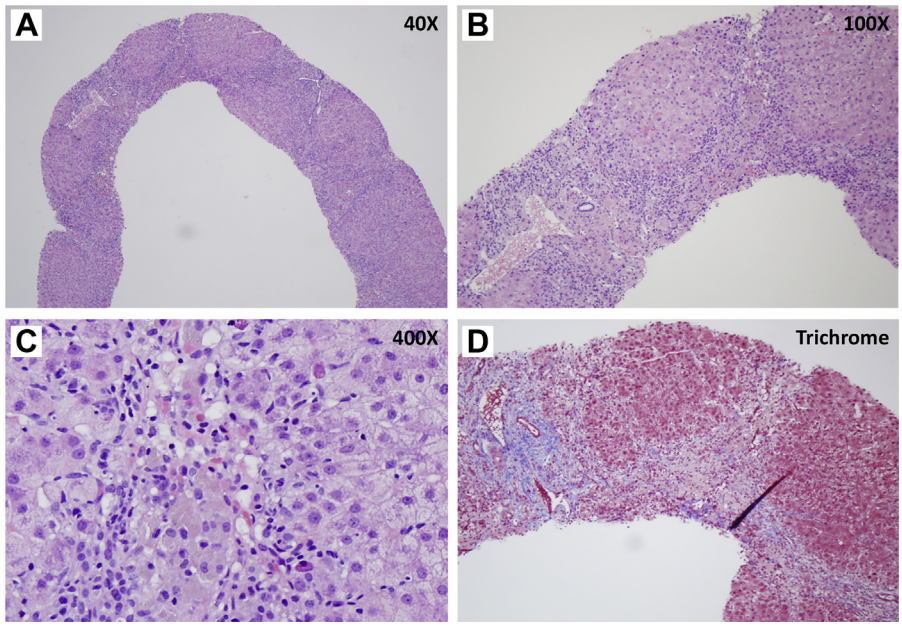
Although there was no resolution of increased transaminases during the first alectinib dose interruption, there was also no further worsening, so alectinib 600 mg twice daily was restarted in late August 2016, given our concern for interval CNS progression. However, alectinib had to be held again in mid-October 2016 as a result of persistent grade 3 hepatotoxicity (Figure 1). Before that, she underwent a liver biopsy to assess the cause of increased transaminases; results revealed marked inflammatory infiltrate and ductular proliferation connecting portal tracts and centrilobular areas, with a nodular pattern of liver parenchyma (Figure 2A and 2B). Centrilobular areas demonstrated hepatocyte dropout and mild hemorrhage, and were filled with lymphocytes, macrophages, plasma cells, and a few acidophil bodies (Figure 2C). Trichrome stain highlighted the collapsed reticulin framework without significant fibrosis, confirming bridging necrosis (Figure 2D).

The final pathology report was severe acute hepatitis with bridging necrosis; differential diagnosis included drug-induced liver injury, autoimmune hepatitis, or viral hepatitis and other infectious diseases. Transaminases eventually normalized after alectinib was withdrawn for 4 weeks. Alectinib 600 mg twice daily was resumed around mid-November 2016 without further hepatotoxicity (Figure 1). Throughout this period, the patient's total bilirubin values were completely normal (Figure 1). In May 2017, the patient was switched to brigatinib at the recommended dosing scheme upon further disease progression; there was no further recurrence of hepatotoxicity.

Discussion

In global[4] and North American[5] phase 2 studies of alectinib in crizotinib-resistant or -intolerant *ALK*-positive NSCLC patients, the incidences of grade 3/4 AST (2% and 5%) and ALT (2% and 6%) elevations were relatively low, respectively. In the J-ALEX randomized phase 3 trial, the incidences of grade 3/4 elevated AST and ALT were only 1% for each with 300 mg twice daily alectinib,[2] while in the ALEX trial, grade 3-5 AST and ALT elevations were both 5% with 600 mg twice daily alectinib.[3] In the 3-year follow-up

Figure 2 Gross Section of Liver Biopsy Sample. (A) Gross Section of Liver Biopsy Sample; Original Magnification, 40×. (B) Marked Inflammatory Infiltrate and Ductular Proliferation Connecting Portal Tracts and Centrilobular Areas, with Nodular Pattern of Liver Parenchyma; Original Magnification, 100×. (C) Centrilobular Areas Show Hepatocyte Dropout and Mild Hemorrhage, Filled With Lymphocytes, Macrophages, Plasma Cells, and Few Acidophil Bodies; Original Magnification, 400×. (D) Trichrome Stain Highlights Collapsed Reticulin Framework Without Significant Fibrosis, Confirming Bridging Necrosis



of the Japanese phase 1/2 study of alectinib at 300 mg twice daily, the incidence of grade 3 ALT elevation was only 3.4%, and there was no recorded incidence of grade 3 AST elevation.[6] Thus, in general, grade 3 or higher incidence of increased transaminases with alectinib is rare and may only increase slightly with increased dose.

Two pooled analyses have demonstrated a lower frequency of hepatotoxicity associated with alectinib compared to crizotinib or ceritinib.[7,8] In addition, the onset of hepatotoxicity in our case was 5 months, which is longer than average; 73% of patients receiving the study therapy experienced elevated transaminases during the first 2 months of receipt of alectinib,[9] thus highlighting the importance of continuous monitoring for hepatotoxicity. Furthermore, the etiology, management, and sequalae of alectinib-induced hepatotoxicity have yet to be elucidated. No one has reported the histologic findings in patients with severe acute hepatitis due to alectinib. Notably, the Hy law (ALT or AST levels $\geq$ 3 times ULN plus total bilirubin $\geq$ 2 times ULN) has been used to predict a drug's likelihood to induce fatal liver injury.[10] In this case, our patient's total bilirubin was always normal, and thus the Hy law could not be applied.

To our knowledge, this is the first report to demonstrate the histologic findings of grade 3 AST and ALT elevations in a patient treated with alectinib. The liver biopsy sample showed severe acute hepatitis with bridging necrosis, and differential diagnosis included drug-induced liver injury, autoimmune hepatitis, and viral hepatitis and other infectious diseases. Our patient was found to be negative for both autoimmune and viral hepatitis. Interestingly, even though the duration of increased transaminases lasted approximately 5 months, the biopsy sample only revealed acute hepatitis without any fibrosis as an anticipated chronic change, indicating potential discordance between liver function tests and histologic abnormalities. Because the histologic changes were acute, complete recovery of liver functions might be expected. Indeed, our patient's hepatotoxicity resolved after the second dose interruption of alectinib. It is unknown whether a longer initial dose interruption followed by dose reduction would have quickened the resolution of this acute hepatitis.

As per the package insert, for ALT or AST $>$ 5 times ULN and total bilirubin $\leq$ 2 times ULN, alectinib should be withheld until ALT/AST $\leq$ 3 times ULN and then resumed at reduced dose (from 600 to 450 mg twice daily).[9] However, our patient experienced interval CNS progression when alectinib was withheld for more than 2 months for the first time, so we decided to rechallenge her earlier than what the guidelines recommend-, and with the same dose in the hope of providing better CNS activity. Because her grade 3 hepatotoxicity became persistent, we withheld alectinib for the second time until she experienced recovery of elevated transaminases close to baseline. Again, the same dose was resumed for CNS coverage, but after knowing complete recovery of liver functions might be possible given the acute histologic changes. Fortunately, our patient derived benefit from alectinib for an additional 6 months without further hepatotoxicity.

Conclusion

This case highlights the importance of close monitoring of patients receiving alectinib for hepatotoxicity. Despite grade 3 or

higher adverse events, resumption of alectinib is possible, which may help provide good efficacy in *ALK*-positive NSCLC.

Disclosure

V.W.Z. has received honoraria from Roche-Foundation Medicine, Roche/Genentech, and Takeda, and consulting fees from TP Therapeutics. Y.L. has no conflict of interest to declare. S.I.O. has received honoraria from Pfizer, Roche-Foundation Medicine, Roche/Genentech and Takeda, and has stock ownership in TP Therapeutics.

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