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Case Report

Successful Treatment with Lorlatinib after the Development of Alectinib-Induced Liver Damage in ALK-Positive Non-Small-Cell Lung Cancer: A Case Report

Go Makimoto Keita Kawakado Masamoto Nakanishi Tomoki Tamura Shoichi Kuyama

Department of Respiratory Medicine, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Japan

Keywords
Alectinib · Lorlatinib · Non-small-cell lung cancer · Anaplastic lymphoma kinase · Hepatotoxicity

Abstract
Alectinib is a key drug for treating *anaplastic lymphoma kinase* (*ALK*)-positive non-small-cell lung cancer (NSCLC). Alectinib-induced hepatotoxicity is less common than that through other ALK inhibitors, such as crizotinib or ceritinib. Herein, we describe a case of *ALK*-positive adenocarcinoma successfully treated with lorlatinib after developing alectinib-induced hepatotoxicity. A 57-year-old Japanese man received alectinib as first-line therapy for *ALK*-positive NSCLC. After 79 days, alectinib was discontinued because of hepatotoxicity and later restarted at 150 mg/day, inducing hepatotoxicity again after 64 days. Switching to lorlatinib treatment (continued for >4 months) caused no severe adverse effects. Hence, lorlatinib may be useful for patients experiencing alectinib-induced hepatotoxicity.

Introduction

In 2007, the *echinoderm microtubule-associated protein-like 4* (*EML4*)-*anaplastic lymphoma kinase* (*ALK*) fusion gene was proven to cause non-small-cell lung cancer (NSCLC) [1]. The *EML4-ALK* fusion gene is present in approximately 3–5% of NSCLC patients [2]. ALK tyrosine kinase gets automatically activated by multimerization with fusion partners, leading to cancers through the overactivation of cell proliferation signals. Hence, blocking the acti-

Go Makimoto
Department of Respiratory Medicine
National Hospital Organization Iwakuni Clinical Center
1-1-1 Atago-machi, Iwakuni, Yamaguchi 740-8510 (Japan)
s_wolfjp@yahoo.co.jp

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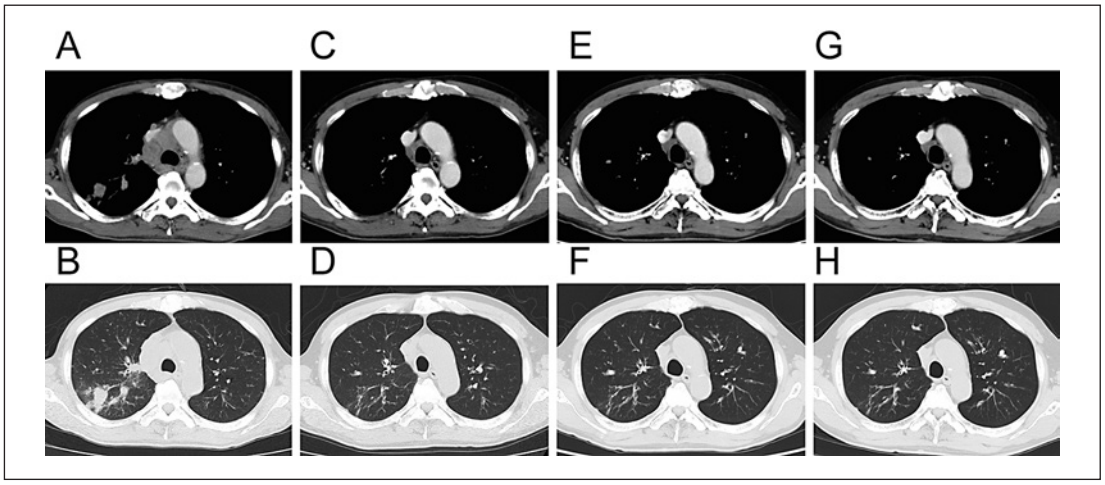

Fig. 1. Computed tomography images of the lung tumor immediately before the administration of alectinib (**A**, **B**), after initial alectinib-induced hepatotoxicity (**C**, **D**), after second-time alectinib-induced hepatotoxicity (**E**, **F**), and 4 months after the initiation of lorlatinib (**G**, **H**). The right upper primary lung tumors almost disappeared at 3 and 7 months after alectinib therapy and 4 months after lorlatinib therapy.

vation of ALK tyrosine kinase significantly inhibits cell proliferation in *ALK* fusion gene-positive cancer cells. To date, four ALK tyrosine kinase inhibitors (ALK-TKIs) have been approved: the first-generation ALK-TKI crizotinib, the second-generation ALK-TKIs alectinib and ceritinib, and the third-generation ALK-TKI lorlatinib. Notably, the second-generation ALK-TKI alectinib has shown a high objective response rate (93.5%) and a long progression-free survival rate in *ALK*-positive NSCLC patients (3-year progression-free survival in 62% of cases) [3]. Additionally, alectinib is associated with fewer severe adverse effects, such as diarrhea and nausea, compared to crizotinib [4]. Thus, alectinib is widely used as the first-line treatment in *ALK*-positive lung cancer patients.

Hepatotoxicity is one of the common adverse effects of ALK-TKIs, such as crizotinib or ceritinib [4, 5]. Alectinib exhibits a lower frequency of hepatotoxicity than crizotinib or ceritinib [6, 7], accounting for fewer reports of alectinib-induced severe liver damage [8]. Although several cases have been reported where crizotinib-induced hepatotoxicity was treated [9], there are no established strategies to overcome the hepatotoxicity of ALK-TKIs, especially alectinib.

The third-generation ALK-TKI lorlatinib was developed as a selective and brain-penetrating ALK inhibitor. In a phase 1 single-arm, first-in-human, dose-escalation study, lorlatinib demonstrated an objective response in 19/41 patients (46%; 95% confidence interval [CI] 31–63) who had received two or more ALK-TKIs [10]. A subsequent global phase 2 study was conducted to evaluate the efficacy of lorlatinib. During this trial, *ALK*-positive NSCLC patients were enrolled in different expansion cohorts. In the ALK-TKI treatment-naive patients (EXP1 group, $n = 30$), the objective response rate was 27/30 (90.0%; 95% CI 73.5–97.9) [11]. The other expansion cohorts consisting of patients resistant to other ALK-TKIs also demonstrated a favorable objective response rate (EXP2–5 group, resistant to other ALK-TKIs; the objective response rate was 93/198 [47.0%; 95% CI 39.9–54.2]). Therefore, lorlatinib was approved in 2018 for ALK-TKI-resistant or -intolerant *ALK*-positive NSCLC.

Herein, we report a rare case of a patient with *ALK*-positive adenocarcinoma who was successfully treated with lorlatinib after the development of alectinib-induced liver damage.

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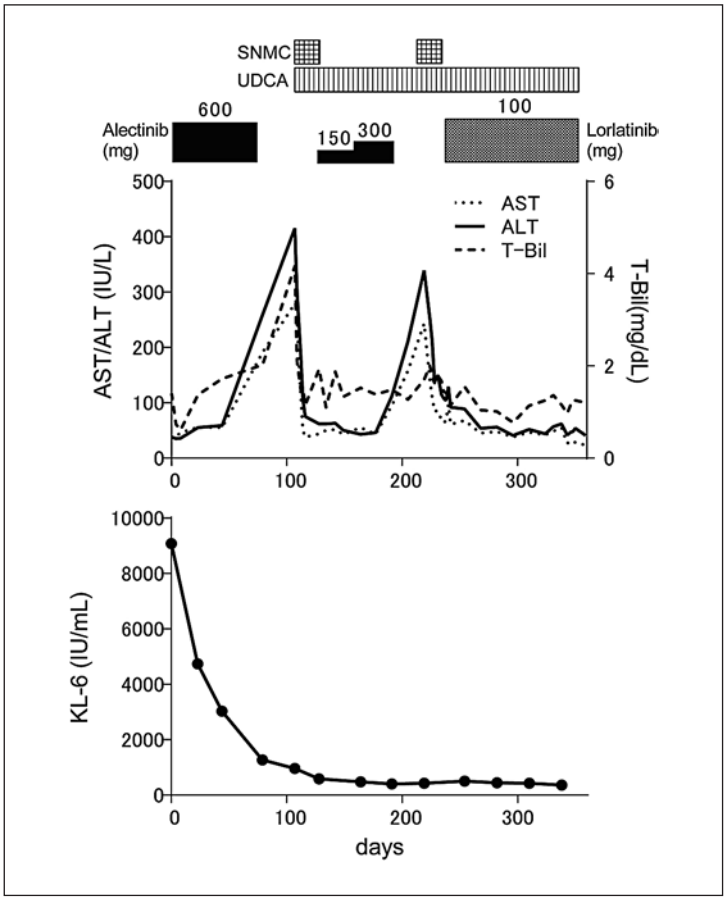

Fig. 2. Change in the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), and tumor markers over the clinical course of the disease. KL-6, Krebs von den Lungen-6; SNMC, glycyrrhizin; UDCA, ursodeoxycholic acid.

Case Report

A 57-year-old man was referred to our hospital because of multiple lung tumors and cervical lymph node swelling and was diagnosed with advanced lung adenocarcinoma (cT1bN3M1c stage IVB) (Fig. 1A, B). Although he was an ex-smoker with 23 pack-years, the tumor was ALK-positive on immunohistochemistry. Moreover, we submitted fresh frozen tissue specimens to the Cancer Genome Screening Project for Individualized Medicine in Japan (SCRUM-JAPAN), following which an *EML4-ALK* fusion was detected using the Oncomine® Comprehensive Assay (version 3). Alectinib (600 mg/day) was then administered as first-line therapy. After the initiation of alectinib, the tumor and lymph node swelling decreased rapidly (Fig. 1C, D). However, on day 79 of treatment, the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased to grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Alectinib was discontinued, but the levels of serum AST and ALT remained elevated. Consequently, he was readmitted to our hospital for treatment of alectinib-induced hepatotoxicity on day 107. Abdominal computed tomography and ultrasonography revealed no significant abnormality of the liver. Hepatitis A, B, and C were also excluded. Antibodies (IgM) to cytomegalovirus and Epstein-Barr virus were also negative. The pattern of liver injury suggested that it was a cholestatic-type injury, according to both the Digestive Disease Week Japan 2004 scale and the *R* value [12, 13]. Therefore, it was determined that the patient had alectinib-induced hepatotoxicity. He was treated with oral ursodeoxycholic acid (UDCA) 600 mg/day and intravenous glycyr-

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rhizin (SNMC). The hepatotoxicity gradually improved to grade 1 (Fig. 2). We then tried to rechallenge the patient with alectinib at a reduced dose of 150 mg/day on day 128. After 3 weeks, the dose was increased to 300 mg/day without severe hepatotoxicity and tumor progression (Fig. 1E, F). However, on day 191, the serum AST and ALT levels increased to CTCAE grade 2 again, necessitating the discontinuation of alectinib treatment. On day 219, the serum AST/ALT level further increased to CTCAE grade 3; therefore, the patient was readmitted for treatment with intravenous SNMC. Subsequently, the hepatotoxicity gradually improved to grade 1. Since alectinib was considered intolerable because of hepatotoxicity, we switched to lorlatinib treatment on day 235. Thereafter, the serum AST/ALT level did not increase to grade 2 or more, and the tumor continued to respond to lorlatinib for over 4 months without any severe adverse effects (Fig. 1G, H, 2).

Discussion

We successfully treated our patient with lorlatinib after development of alectinib-induced liver damage. Among the ALK-TKIs, alectinib is recommended as the first-line treatment for *ALK*-positive NSCLC because of its safety and efficacy in the first-line setting [4, 5]. Although drug-induced hepatotoxicity is more common with crizotinib or ceritinib than alectinib [6, 7], approximately 1–5% of patients experience alectinib-induced liver damage [4]. Nevertheless, there have been no previous reports describing a protocol to overcome alectinib-induced liver damage.

Regarding overcoming ALK-TKI-induced hepatotoxicity, several cases have been reported, especially for crizotinib [9, 14]. In one such report, the majority of the liver damage was of the hepatocellular type, and crizotinib was successfully resumed later at a lower dose (100 mg/day) [14]. However, in the present case, the liver damage pattern was cholestatic type according to both the Digestive Disease Week Japan 2004 scale and the *R* value, and rechallenge with a lower dose of alectinib (a quarter of the full dose) was unsuccessful. Therefore, we sought a better method to overcome liver damage.

Lorlatinib, which is a third-generation ALK-TKI, is effective for treating *ALK*-positive NSCLC in both ALK-TKI treatment-naive and ALK-TKI-pretreated patients [11]. Its pharmacokinetic property is different from that of other ALK-TKIs as it is metabolized mainly by CYP3A4 and UDP-glucuronosyltransferase (UGT1A4), whereas crizotinib, ceritinib, and alectinib are predominantly metabolized by the cytochrome P450 (CYP450) pathway [15]. In addition, lorlatinib-induced hepatotoxicity is relatively rare compared to that induced by crizotinib or ceritinib (grade 3 or higher serum AST/ALT elevation; lorlatinib, crizotinib, ceritinib: –1%, 11–15%, and 17–31%, respectively) [4, 5, 11]. Consequently, we switched to lorlatinib and successfully continued the treatment.

In conclusion, we have described a case in whom alectinib-induced hepatotoxicity was treated successfully with lorlatinib. Although there are no established protocols to overcome ALK-TKI-related liver damage, ALK-TKIs can achieve better clinical outcomes compared with conventional cytotoxic chemotherapy. Therefore, a more data-driven approach for appropriate protocols to manage molecular targeted drug-induced hepatotoxicity is needed for patients suffering from drug-induced adverse effects.

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Statement of Ethics

This case report was prepared and completed following the guidelines reported in the revised Helsinki Declaration of 2013. Written informed consent was obtained from the patient for the publication of the case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors contributed to the treatment of the patient.

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