CASE REPORT

Successful Desensitization with Crizotinib after Crizotinib-induced Liver Injury in ROS1-rearranged Lung Adenocarcinoma

Takayo Ota, Noriyuki Masuda, Kaoru Matsui, Takao Yamada, Noriko Tanaka, Shunsuke Fujimoto and Masahiro Fukuoka

Abstract:
Crizotinib has been approved for patients with advanced lung adenocarcinoma harboring rearrangements of the c-ROS-1 (ROS1) and anaplastic lymphoma kinase (ALK) genes. We report a patient with ROS1-rearranged lung adenocarcinoma who developed a crizotinib-induced mixed/cholestatic type of liver injury. The patient discontinued crizotinib after 34 days due to liver toxicity. Twenty-four days later, when transaminases and C reactive protein (CRP) were normalized, crizotinib was resumed using an oral desensitization method. The patient was successfully treated for manageable recurrence of liver injury and has been able to continue the treatment.

Key words: c-ROS oncogene 1, crizotinib, liver injury, desensitization

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Introduction

ROS1 is a receptor tyrosine kinase encoded by the c-ros-1 proto-oncogene identified in 1986 (1). ROS1 rearrangements were discovered in non-small cell lung cancer (NSCLC) through a phospho-tyrosine screen that analyzed tyrosine kinase signaling in cell lines and tumor samples (2). Rearrangement of the ROS1 gene results in a constitutively active kinase domain, which drives oncogenesis (3). ROS1 rearrangements have a prevalence of 1%-2% among NSCLC cases (3).

Crizotinib is a small-molecule tyrosine kinase inhibitor (TKI) that was initially designed as an inhibitor of c-Met (4). Crizotinib also inhibits ALK and ROS1 kinases. In ROS1-rearranged advanced NSCLC, crizotinib has shown significant antitumor effects (5) and has been approved for treatment since March 2016 in the United States and May 2017 in Japan.

We herein report the first case of a mixed/cholestatic type of liver injury caused by crizotinib in ROS1-rearranged lung adenocarcinoma. Slow oral desensitization to crizotinib has been effective for treatment with manageable recurrence of liver toxicity.

Case Report

In November 2017, a 66-year-old woman was referred to our hospital to evaluate a mass in the right lower lobe of her lung. Her personal history indicated a 45-pack-year smoking history but no history of alcohol intake. She presented with complaints of cough for two months. Chest computed tomography (CT) revealed a mass (52 mm×84 mm) in the right-lung lower lobe with thickened bronchovascular bundles, a second mass (16 mm×10 mm) in the inferior lingular segment of the left lung, and multiple enlarged lymph nodes (Fig. 1). No abnormalities were found in the bile ducts. A bronchial biopsy from the mass in the right lower lobe showed adenocarcinoma. The cancer stage was determined to be cT4N3M1a, cStage IV. Molecular testing of the biopsied tissue was negative for epidermal growth factor receptor (EGFR) mutations and ALK gene rearrangements. The tu-
Figure 1. Computed tomography (CT) shows (A-D) when lung cancer was diagnosed and (E-I) when liver injury was diagnosed. Chest CT shows (A) a mass in the right lower lobe (black arrow) and a second mass in the inferior lingual segment of the left lung (black arrowhead), (B) thickened bronchovascular bundles (white arrow), and (C, D) multiple lymph node metastases (white arrowheads); (E) the mass (black arrow) and second mass were smaller, (F) bronchovascular bundles were improved (white arrow), and (G, H) lymph node metastases were smaller; (I) abdominal CT shows no mass in the liver. (A, B, E, F) Images obtained with lung-window settings. (C, D, G, H, I) Images obtained with mediastinal-window settings.

As a first-line therapy, the patient was administered cisplatin (75 mg/m²) on day 1 and pemetrexed (500 mg/m²) on day 1 for a 3-week cycle. After 3 cycles, a partial response was observed. Blood tests revealed increased levels of eosinophils (390.5/μL, 7.1%) and slightly increased levels of serum aminotransferases and alkaline phosphatase (ALP) showed grade 1 toxicity levels but normal total bilirubin. Glutathione 300 mg/day was added to her regimen. The next day, she presented to the emergency department with complaints of a high fever and general fatigue, and three days later, on day 35 of crizotinib administration, she was hospitalized due to a continuous high fever. Blood tests revealed increased levels of eosinophils (390.5/μL, 7.1%) and slightly increased levels of serum aminotransferases, whereas CRP increased to 10.54 mg/dL, and ALP showed grade 2 toxicity levels (Table 1; Fig. 2). Abdominal CT and ultrasonography revealed fatty liver. Hepatitis A and C were excluded. Re-test for HBV-DNA was negative. Antibodies to cytomegalovirus and Epstein-Barr virus were also negative. The pattern of liver injury was diagnosed as a cholestatic and mixed type of liver injury by the Digestive Disease Week Japan 2004 (DDW-J 2004) scale (6) or a cholestatic type by R-value (7). Crizotinib was discontinued. Although crizotinib was discontinued, ALP was still increased. Ursodeoxycholic acid was doubled to 600 mg/day. The patient’s symptoms gradually resolved. A drug-induced lymphocyte stimulation test.

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A 79-year-old man was diagnosed with advanced ROS1-rearranged NSCLC. After treatment with crizotinib, the patient experienced liver toxicity with manageable recurrence of crizotinib-induced liver toxicity. To assess the liver toxicity recurrence, we confirmed the preceding liver toxicity and (ii) rechallenge of crizotinib induced similar toxicity.

A liver biopsy was performed, and we found that the serum was weakly positive for anti-nuclear antibody (1:40) and negative for anti-smooth muscle antibody. Given that (i) dechallenge of crizotinib improved liver toxicity and (ii) rechallenge of crizotinib induced similar liver toxicity recurrence, we confirmed the preceding liver toxicity to have been due to crizotinib.

In December 2018, the patient had stable disease with manageable recurrence of crizotinib-induced liver toxicity.

Liver toxicity, particularly hepatocellular but not cholestatic, is one of the most common side effects of crizotinib. In phase III trials of advanced ALK-rearranged NSCLC, any grade of liver enzyme elevation was observed in 36%-38% of patients, including grades 3-4 in 14%-16% (8, 9). In a phase 1 trial of crizotinib, which included an expansion cohort of patients with advanced ROS1-rearranged NSCLC, grades 1-3 liver enzyme elevation occurred in 14%-22% of patients within 28 days (5).

Thus far, 10 cases of crizotinib-induced liver toxicity have been reported since 2013, including the present case (10-17). In all except ours, the cases were hepatocellular-type liver toxicity in eight ALK-rearranged and one ROS1-rearranged NSCLC. Four cases were fulminating hepatitis, including three fatal cases. Crizotinib was initially administered at doses between 200 and 500 mg/day. The onset of liver enzyme abnormalities ranges from 10 to 301%.

Two weeks later, serum transaminases and CRP were normalized, the patient resumed crizotinib. The dose was started at 100 mg/day and gradually increased to 400 mg/day (200 mg twice daily; Fig. 2). During the administration of 300 mg/day, 200 mg crizotinib was given daily, and another 200 mg was given every other day. When the dose was increased to 300 or 400 mg/day, we noticed a slight ALT increase. While this report was being written, we found that the serum was weakly positive for anti-nuclear antibody (1:40) and negative for anti-smooth muscle antibody. Given that (i) dechallenge of crizotinib improved liver toxicity and (ii) rechallenge of crizotinib induced similar liver toxicity recurrence, we confirmed the preceding liver toxicity to have been due to crizotinib.

In December 2018, eight months after starting the re-administration of crizotinib, the patient had stable disease with manageable recurrence of crizotinib-induced liver toxicity.

### Table 1. Laboratory Findings on Admission.

| Complete Blood Count | Biochemistry |
|----------------------|--------------|
| White Blood Cells    | Total Bilirubin 0.67 mg/dL |
| Neutrophil           | Direct Bilirubin 0.29 mg/dL |
| Lymph                | Total Protein 6.3 g/dL |
| Mono                 | Albumin 2.9 g/dL |
| Eosin                | AST 61 U/L |
| Mono                 | ALT 123 U/L |
| Red Blood Cells      | LDH 330 U/L |
| Hemoglobin           | ALP 786 U/L |
| Hematocrit           | γ-GTP 391 U/L |
| MCV                  | CPK 82 U/L |
| MCH                  | Creatinine 1.22 mg/dL |
| MCHC                 | Na 133 mEq/L |
| RDW                   | K 3.7 mEq/L |

Coagulation (3 days before admission):
- PT 101.3 %
- PT-INR 0.99
- APTT 22.6 sec

Serologic tests:
- CRP 10.54 mg/dL
- Anti-nuclear antibody: 1:40 (Homogeneous/Speckled type)
- Anti-Sm antibody: negative
- IgG 1.275 mg/dL
- IgM 370 mg/dL
- IgA 80 mg/dL

**Discussion**

Liver toxicity, particularly hepatocellular but not cholestatic, is one of the most common side effects of crizotinib.
70 days (median 29.5 days) following initial crizotinib administration and is unrelated to clinical symptoms. The median duration to the onset of liver enzyme abnormalities for the 3 fatal cases was 17 days (Supplementary Table 1). From these findings, we can conclude that (i) most crizotinib-induced liver toxicity is hepatocellular type, (ii) crizotinib-induced liver toxicity is not associated with the initial prescribed dose, and (iii) the onset of liver enzyme abnormalities is shorter for fatal cases than for total cases. Crizotinib-induced transaminase abnormalities generally occur within the first two months of treatment. Therefore, performing liver function tests every two weeks during the first two months is recommended (18). Considering the potential early onset of hepatotoxicity, more frequent observation might be needed in order to prevent fatal outcomes.

The mechanism underlying crizotinib-induced liver toxicity is unknown. Drug-induced liver injury (DILI) is largely classified into two categories: intrinsic or idiosyncratic (7). Intrinsic injuries are dose-dependent and predictable and are caused by direct toxicity to the liver at high doses. Idiosyncratic injuries are not dose-dependent and not predictable and have a variable latency period often mediated by the adaptive immune response (19, 20). Immune-related DILI demonstrates classical features of allergic reactions, such as a fever, rash, and eosinophilia. Drug or drug metabolites bind to cellular proteins and are presented as antigens to the major histocompatibility complex (MHC), which triggers the adaptive immune response. In the present case, the patient presented with a fever and increased eosinophils, indicating that crizotinib-induced liver injury is immune-related, as suggested in other reported cases.

The risk factors that predispose patients to develop DILI include genetic, host-related, and environmental factors, but there is little evidence to validate these risk factors for each drug (7, 20). One study reported that risk factors associated with crizotinib-induced liver injury are (i) the presence of liver disease or HBV carriers or (ii) the concurrent use of an H2-antagonist or H2-antagonist/proton pump inhibitors (PPIs; 21). Crizotinib is metabolized largely via cytochrome P450 (CYP) 3A4 (18) and may have drug interactions with CYP3A4 inhibitors or inducers. In the present case, the patient’s HBV serology status showed resolved HBV infection. The patient was administered neither H2 antagonists/PPIs nor CYP3A4-related drugs. We therefore cannot conclude the definite risk factors for the present case.

Desensitization methods are used to restart small-molecule kinase therapies (22-24). There are two methods of desensitization: slow and rapid. While rapid procedures have the advantage of reaching optimal drug concentrations in a shorter period, slow procedures are safer with higher success rates (25). Crizotinib desensitization was reported previously, in both rapid and slow protocols (15, 22, 23). In the reported liver toxicity cases with crizotinib, six cases, including our own, were rechallenged (Table 2). However, only two cases that began with ≤100 mg successfully achieved desensitization (15 and present case). There are no defined protocols for crizotinib desensitization. These previous findings suggest that it may be safe to achieve a targeted dose of crizotinib if dosing begins with ≤100 mg of crizotinib.

In conclusion, we encountered a case of liver toxicity induced by crizotinib in ROS1-rearranged lung adenocarci-
The authors state that they have no Conflict of Interest (COI).

**Consent**

The patient provided her written informed consent for the publication of this case report and any accompanying images. A copy of the consent form has been made available for review by the Editor-in-Chief of this journal.

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**References**

1. Matsushima H, Wang LH, Shibuya M. Human c-ros-1 gene homologous to the v-ros sequence of UR2 sarcoma virus encodes for a transmembrane receptor like molecule. Mol Cell Biol 6: 3000-3004, 1986.
2. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 131: 1190-1203, 2007.
3. Davies KD, Doebele RC. Molecular pathways: ROS1 fusion proteins in cancer. Clin Cancer Res 19: 4040-4045, 2013.
4. Zou HY, Li Q, Lee JH, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res 67: 4408-4417, 2007.
5. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371: 1963-1971, 2014.
6. Watanabe M, Shibuya A. Validity study of a new diagnostic scale for drug-induced liver injury in Japan-comparison with two previous scales. Hepatol Res 30: 148-154, 2004.
7. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 109: 950-966, 2014.
8. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368: 2385-2394, 2013.
9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371: 2167-2177, 2014.
10. Ripault MP, Pinzani V, Fayolle V, Pageaux GP, Larrey D. Crizotinib-induced acute hepatitis: first case with relapse after reintroduction with reduced dose. Clin Res Hepatol Gastroenterol 37: e21-e23, 2013.
11. Sato Y, Fujimoto D, Shibata Y, et al. Fulminant hepatitis following crizotinib administration for ALK-positive non-small-cell lung carcinoma. Jpn J Clin Oncol 44: 872-875, 2014.
12. Tsukita Y, Fukuhara T, Kobayashi M, et al. Alternate-day Treatment with Crizotinib for Drug-induced Esophagitis and Liver Damage in a Patient with EML4-ALK Fusion Gene-positive Lung Adenocarcinoma. Intern Med 54: 3185-3188, 2015.
13. Sassier M, Mennecker B, Gschwend A, et al. Successful treatment with ceritinib after crizotinib induced hepatitis. Lung Cancer 95: 15-16, 2016.
14. van Geel RM, Hendriks IJ, Vahl JE, et al. Crizotinib-induced fatal fulminant liver failure. Lung Cancer 93: 17-19, 2016.
15. Yasuda Y, Nishikawa Y, Sakamori Y, et al. Successful oral desensitization with crizotinib after crizotinib-induced hepatitis in an anaplastic lymphoma kinase-rearranged non-small-cell lung cancer patient: A case report. Mol Clin Oncol 7: 295-297, 2017.
16. Adhikari N, Kumar P, Venkatesulu BP, et al. Crizotinib-Induced Fulminant Hepatic Failure: A Rare Adverse Event. J Glob Oncol 4: 1-4, 2018.
17. Charville GW, Padda SK, Sibley RK, Puthillath A, Kwo PY. Resolution of Crizotinib-Associated Fulminant Hepatitis following Cessation of Treatment. Case Reports Hepatol 2018: 3413592, 2018.
18. FDA. Prescribing information Xalkori® crizotinib, 2013.
19. Yuan L, Kaplowitz N. Mechanisms of drug-induced liver injury. Clin Liver Dis 17: 507-518, 2013.
20. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 89: 95-106, 2014.
21. Jung D, Han JM, Yee J, Kim JY, Gwak HS. Factors affecting crizotinib-induced hepatotoxicity in non-small cell lung cancer patients. Med Oncol 35: 154, 2018.
22. Awad MM, Lax TP, Slawski BR, Shaw AT. Successful desensitization of two patients with ALK-positive lung cancer and hypersensitivity to crizotinib. J Thorac Oncol 9: 1726-1728, 2014.
23. Sánchez-López J, Viñoñes N, Muñoz-Caneco R, et al. Successful Oral Desensitization in a Patient With Hypersensitivity Reaction to Crizotinib. J Investig Allergol Clin Immunol 25: 307-308, 2015.
24. Shirasawa M, Kubota M, Harada S, et al. Successful oral desensitization against skin rash induced by alectinib in a patient with anaplastic lymphoma kinase-positive lung adenocarcinoma: A case report. Lung Cancer 99: 66-68, 2016.
25. Scherer K, Brockow K, Aberer W, et al. Desensitization in delayed drug hypersensitivity reactions -- an EAACI position paper of the Drug Allergy Interest Group. Allergy 68: 844-852, 2013.

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