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【 CASE REPORT 】

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

Takayo Ota[1], Noriyuki Masuda[1], Kaoru Matsui[1], Takao Yamada[2], Noriko Tanaka[3], Shunsuke Fujimoto[2] and Masahiro Fukuoka[1]

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

c-ROS-1 (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 anaplastic lymphoma kinase (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-

[1]Department of Medical Oncology, Izumi City General Hospital, Japan, [2]Department of Gastroenterology, Izumi City General Hospital, Japan and [3]Department of Radiology, Izumi City General Hospital, Japan
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Correspondence to Dr. Takayo Ota, takayo.ota@gmail.com

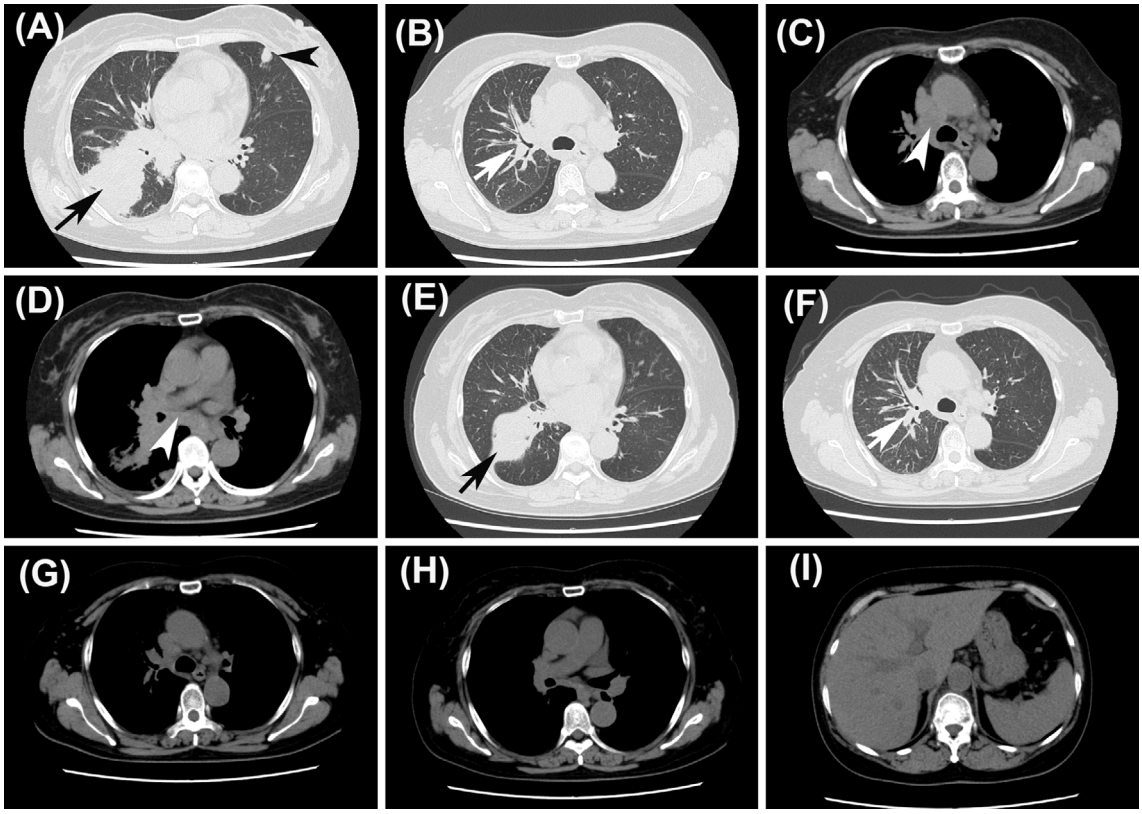

Figure 1. **Computed tomography (CT) shows (A-D) when lung cancer was diagnosed and (E-I) when liver injury was diagnosed. Chest CT shows (A) a mass in the right lower lobe (black arrow) and a second mass in the inferior lingular segment of the left lung (black arrowhead), (B) thickened bronchovascular 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.**

mor proportion score of programmed death ligand 1 (PD-L 1) expression in the tissue was 0%. Baseline liver and renal function tests were within normal limits. Prior to starting chemotherapy, hepatitis viral screening revealed that hepatitis B (HB) surface antigen (HBsAg) and HB e antigen (HBeAg) were negative and that HB surface (anti-HBs), total HB core (anti-HBc), and HB e (anti-HBe) antibodies were positive. HBV- DNA was not detected by polymerase chain reaction (PCR).

As a first-line therapy, the patient was administered cisplatin (75 mg/m^2) on day 1 and pemetrexed (500 mg/m^2) on day 1 for a 3-week cycle. After 3 cycles, a partial response was observed, but serum creatinine levels had increased to 1.0 mg/dL and the estimated glomerular filtration rate (eGFR) was 43 mL/min. Additional molecular testing of the biopsied tissue showed ROS1 rearrangements. As a second-line therapy, from March 2018, crizotinib was started at 250 mg twice daily. After 23 days, blood tests showed a slight increase in alanine aminotransferase (ALT). Ursodeoxycholic acid 300 mg/day was administered. Seven days later, she presented with loss of taste. Blood tests showed that, in addition to an increase in C-reactive protein (CRP) to 7.34 mg/dL, liver function tests worsened: 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 and 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

Table 1. Laboratory Findings on Admission.

Complete blood count		Biochemistry	
White blood cells	55×10^2 /μL	Total bilirubin	0.67 mg/dL
Neutrophil	72.4 %	Direct bilirubin	0.29 mg/dL
Lymph	10.6 %	Total protein	6.3 g/dL
Mono	9.6 %	Albumin	2.9 g/dL
Eosino	7.1 %	AST	61 U/L
Baso	0.30 %	ALT	123 U/L
Red blood cells	280×10^4 /μL	LDH	330 U/L
Hemoglobin	9.1 g/dL	ALP	786 U/L
Hematocrit	27.3 %	γ-GTP	391 U/L
MCV	97.7 fL	CPK	82 U/L
MCH	32.5 pg	BUN	17.2 mg/dL
MCHC	33.2 %	Creatinine	1.22 mg/dL
RDW	14.2	Na	133 mEq/L
Platelet	29.9×10^4 /μL	K	3.7 mEq/L
		Cl	95 mEq/L
Coagulation (3 days before admission)			
PT	101.3 %		
PT-INR	0.99		
APTT	22.6 s		
Serologic test			
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		

Serologic tests except CRP and hepatitis virus test were not measured on admission.
MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, PT: prothrombin time, PT-INR: prothrombin time-intenational normalized ratio, APTT: activated partial thrombin time, CRP: C-reative protein, IgG: immunogloblin G, IgM: immunogloulin M, IgA: immunogloulin A, AST: asparate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, CPK: creatine kinase, BUN: blood urea nitrogen

resolved. A drug-induced lymphocyte stimulation test (DLST) of crizotinib was positive (stimulation index: 301%).

Twenty-four days later, when 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.

Discussion

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 fulmi-

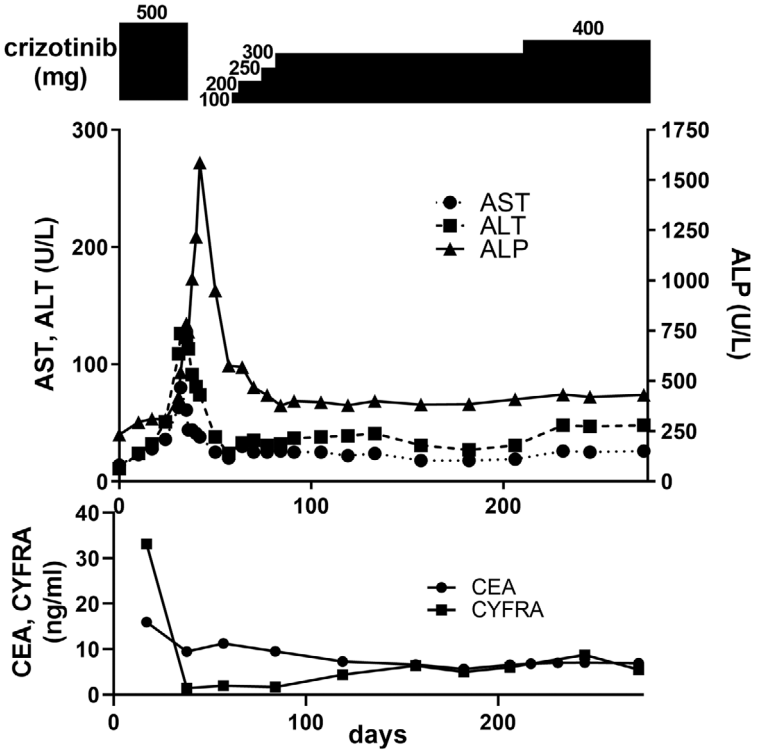

Figure 2. **Clinical course of the patient treated with crizotinib.**

nant 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 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 Material). 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

Table 2. Clinical Findings in Patients with Crizotinib Induced Liver Injury, Rechallenged Cases.

Reference	Age	Sex	Rechallenge crizotinib	
			Interval (after stopped)	Dose
Successful cases				
(15)	51	female	NA	50 mg/day → 250 mg/day
Current case	66	female	24 days	100 mg/day → 200mg×2/day
Failed cases				
(10)	69	female	29 days	250 mg/day
(12)	44	female	7 months	200 mg/day alternate day → 250 mg×2/day
(13)	30	male	4 months	200 mg/day alternate day
(13)	62	female	20 days	200 mg/day

NA: not assessed

crizotinib.

In conclusion, we encountered a case of liver toxicity induced by crizotinib in ROS1-rearranged lung adenocarcinoma. The patient was able to continue crizotinib following desensitization.

The authors state that they have no Conflict of Interest (COI).

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