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CASE REPORT

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An 83-year-old patient with RET fusion-positive non-small cell lung cancer experiencing severe hepatic disorder due to selpercatinib administration

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Abstract

An 83-year-old woman with RET fusion-positive advanced lung adenocarcinoma was administered selpercatinib 320 mg/day. Despite the shrinking of the tumour, fever, fatigue, and anorexia developed on day 17. Selpercatinib administration was interrupted. On day 21, elevated blood aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed. On day 28, AST and ALT levels increased to demonstrate Grade 4 in CTCAE Ver.5. The patient received a glycyrrhizin-compounding agent and steroid treatment, and AST and ALT levels gradually decreased. On day 63, selpercatinib 160 mg/day was restarted after improvement of the hepatic disorder. Since then, selpercatinib was continued without any severe adverse events. Selpercatinib is a reasonable treatment option for RET fusion-positive advanced non-small cell lung cancer even in older patients. However, old age may be a risk factor for adverse events including hepatic disorders. For safe treatment in such patients, careful follow-up is required.

KEYWORDS
hepatic disorder, lung cancer, old patient, RET fusion, Selpercatinib

INTRODUCTION

The prognosis of patients with advanced non-small-cell lung cancer (NSCLC) is poor. However, tyrosine kinase inhibitors are reportedly effective against NSCLC that harbours driver mutations, such as epidermal growth factor receptor gene mutations.[1]

RET fusion is an oncogenic driver in 1.9% of Japanese adenocarcinoma patients.[2] Drilon et al. reported the efficacy of selpercatinib for RET fusion-positive NSCLC.[3] In Japanese guidelines, selpercatinib is recommended as the first-line of treatment for such patients.[4] In Drilon's report on selpercatinib, the median age in the previous platinum chemotherapy group ($n = 105$) was 61 years (range: 23–81) and that in the previously untreated group ($n = 39$) was 61 years (range: 23–86).[3] This report included only a few 80-year old patients. Hence, the efficacy and safety of selpercatinib in older patients remain unclear.

Here, we report a case of an old female patient with RET fusion-positive NSCLC who experienced severe hepatic disorder caused by selpercatinib.

CASE REPORT

An 83-year-old Japanese woman without a history of smoking was referred to our hospital for evaluation and control of right pleural effusion observed on chest radiography (Figure 1A). Her condition was independent of her daily lifestyle activities. She had hypertension and hyperlipidemia as comorbidities. Computed tomography of the chest showed a tumour in the right lower lung lobe, enlarged mediastinal lymph nodes, and right pleural effusion. She was diagnosed with Stage IVA (clinical T3N2M1a) lung adenocarcinoma based on pleural effusion cytology. Liver

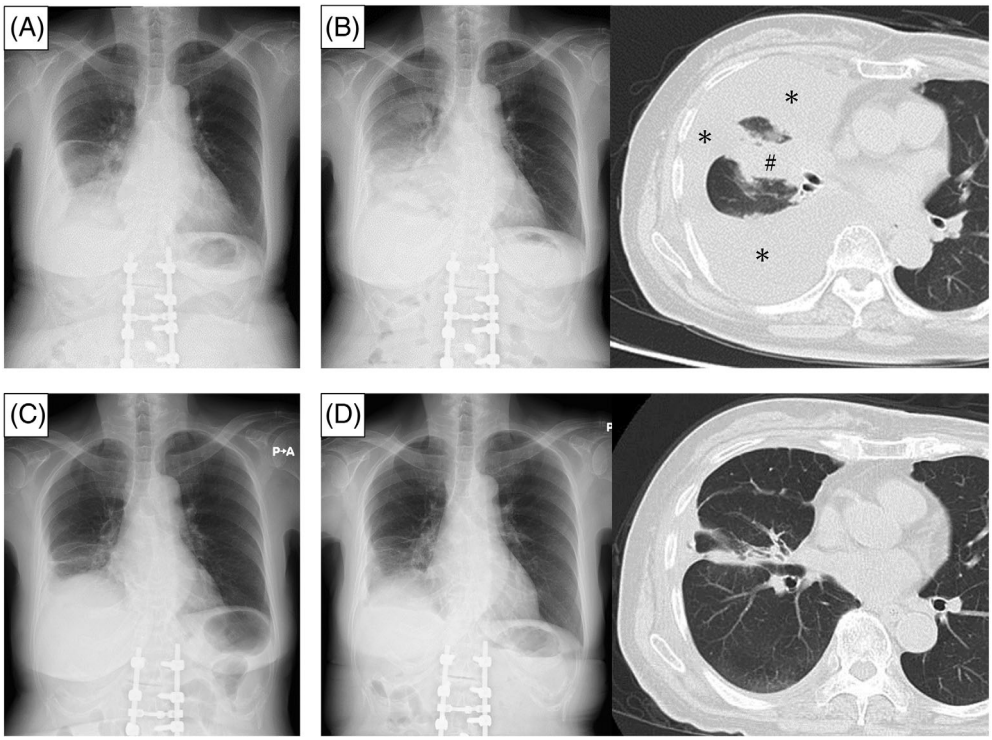

FIGURE 1 Image findings. (A) At the initial visit. (B) At the start of selpercatinib administration. Pleural effusion remained despite conducting pleurosclerosis (*). The primary tumour in in the right lobe (#). (C) At the appearance of liver hepatic disorder. D: At the latest follow-up

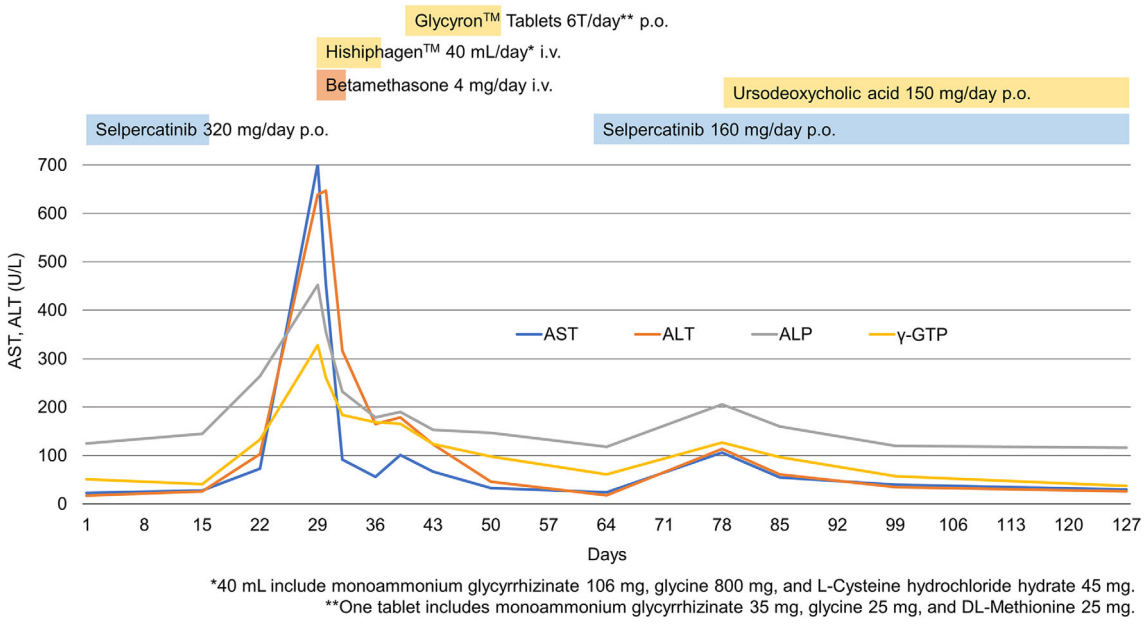

FIGURE 2 Transition of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels over time (in days).i.v., intravenous; p.o., post-orally

metastasis was not observed. There were no cases of hepatitis B or C viral infection.

Thoracic drainage and pleurosclerosis were performed. Simultaneously, the driver mutation of cancer was tested using a pleural effusion cell block, and RET fusion was detected using the Oncomine Dx Target Test Multi-CDx System. The patient was administered selpercatinib 320 mg/day (Figure 1B). At this point, her blood aspartate aminotransferase (AST: Upper limit of normal, 30 U/L) was 23 U/L, alanine aminotransferase (ALT: Upper limit of normal, 23 U/L) was 17 U/L, alkaline phosphatase (ALP: Upper limit of normal, 113 U/L) was 125 U/L, and γ-glutamyl transpeptidase

(γ-GTP: upper limit of normal, 32 U/L) was 51. Her Eastern Cooperative Oncology Group performance status was 1. Fever, fatigue, and anorexia were observed on day 17. She discontinued selpercatinib based on her judgement.

On day 21, although the tumour shrank (Figure 1C), the AST, ALT, ALP, and γ-GTP levels were elevated to 73, 103, 264, and 133 U/L, respectively. However, on day 29, AST, ALT, ALP, and γ-GTP levels increased to 702, 639, 453, and 328 U/L, respectively. The AST and ALT elevations were equal to grade 4 (Common Terminology Criteria for Adverse Events: CTCAE Ver.5)[5] (Figure 2). Serum bilirubin levels did not increase. Fatigue and anorexia worsened to Grade 3. Grade 1 elevated blood creatinine levels, mild rash on her trunk, and pruritus were also observed. At this point, her performance status was 3, and she was hospitalized in an emergency. Abdominal ultrasonography and computed tomography showed no organic abnormalities. No new drug was started, except for selpercatinib. Consequently, the patient was diagnosed with selpercatinib-induced liver disorder.

Therefore, selpercatinib administration was interrupted. She was administered glycyrrhizin as a compounding agent. In addition, steroid (betamethasone 4 mg/day) was administered for 3 days. The AST and ALT levels gradually decreased. Other adverse events and performance statuses also improved. On day 45, the patient was discharged from the hospital (Figure 2).

On day 64, selpercatinib 160 mg/day was restarted after improvement of the hepatic disorder. The AST and ALT levels again increased to grade 2 on day 78, and ursodeoxycholic acid treatment was started. The values resolved without interruption of selpercatinib. Since then, selpercatinib was continued without any severe adverse events. At the latest follow-up, 7 months after commencing selpercatinib treatment, there was no evidence of progression of hepatic disorder or any remarkable toxicity (Figure 1D).

DISCUSSION

Herein, we successfully administered selpercatinib treatment to an older female patient, although she experienced AST and ALT elevation to Grade 4. AST and ALT elevations of any grade are common (26%–30%) adverse events. However, grade 4 is rare (1%–2%).[3] Furthermore, a report describing cases in which severe hepatic disorder occurred due to selpercatinib is lacking. This case study is thus significant as it reports on an older patient receiving selpercatinib treatment and shows that severe AST and ALT elevation could be controlled.

The mechanism of liver disorders caused by selpercatinib is poorly understood. The clinical exacerbating factors are also unclear. In our case, marked ALT elevation suggested hepatocyte damage. In contrast, ALP and γ-GTP levels were slightly higher at baseline. In addition, when AST and ALT levels increased after restarting selpercatinib, ursodeoxycholic acid treatment, which has choleretic action, was effective. From the above courses, cholestasis associated with older age might be a risk factor for hepatic disorders caused by selpercatinib. Our patient experienced hypersensitivity reaction-like symptoms such as fever, rash, and pruritus. Allergic mechanism could be also associated with hepatic disorder. Therefore, steroid treatment might improve AST and ALT levels.

Although the AST and ALT levels were elevated to grade 4, they were fortunately improved by interruption of selpercatinib, administration of glycyrrhizin-compounding agent, and steroid therapy. We continued selpercatinib treatment after the dose reduction. However, attention must be paid to the occurrence of adverse events due to selpercatinib, especially in the first 1–2 months of the treatment. According to a previous report, dose reduction was warranted in 30% of patients, and 2% discontinued selpercatinib because of treatment-related adverse events.[3] Early drug interruption might be a good choice for older patients before severe adverse events occur.

Selpercatinib is a reasonable treatment option for RET-fusion-positive advanced non-small cell lung cancer, even in older patients. To conduct safe treatment for such patients, careful follow-up is required.

AUTHOR CONTRIBUTIONS

Kazuhisa Nakashima: Attending doctor; Writing-original draft preparation. **Yuki Mitarai, Seiko Tanaka, Mika Nakao, Takae Okuno, Tamio Okimoto, Ryo Tanabe, and Takashi Yanagawa**: Attending Doctors. **Yukari Tsubata**: Reviewing and Editing. **Takeshi Isobe**: Supervision.

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CONFLICT OF INTEREST STATEMENT

Kazuhisa Nakashima has received honoraria from Eli Lilly Japan K.K.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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