


Enteral lorlatinib after alectinib as a treatment option in anaplastic lymphoma kinase-positive non-small cell lung cancer with triple problems: carcinomatous meningitis, poor performance status, and dysphagia—a case report

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Keywords

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Abstract

Alectinib treatment is effective in patients with anaplastic lymphoma kinase (*ALK*) gene rearrangement-positive non-small cell lung cancer (NSCLC; hereafter *ALK*-positive NSCLC) who exhibit central nervous system (CNS) relapse and poor performance status (PS). Lorlatinib treatment is effective upon failure of other *ALK* inhibitor-based treatments. However, much remains unknown about the efficacy of lorlatinib in patients with *ALK*-positive NSCLC, who have triple problems, carcinomatous meningitis, poor PS, and dysphagia, after alectinib treatment. Here, we report the remarkable response of a 73-year-old patient with *ALK*-positive NSCLC showing carcinomatous meningitis due to CNS metastases, poor PS, and dysphagia to lorlatinib. Lorlatinib administration through a nasogastric tube alleviated complications related to consciousness within three days, and the patient survived for 16 months after CNS relapse. Lorlatinib could be a treatment option for patients with *ALK*-positive NSCLC showing carcinomatous meningitis, poor PS, and dysphagia upon failure of other *ALK* inhibitor-based treatments.

Introduction

Based on the appreciable efficacy and mild adverse events, alectinib is useful as the first-line chemotherapy for patients with anaplastic lymphoma kinase (*ALK*) gene rearrangement-positive non-small cell lung cancer (*ALK*-positive NSCLC) [1]. Lorlatinib or systemic chemotherapy is recommended as a second-line treatment for patients with symptomatic *ALK*-positive NSCLC exhibiting central nervous system (CNS) relapse upon failure of alectinib treatment. However, patients with *ALK*-positive NSCLC showing multiple CNS metastases often experience complications related to consciousness, such as carcinomatous meningitis and symptomatic epilepsy. Consciousness disorders and dysphagia restrict treatment options for patients with *ALK*-positive NSCLC because all *ALK*-tyrosine kinase inhibitors (*ALK* inhibitors) are oral drugs, and there is no indication of systemic chemotherapy for poor performance status (PS).

Here, we report a case where the following were highlighted: (1) lorlatinib may be helpful in consciousness disorders due to CNS metastases and carcinomatous meningitis; and (2) enteral administration could be considered for patients with *ALK*-positive NSCLC, for whom oral drug administration is not possible. We successfully treated a patient with *ALK*-positive NSCLC with triple problems—carcinomatous meningitis, poor PS, and dysphagia—using a simple suspension method for lorlatinib administration via a nasogastric tube [2]. The patient survived for 16 months after CNS relapse.

Case Report

A 71-year-old man was diagnosed with *ALK*-positive NSCLC and multiple liver and gastric metastases (cStage

IVB). A biopsy of liver metastasis revealed *ALK* gene rearrangements confirmed via fluorescent in situ hybridization (FISH). Initially, the patient ingested alectinib 300 mg twice a day orally. After approximately six months, the original lung tumour shrunk, and multiple liver metastases disappeared. The patient continued alectinib to maintain tumour regression. However, 26 months after the initiation of alectinib treatment, seizures and consciousness disorders occurred. Enhanced brain magnetic resonance imaging (MRI) revealed intracranial diffuse small metastases, left brainstem metastasis, and carcinomatous meningitis (Fig. 1A–C). The patient lost consciousness, showing a Glasgow Coma Scale of 3, PS of 4, and dysphagia. Primary site regrowth and metastases outside the CNS were not present, and then another cancer tissue biopsy was difficult. We treated status epilepticus for a week; however, the patient's consciousness did not improve. There were a few systemic chemotherapy indications. In addition, the patient's family did not desire any chemotherapy except for *ALK* inhibitor-based therapy. Therefore, we inserted a nasogastric tube and administered lorlatinib 100 mg/day using a simple suspension method (Fig. 2). Within three days, the patient's consciousness improved, showing a

Glasgow Coma Scale of 13. Four weeks after initiating lorlatinib, the patient could ingest lorlatinib. The brain MRI showed that the intracranial diffuse metastases and carcinomatous meningitis had disappeared (Fig. 1D–F). During the treatment course, a left brainstem haemorrhage occurred due to brain metastasis. However, after blood pressure management and rehabilitation, despite grade 2 CNS effects of lorlatinib, including slow speech, mentation, and word-finding difficulty, there was no hindrance to daily life. The patient's condition improved to a PS of 1. The patient was discharged home on foot. Although the patient continued lorlatinib for 15 months and maintained tumour regression, the patient gradually succumbed at home with palliative care. A pathological autopsy revealed the cause of death was respiratory failure due to cancer-associated thrombosis; however, the patient survived for 16 months after CNS relapse.

Discussion

Lorlatinib was effective in a 73-year-old patient with *ALK*-positive NSCLC, showing carcinomatous meningitis, poor PS, and dysphagia upon failure of alectinib treatment.

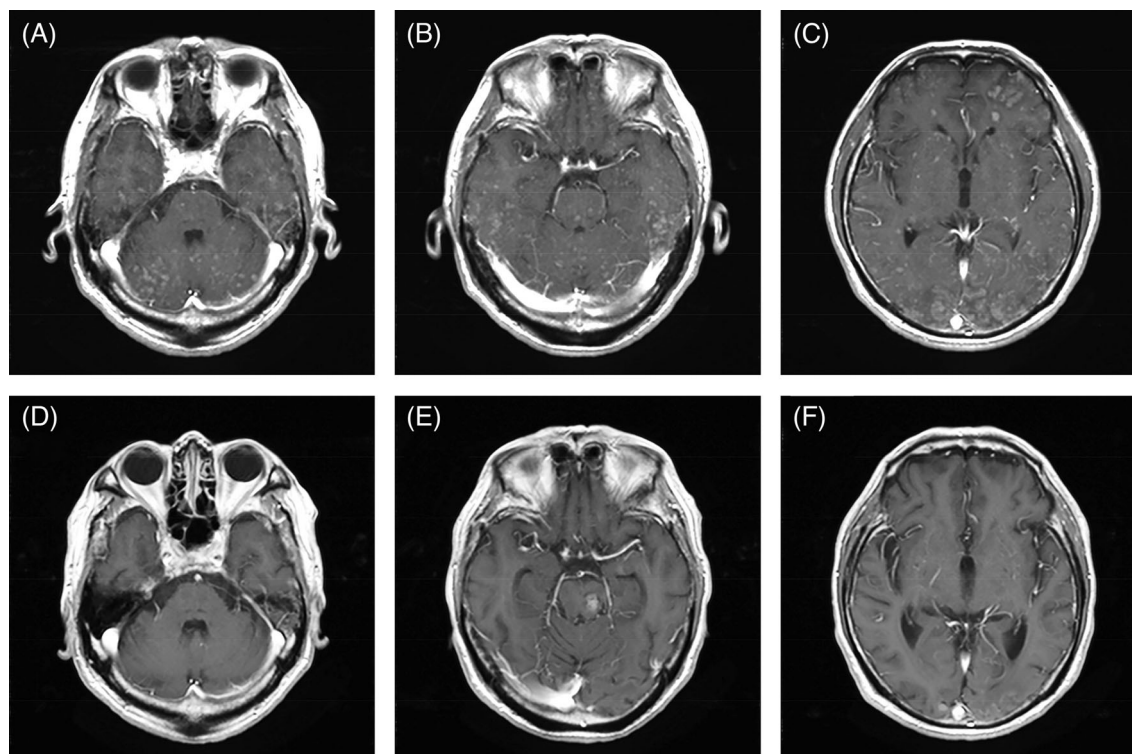


Figure 1. Enhanced brain magnetic resonance imaging (MRI). (A–C) Diffuse small brain metastasis and carcinomatous meningitis occurred 2.6 years after the initiation of 300 mg/day alectinib administration. (D–F) Brain metastasis regression occurred eight weeks after the initiation of lorlatinib treatment. Central nervous system relapse in the patient with anaplastic lymphoma kinase gene rearrangement-positive non-small cell lung cancer occurred after alectinib treatment failure. Left brainstem haemorrhage occurred seven days after lorlatinib initiation due to brain metastasis. However, after blood pressure management and rehabilitation, the patient was discharged home on foot.



Figure 2. Simple suspension method for lorlatinib administration using a nasogastric tube. We added lorlatinib and lukewarm water (approximately 55°C) into a polythene bag. We sealed the bag and dissolved the mixture well (A). We then injected the drug through a nasogastric tube and rinsed the tube with saline after injection (B).

Enteral ALK inhibitor administration may be a treatment strategy for patients with *ALK*-positive NSCLC, for whom the ingestion may pose a difficulty.

ALK-positive NSCLC accounts for approximately 4–5% of the NSCLC cases. Patients with *ALK*-positive NSCLC treated with ALK inhibitors show long-term survival compared with NSCLC patients without driver gene mutations. CNS metastasis is a significant concern in patients with NSCLC. Alectinib and lorlatinib efficiently penetrate the blood–brain barrier (BBB) and show reasonable CNS response rates [3]. Alectinib is useful as the first-line chemotherapy with or without brain metastases because of its higher efficacy and milder adverse events than lorlatinib. Moreover, lorlatinib is recommended as a second-line treatment for symptomatic *ALK*-positive NSCLC patients with CNS relapse after alectinib [1]. However, in *ALK*-positive NSCLC patients with CNS relapse, carcinomatous meningitis and uncontrollable symptomatic epilepsy cause consciousness disorders. Oral administration of *ALK* inhibitors is difficult for unconscious patients. In addition, there is no established systemic chemotherapy regimen for patients with poor PS, and palliative care is the only option.

Previous reports showed that lorlatinib treatment is effective in patients with *ALK*-positive NSCLC, showing CNS relapse and impaired consciousness with poor PS upon failure of other ALK inhibitors [4–6]. However, few case studies have reported long-term survivorship similar to this case. Our findings indicate the potential of lorlatinib to treat patients with *ALK*-positive NSCLC showing complications related to consciousness due to carcinomatous meningitis after other ALK inhibitor treatment.

Resistant gene mutations are a cause of ALK inhibitor resistance. L1196M, L1198F, and G1202R have been identified as resistant variants of ALK [3]. G1202R may be a

target of lorlatinib upon failure of alectinib treatment. Furthermore, L1196M/L1198F may be another target of crizotinib upon failure of lorlatinib in patients who have not received crizotinib, although there is a problem with BBB penetration.

In conclusion, lorlatinib may be a treatment option for patients with *ALK*-positive NSCLC showing carcinomatous meningitis and poor PS upon failure of other *ALK* inhibitor treatments. Enteral administration using a simple suspension method via a nasogastric tube is another treatment option for patients with *ALK*-positive NSCLC showing dysphagia and poor PS.

Disclosure Statement

We obtained written informed consent from the patient to publish the case report and received approval from the Ethics Committee of Aomori Kyoritsu Hospital.

Conflict of Interest

Atsushi Sato received research donations from Chugai Pharmaceutical Co., Ltd., Tahio Pharmaceutical Co., Ltd., Eli Lilly and Co., Ono Pharmaceutical Co., Ltd., and Daiichi Sankyo Co., Ltd. Their donations were not associated with the present case. All other authors have no conflicts of interest to disclose.

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Author Contribution Statement

Kota Sasaki: Conceptualization and writing - original draft. Yusuke Yokota: Project administration, supervision, and writing - review and editing. Toshihito Isojima: Conceptualization and writing - review and editing. Mayumi Fujii: Conceptualization, visualization, and writing - review and editing. Kengo Hasui: Supervision and writing - review and editing. Yu Chen: Supervision and writing - review and editing. Kensuke Saitou: Supervision and writing - review and editing. Takenori Takahata: Supervision and writing - review and editing. Seiko Kindaichi: Project administration, supervision, visualization, and writing - review and editing. Atushi Sato: Supervision and writing - review and editing.

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