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CASE REPORT

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Efficacy of lorlatinib treatment in *ALK* rearrangement lung cancer with severe symptomatic central nervous system metastases and poor performance status

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Abstract

Lorlatinib treatment should be positively considered even for patients with ALK-positive NSCLC with severe neurocognitive disturbance and poor performance status due to CNS metastases, including leptomeningeal carcinomatosis.

KEYWORDS

ALK, CNS metastases, lorlatinib

1 | INTRODUCTION

Lorlatinib is a third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) designed to penetrate the blood-brain barrier. We report 2 cases of patients with *ALK* rearrangement non–small-cell carcinoma associated with severe symptomatic CNS metastases and poor performance status. Treatment with lorlatinib improved their neurological condition and performance status.

Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 3%-5% of non–small-cell lung cancer (NSCLC) cases.[1] Clinical outcomes of patients with advanced *ALK*-positive NSCLC have considerably improved with the development of *ALK*-TKIs. However, the incidence of CNS metastases, including brain metastases and leptomeningeal carcinomatosis (LC), is high among those with *ALK* rearrangement NSCLC,[2] which is associated with a high mortality rate and often with poor performance status that impedes treatment. No effective treatment is yet established, particularly in cases of LC.

Lorlatinib is a third-generation *ALK*-TKI designed to penetrate the blood-brain barrier (BBB).[3] The clinical efficacy and intracranial activity of lorlatinib in advanced *ALK*-positive NSCLC including in patients who had failed prior *ALK*-TKIs has been proven.[4] However, reports on the effectiveness and safety of lorlatinib in patients with *ALK*-positive NSCLC with severe symptomatic CNS metastases including LC and poor performance status are lacking.

We herein report 2 cases of *ALK* rearrangement lung cancer with CNS metastases associated with severe neurocognitive dysfunction and poor performance status responding considerably and rapidly to lorlatinib treatment without serious adverse effects.

2 | CASE PRESENTATION

2.1 | Case 1

The patient was a 76-year-old woman without any history of smoking. Stage Ⅳ *ALK* rearrangement lung adenocarcinoma including pleural dissemination and liver metastases was diagnosed. Alectinib was started and switched to crizotinib 2 years later because of the progression of the pleural lesion. Crizotinib was interrupted because of nausea a month later, and ceritinib was started. After 4 months of ceritinib treatment, the primary lesion progressed and nivolumab treatment was started. After 5 courses of nivolumab, the pleural lesion progressed again. Carboplatin, pemetrexed, and bevacizumab regimen were then introduced. After 4 courses, pemetrexed and bevacizumab were continued for a year. Although the intrathoracic lesions were controlled, she complained of

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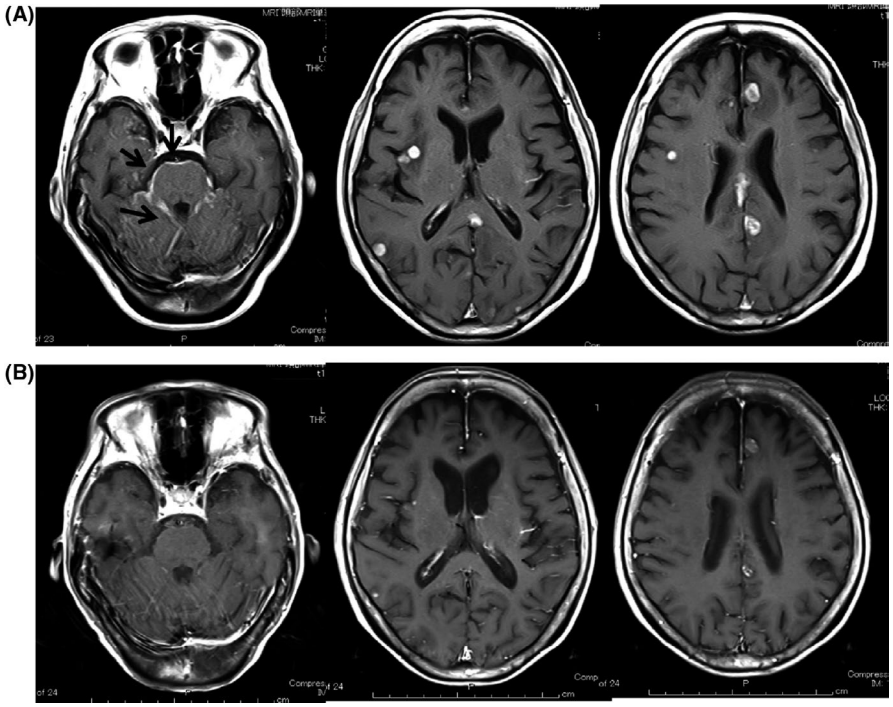

FIGURE 1 Multiple nodules in the cerebrum and abnormal leptomeningeal enhancement in the subarchnoid cavity(arrows) were present(A). One month after lorlatinib initiation, the multiple nodules clearly improved and the abnormal leptomeningeal enhancement disappeared (B)

anorexia. Brain magnetic resonance imaging (MRI) revealed multiple brain metastases and the contrast effect in subarachnoid cavity, indicating LC (Figure 1A). After admission, she developed apraxia, dysarthria, and impaired consciousness (Glasgow Coma Scale 11 [E3V3M5]). She was then treated with lorlatinib.

However, she developed aspiration pneumonitis associated with severe respiratory failure after 3 days. Lorlatinib treatment was interrupted, and sulbactam/ampicillin was administered for 9 days. Her respiratory condition improved. However, she became more drowsy and her performance status deteriorated. Treatment with lorlatinib suspended in saline was readministered 1 mL at a time to prevent aspiration. A week after resuming lorlatinib, her neurological symptoms were mostly resolved. Brain MRI revealed marked regression in multiple brain metastases and disappearance of the contrast effect in the subarachnoid cavity (Figure 1B). An MRI scan after 1 year did not show regression of the cerebral and leptomeningeal metastases, whereas intrathoracic disease had slightly progressed. She had no symptoms, and lorlatinib treatment is being continued.

2.2 | Case 2

A 56-year-old woman without any history of smoking presented with back pain. Computed tomography revealed a 32-mm solitary tumor in the left upper lobe. Spinal MRI revealed multiple spine metastases. The pathology of the transbronchial biopsied specimens demonstrated adenocarcinoma. *ALK* gene rearrangement was observed on both immunohistochemistry and fluorescence in situ hybridization assays. Epidermal growth factor receptor mutations were not observed. She was initially treated with alectinib 400 mg/day orally. Radiation therapy was administered on thoracic vertebrae (T7-T11) to moderate her pain. Thereafter, she achieved partial response and her back pain resolved.

Approximately 1 year later, she complained again of back pain and anorexia. Spinal MRI showed no changes. Regardless, her symptoms had persisted, and she developed aphasia and impaired consciousness. She was admitted to another hospital with a suspicion of stroke. Cerebrospinal fluid cytology revealed adenocarcinomatous cells. Furthermore, contrast-enhanced MRI showed a contrast effect on the brain surface and no brain metastases(Figure 2). Leptomeningeal carcinomatosis was then diagnosed. She was transferred to our hospital in a comatose state. Lorlatinib could not be administered orally. Although we recommended palliative care, her family opted for lorlatinib treatment. Lorlatinib administration was started at 100 mg/day through a nasogastric tube. Four days after lorlatinib treatment, she developed gastrointestinal bleeding from gastric polyps. Although we withheld the treatment, her consciousness improved rapidly and she could hold a simple conversation. After the cessation of the treatment for 5 days, we resumed the lorlatinib treatment. One month after resuming the treatment, her consciousness recovered completely. Although the sequelae of lower limbs paralysis remained, the paralysis of upper limbs clearly improved. She was continued on lorlatinib treatment. However, LC recurred after 6 months. She and her family opted for

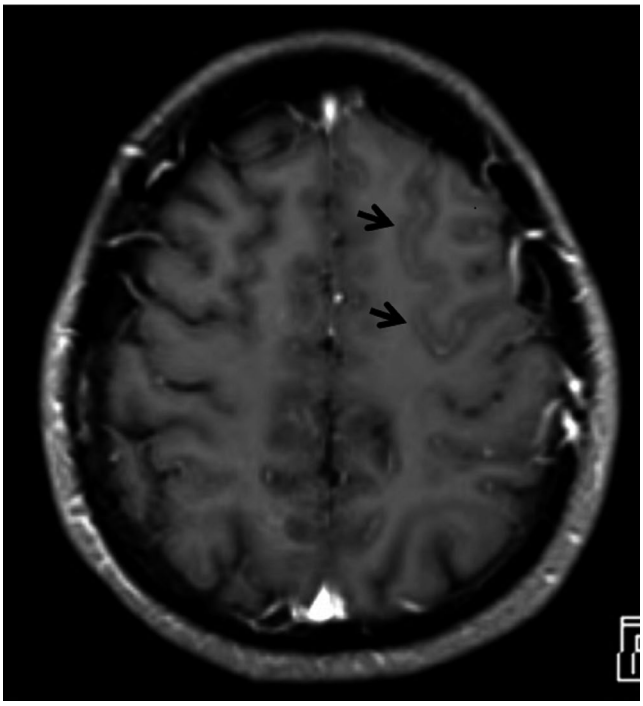

FIGURE 2 Brain magnetic resonance imaging revealed enhanced area of the surface of brain(arrows) and no brain metastasis

palliative care. She died 8 months after the introduction of lorlatinib.

3 | DISCUSSION

In our patients, lorlatinib treatment achieved resolution of severe neurological symptoms and improved performance status without serious adverse events. Our experience shows that lorlatinib treatment should be considered even for patients with *ALK*-positive NSCLC with severe neurocognitive disturbance and poor performance status due to CNS metastases, which are impediments to aggressive treatment. Moreover, lorlatinib could be used in patients with LC, which lacks specific effective therapies.

CNS metastases are often complications in cases of ALK-positive NSCLC and considerably affect the prognosis and quality of life of patients.[1] Managing CNS metastases hence becomes a significant issue in the management of *ALK* rearrangement NSCLC *ALK*-TKIs include the first-generation TKI crizotinib and the second-generation TKIs alectinib and ceritinib. Crizotinib has poor CNS penetration, resulting in a high frequency of recurrence in the CNS.[5] The second-generation ALK-TKI was developed to be more potent and BBB permeation; however, occurrence and progression of CNS metastases during treatment remains clinically as these cases.[6-8] The third-generation *ALK* inhibitor, lorlatinib, was designed specifically to target mutations that drive resistance to other ALK inhibitors and to penetrate the BBB.[4] Its efficacy in intracranial metastases and safety even after progression compared with the previous-generation *ALK* inhibitors were demonstrated in a phase II trial.[4] However, the trial had included patients with asymptomatic CNS metastases.[4] Our patients had *ALK*-positive NSCLC with severe symptomatic CNS metastases. Selecting a positive treatment for CNS metastases in severe impaired consciousness and poor performance status is often challenging. In our cases, confirming patient intent about the treatment was challenging because of their disturbed consciousness. In addition, further deterioration of the performance status and the occurrence of serious adverse events adds to the challenge.

LC is associated with poor prognosis with a median survival of 3-6 months among NSCLC patients.[9] Thus, LC is an exclusion criterion in most NSCLC trials.[9] Reports on the efficacy of lorlatinib in patients with LC are only few. Viola et al demonstrated the efficacy of lorlatinib in 9 ALK-positive patients and 2 c-ros oncogene 1 (ROS-1)-positive patients with LC.[10] The overall intracranial response rate, intracranial disease control rate, and median progression-free survival (PFS) were 45%, 91%, and 9.3 months, respectively.[10] In our second patient, LC recurred 6 months after starting lorlatinib treatment. However, the patient was in coma initially, and her neurological condition improved significantly after lorlatinib initiation. Therefore, lorlatinib treatment was clinically significant.

In conclusion, lorlatinib treatment can be effective in *ALK*-positive patients with severe symptomatic CNS metastases including LC and poor performance status. Patients with *ALK* rearrangement NSCLC are mostly juvenile, and hence, positive outcomes of lorlatinib treatment even in cases of severe CNS metastases should be considered.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTION
TT: contributed to write-up of abstract, introduction, case presentation, discussion, and images. TN: reviewed and edited the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Ethics approval was not necessary for this case report. All patient' s data and images are de-identified.

INFORMED CONSENT
Written informed consent was obtained from the patient for publication of this case report .

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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