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Case Report

Long-Term Response of Lorlatinib to Leptomeningeal Metastasis in Patients with Anaplastic Lymphoma Kinase Fusion Positive Non-Small Lung Cancer: A Case Report

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Keywords
Anaplastic lymphoma kinase fusion · Leptomeningeal metastasis · Lorlatinib · Non-small cell lung cancer

Abstract
Introduction: Patients with anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) are at increased risk of central nervous system (CNS) metastasis at initial diagnosis and throughout treatment. In a phase 3 trial, lorlatinib, a third-generation ALK tyrosine kinase inhibitor, significantly improved progression-free survival. In further analysis, lorlatinib revealed superior intracranial efficacy and prolonged time to intracranial progression compared with crizotinib. ***Case Presentation:*** Herein, we report a case of ALK-positive NSCLC with leptomeningeal metastasis that was successfully treated with lorlatinib after progression to brigatinib and alectinib. This case demonstrates the potential of lorlatinib in managing leptomeningeal metastasis in ALK-positive NSCLC. ***Conclusion:*** The case suggests a paradigm shift in therapeutic approaches for CNS metastasis, including brain and leptomeningeal metastases.

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Introduction

The discovery of driver mutations in advanced non-small cell lung cancer (NSCLC) has considerably influenced treatment approaches based on the molecular characteristics of the tumor [1, 2]. Molecular targeted agents (MTAs) demonstrate high efficacy and durability; however, most patients eventually develop resistance [3]. The main types of resistance to tyrosine kinase inhibitors (TKIs) include acquired mutations in the kinase domain of cancer cells, activation of bypass signaling pathways, and progression in sanctuary sites, such as the central nervous system (CNS), where TKI penetration is limited.

Anaplastic lymphoma kinase (ALK)-rearranged NSCLC accounts for 2%–5% of lung adenocarcinomas. These patients have a higher risk of brain metastasis at initial diagnosis and throughout treatment than those with non-ALK NSCLC [4–6]. As of 2024, five ALK-TKIs, namely crizotinib, alectinib, ceritinib, lorlatinib, and brigatinib, have been approved for the treatment of advanced ALK-positive NSCLC. As brain and CNS metastases significantly lead to a decreased quality of life and poor survival, treatment is performed with these concerns [7]. Lorlatinib, a third-generation ALK-TKI, has been engineered to overcome many ALK resistance mutations and enhance CNS penetration [8].

In the CROWN trial, lorlatinib significantly improved progression-free survival [9]. Further analysis revealed superior intracranial efficacy and prolonged time to intracranial progression compared with crizotinib, even in patients with and without preexisting brain metastases [9–11]. Although patients with leptomeningeal metastasis were excluded from the CROWN trial, this case report discusses a patient with ALK-positive + NSCLC who experienced a durable response to lorlatinib after developing leptomeningeal metastases. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540445).

Case Presentation

A 35-year-old man with a 17-pack-year smoking history presented with headache and diplopia prompting an emergency room visit in January 20XX. Computed tomography (CT) and brain magnetic resonance imaging showed a 40 mm long solitary brain tumor in the left temporal lobe causing a midline shift (Fig. 1a, b). CT revealed a primary lung cancer in the left lower lobe (Fig. 1c). After brain tumor surgery, a metastatic brain tumor from NSCLC was pathologically diagnosed, and the EML4-ALK fusion was identified through fluorescence in situ hybridization and immunohistochemistry testing (Fig. 2a–f). We initially diagnosed the NSCLC as stage IVA (cT2bN2M1b in the TNM 8th edition).

In March 20XX, he started receiving crizotinib for 2 years, followed by alectinib for 1 year and brigatinib for 3 years due to disease progression. In September 20XX + 6, he developed leptomeningeal metastases with diplopia, as confirmed by magnetic resonance imaging (Fig. 1d, 3; online suppl. Fig. 1A) and started to receive lorlatinib. However, lorlatinib at 100 mg/day caused adverse psychological events, including dementia and mood alterations, including depression and suicidal ideation. He hoped to switch back to alectinib, but leptomeningeal metastases progressed 3 months after re-administration of alectinib (Fig. 3; online suppl. Fig. 1B, C). A carefully shared decision-making process led to the resumption of lorlatinib at a reduced dose of 75 mg/day from June 20XX + 7. He developed dyslipidemia;

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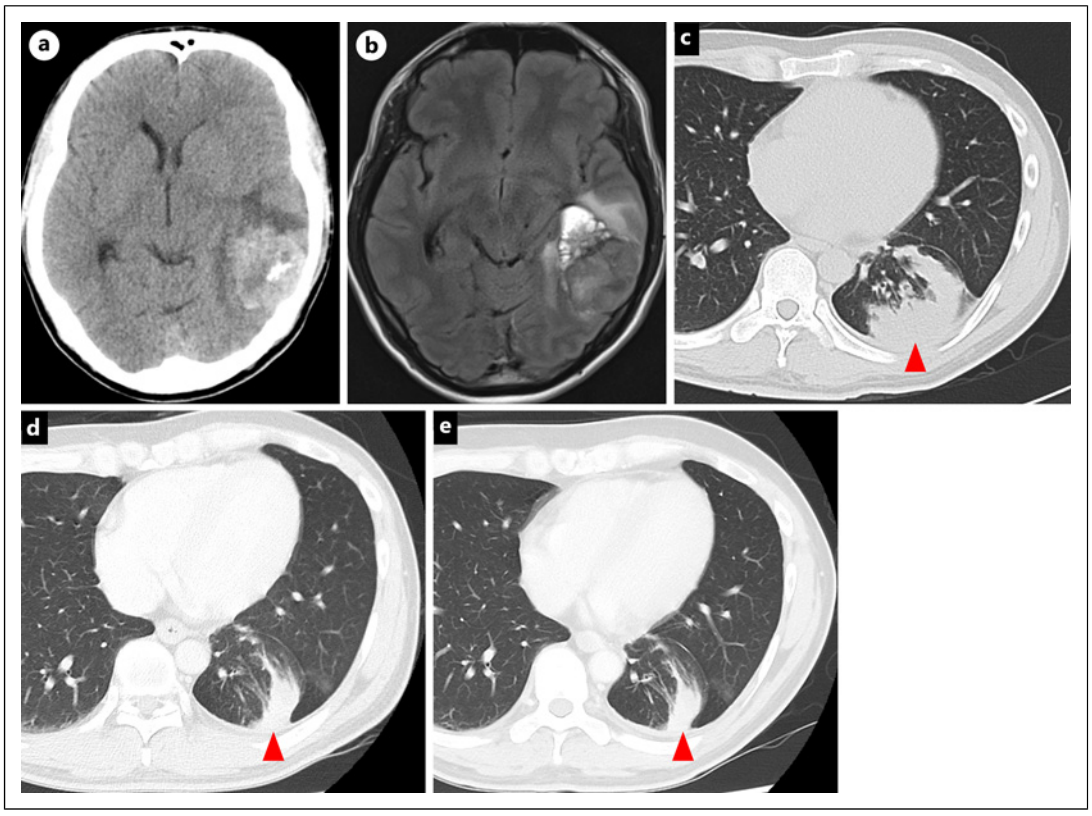

Fig. 1. Brain CT (**a**), MRI (**b**), and chest CT (**c**) at initial diagnosis. Chest CT at the onset of leptomeningeal metastases (**d**) and 2 years after lorlatinib (**e**). Red arrow: primary lung lesion. CT, computed tomography; MRI, magnetic resonance imaging.

however, psychological events and mood alterations did not recur. He continued lorlatinib treatment, with a sustained complete response to the leptomeningeal metastases after 2 years (Fig. 1e, 3; online suppl. Fig. 1D, E).

Discussion

This report highlights the potential efficacy of lorlatinib in treating leptomeningeal metastases in patients with ALK-positive NSCLC, even when brigatinib and alectinib failed to treat leptomeningeal metastases. Adjusting the lorlatinib dose effectively managed the adverse psychological effects, emphasizing the importance of personalized treatment strategies to balance efficacy and quality of life.

Pathological findings of the brain tumor revealed a predominantly solid adenocarcinoma with mixed spindle and acinar components, all of which were positive for ALK-immunohistochemistry staining. The EML4-ALK variant 1 (E13:A20) using Ion Torrent S5 Sequencer™ (Thermo Fisher Scientific, Wilmington, DE, USA) was confirmed in this patient (Fig. 2g). EML4-ALK fusion accounts for approximately 85% of the ALK fusion variants with many of the EML4-ALK variants depending on the fusion breakpoint of EML4 to the exon 20 of the ALK gene. EML4-ALK variant 1 (E13:A20) is one of the most common EML4-ALK variants, along with variant 2 (E20:A20) and variant 3 (E6:A20) [12]. ALK-TKIs are generally longer progression-free survival in patients with EML4-ALK

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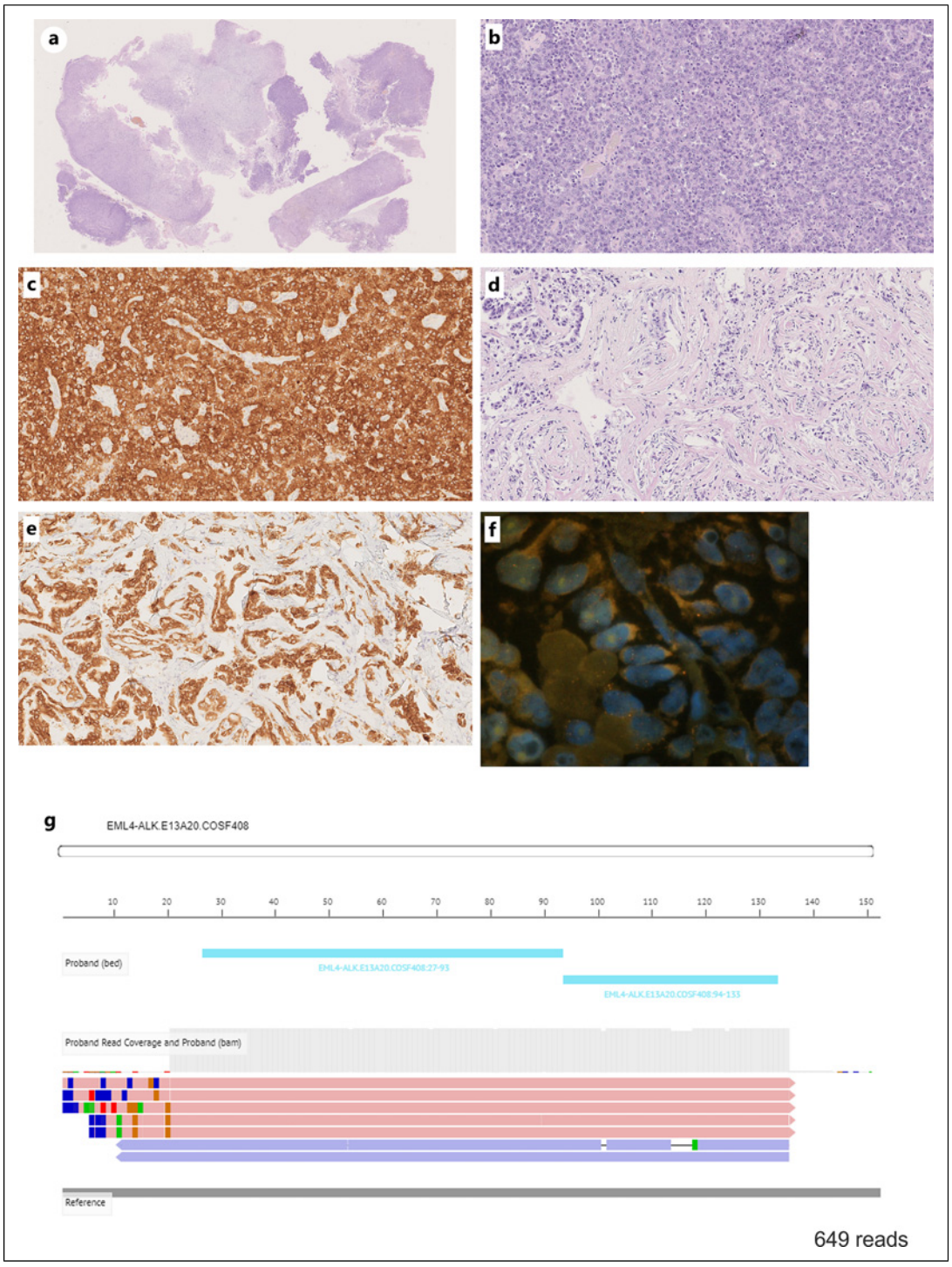

Fig. 2. Histopathological findings of brain metastasis in low power field (**a**). Hematoxylin and eosin (HE) stained shows a predominant solid adenocarcinoma (**b**) with mixed spindle and acinar components (**c**). ALK-IHC staining (5A4, Abcam) was positive in both solid adenocarcinoma (**d**) and acinar components (**e**). FISH testing detected ALK rearrangement (**f**). Next generation panel sequence detected EML4-ALK variant 1 (E13:A20) (**g**). FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.

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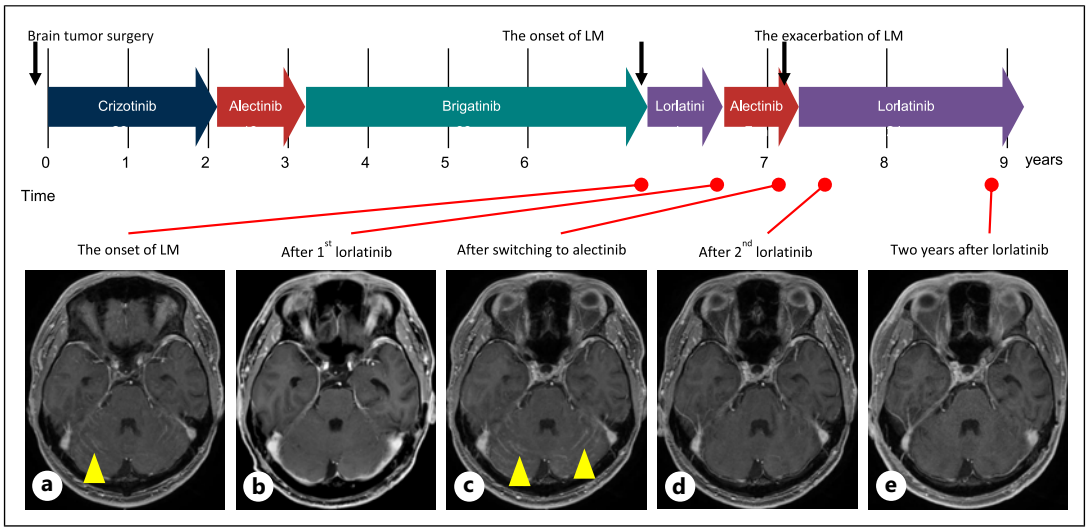

Fig. 3. Timeline of the patient's treatment history and representative brain MRI. Brain MRI at the onset of LM (**a**), after 1st lorlatinib (**b**), after switching to alectinib (**c**), after 2nd lorlatinib (**d**), and at present (**e**). Yellow arrow: leptomeningeal metastases. LM, leptomeningeal metastases; MRI, magnetic resonance imaging.

variant 1 than in those with EML4-ALK variant 3 [13–15]. The patient had a highly sensitive variant 1 to ALK-TKIs, which may have contributed to his long-term survival.

It has previously been noted that the cerebrospinal/plasma concentration ratio observed with lorlatinib (range: 0.61–0.96) was much higher than with crizotinib (range: 0.0006–0.026) and alectinib (range: 0.002–0.005), although alectinib also had antitumor activity in patients with CNS metastasis [16, 17]. The superior CNS penetration of lorlatinib was attributed to the complete and reproducible response on leptomeningeal metastasis in this patient, even when leptomeningeal metastasis was progressed with brigatinib and alectinib. Highly potent ALK inhibition of lorlatinib may avoid the need for whole-brain irradiation in such cases [18, 19].

Several studies have discussed the mechanism of ALK-TKI resistance [20–24]. Gainor et al. [20] reported that lorlatinib retained its potency against G1202R, G1202del, and D1203N+E1210K mutations, whereas other ALK-TKIs were inactive. This patient might have a mutation that was resistant to crizotinib, alectinib, and brigatinib but sensitive to lorlatinib. Because the progressive site was only the leptomeningeal metastasis, no tissue specimens were available after progression to these previous ALK-TKIs. This is a limitation of this case report.

Conclusion

This case demonstrates the potential of lorlatinib in managing leptomeningeal metastasis in ALK-positive NSCLC, suggesting a paradigm shift in therapeutic approaches for CNS metastasis.

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Statement of Ethics

This case report was approved by the Ethics Committee of Aichi Cancer Center, Nagoya, Japan (permit no. T06004). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

Y.F. reports receiving personal fees for honoraria for lectures from AstraZeneca, Amgen, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Merck Biopharma, Merck Sharp & Dohme, Novartis, Novocure, Ono Pharmaceutical, Pfizer, Takeda, and Taiho Pharmaceutical, outside the submitted work; personal fees for being on the advisory board from AstraZeneca, Chiome Bioscience, Daiichi-Sankyo, Micron, Otsuka Pharmaceutical, and Ono Pharmaceutical, outside the submitted work; and research grants from AbbVie, Amgen, AnHeart, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Eli Lilly, Incyte, Merck KGaA, Merck Sharp & Dohme, and Taiho Pharmaceutical, outside the submitted work. R.M. reports receiving personal fees for honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chugai, Eli Lilly, Merck Sharp & Dohme, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical, outside the submitted work. T.Y. reports receiving personal fees for honoraria for lectures from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck Biopharma, Merck Sharp & Dohme, Ono Pharmaceutical, and Taiho Pharmaceutical, outside the submitted work, and reports receiving personal fees for being on the advisory board from Daiichi-Sankyo. J.S. reports receiving personal fees for honoraria for lectures from AstraZeneca, Amgen, Chugai, Merck Biopharma, Merck Sharp & Dohme, Novartis, Pfizer, Taiho Pharmaceutical, and Takeda Pharmaceutical, outside the submitted work. The other authors have no conflicts of interest to declare.

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Author Contributions

Y.F. was responsible for the clinical management of the patient and contributed to writing this manuscript. K.M. and E.S. interpreted the histological data and contributed to the histological analysis. R.M., T.Y., N.W., J.S., and Y.H. wrote, reviewed, and edited the manuscript. All the authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed in this study have been included in the published article. Further inquiries can be directed to the corresponding authors.

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