

CASE REPORT

ALK-positive lung cancer in a patient with recurrent brain metastases and meningeal dissemination who achieved long-term survival of more than seven years with sequential treatment of five ALK-inhibitors: A case report

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Abstract

The incidence of central nervous system (CNS) metastases in patients with anaplastic lymphoma kinase (ALK) fusion gene-positive (ALK+) non-small cell lung cancer (NSCLC) is high, ranging from approximately 20%–70%. Although ALK inhibitors (ALKis) are generally effective for CNS metastases in patients with ALK+ NSCLC, relapse with CNS metastases is frequently observed. A 37-year-old woman with a high level of carcinoembryonic antigen was diagnosed with right lung adenocarcinoma (pathological stage IIIA) and underwent right lower lobectomy. Despite the administration of postoperative chemotherapy, her carcinoembryonic antigen (CEA) level remained elevated. Although crizotinib was administered due to the positivity for ALK fusion, brain metastases appeared at 19.0 months after the start of treatment. Treatment with alectinib following crizotinib resulted in the complete disappearance of brain metastases. However, brain metastases relapsed, and meningeal dissemination appeared at 38.3 months after the start of treatment with alectinib. Although ceritinib, brigatinib, and alectinib rechallenge were attempted, the CNS lesions worsened. Lorlatinib was then administered, resulting in the normalization of the CEA level (4.5 ng/ml) 4.1 months after the start of lorlatinib. The brain metastases and meningeal dissemination almost disappeared. The overall time from the start of crizotinib to lorlatinib is 89.5 months at present, and the patient continues to be treated with lorlatinib without relapse. Lorlatinib was effective in this case with brain metastases and meningeal dissemination after resistance to first- and second-generation ALKis. Appropriate sequential treatment with first-, second- and third-generation ALKis can lead to a long-term survival in ALK+ patients with brain metastases and meningeal dissemination.

KEYWORDS

anaplastic lymphoma kinase, brain metastases, lorlatinib, non-small cell lung cancer

INTRODUCTION

Anaplastic lymphoma kinase (ALK) is a transmembrane receptor-type tyrosine kinase belonging to the insulin receptor family.¹ ALK has been found to fuse with *EML4* in non-small cell lung cancer (NSCLC), resulting

in constitutive activation.² As a result, it exerts potent oncogenic activity through downstream pathways, such as the PI3K/AKT and Ras/MAPK pathways.³ The ALK fusion gene is identified in NSCLC with a frequency of 4%–7%. ALK inhibitors (ALKis) show potent antitumor activity in ALK-positive lung cancer; however, most

patients experience acquired resistance and central nervous system (CNS) metastases.

We herein report a patient with *ALK*-positive NSCLC who experienced recurrence of brain metastases and meningeal dissemination after curative resection but achieved a long-term survival by the sequential administration of five *ALK* inhibitors.

CASE REPORT

The patient was a 37-year-old female non-smoker. Her carcinoembryonic antigen (CEA) level was high (28.5 ng/ml),

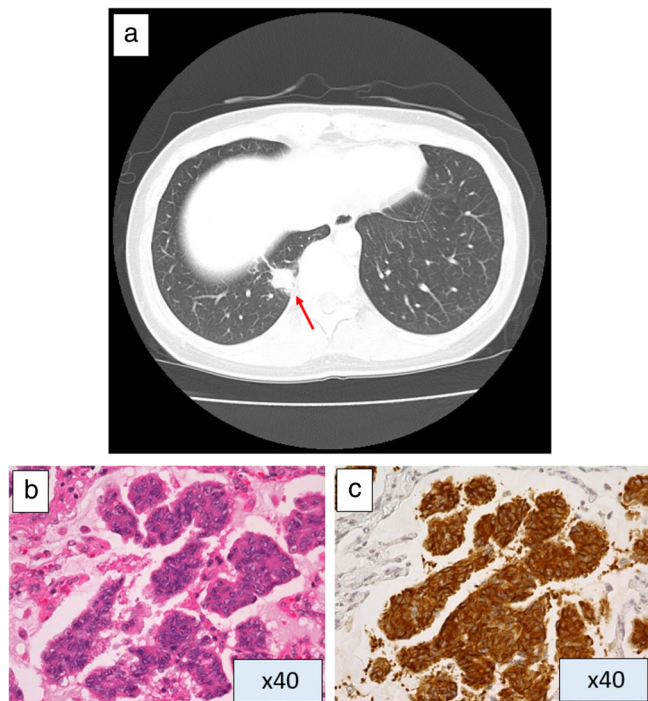


FIGURE 1 Computed tomography (CT) findings at the first diagnosis of adenocarcinoma. (a) The arrow indicates a nodular shadow in segment S10 with a maximum diameter of 2.7 cm. A pathological examination of the resected tumor. Hematoxylin and eosin (HE) staining shows heteromorphic cells with a large N/C ratio (b), and almost all of the cancer cells are immunopositive for anaplastic lymphoma kinase on immunohistochemical staining (c)

and computed tomography (CT) revealed an enhanced nodule with a maximum diameter of 1.7 cm in the right lower lung (Figure 1(a), arrow). Bronchoscopy revealed the nodule to be adenocarcinoma (cT1bN0M0, cStage IA2), and right lower lung lobectomy and lymph node dissection were performed. The histopathological findings showed papillary spread of atypical cells with a large N/C ratio and multiple metastases to the hilar and mediastinal lymph nodes (pT1cN2M0, pStageIIIA; Figure 1(b)). Immunohistochemistry showed strong positivity for *ALK* (Figure 1(c)).

Although adjuvant chemotherapy was administered, the CEA level was elevated (25.8 ng/ml). Based on the decision of the patient, four cycles of carboplatin + pemetrexed + bevacizumab were administered although no definite lesions were identified by CT and magnetic resonance imaging (MRI). However, the CEA level continued to rise. Crizotinib was then started, and the CEA level decreased to 6.7 ng/ml at 2.7 months after the start of crizotinib.

However, the CEA level increased again to 77.7 ng/ml at 33.0 months after surgery, and cerebellar metastases appeared on MRI (Figure 2(a)). Alectinib was administered at 600 mg/day, resulting in the complete disappearance of brain metastases at 3.1 months (Figure 2(b)).

At 38.3 months after the start of alectinib treatment, the CEA level elevated and relapse of the CNS lesions was observed (Figure 3(a)). Ceritinib, brigatinib and alectinib (rechallenge) were then sequentially administered; however, the disease continued to progress (Figure 3(b)).

After the approval of lorlatinib in Japan, lorlatinib (100 mg/day) was administered. At 4.1 months after the start of lorlatinib, the CEA level normalized to 4.5 ng/ml, and the CNS lesions had almost disappeared (Figure 4(a), (b)).

DISCUSSION

Crizotinib was originally developed as a *c-MET* inhibitor but was later proven to have potent inhibitory activity against *ALK*.⁴ In addition, alectinib has been shown to be approximately 10 times more effective than crizotinib in inhibiting *ALK* and is also effective against many secondary

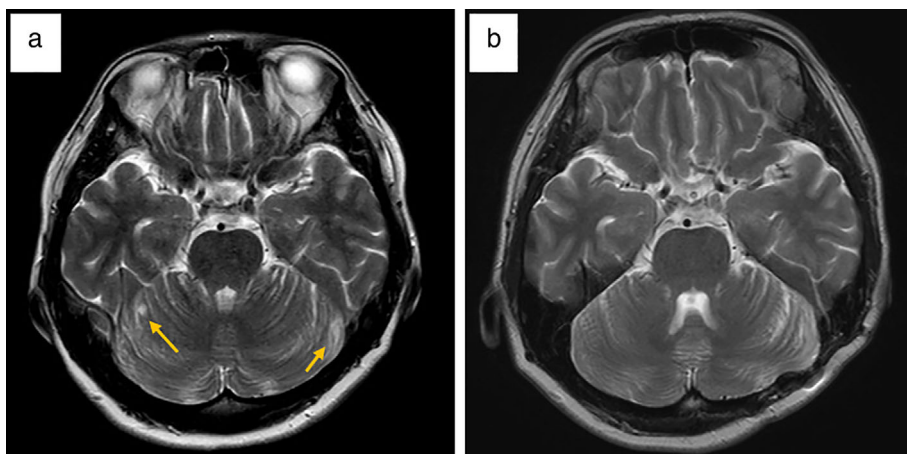


FIGURE 2 T2-weighted images on magnetic resonance imaging (MRI) before (a) and after (b) the administration of alectinib

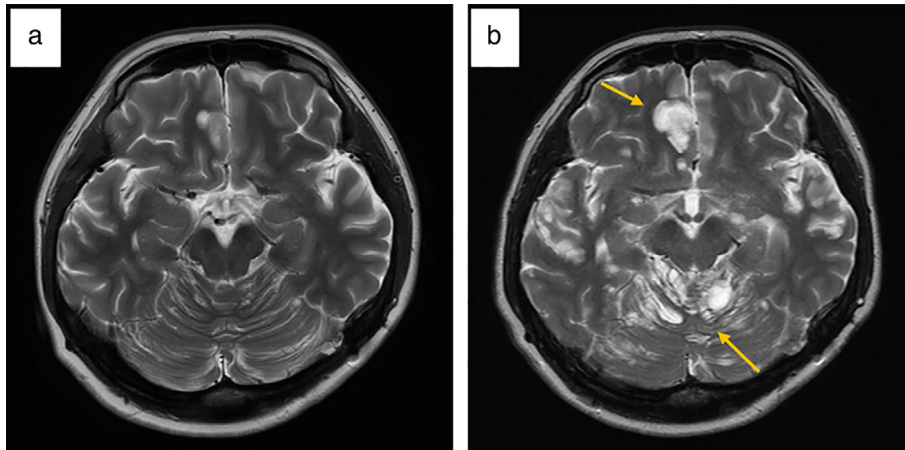


FIGURE 3 T2-weighted images on magnetic resonance imaging (MRI) before (a) and after (b) the administration of ceritinib, brigatinib and alectinib (rechallenge)

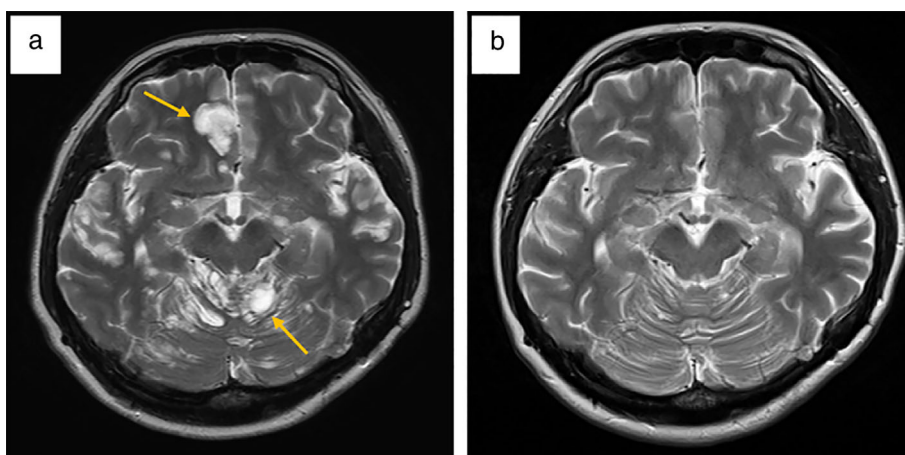


FIGURE 4 T2-weighted images on magnetic resonance imaging (MRI) before (a) and after (b) the administration of lorlatinib

mutations that induce crizotinib resistance.⁵ Clinically, two phase III trials showed the superiority of alectinib with crizotinib in first-line therapy.^{6,7} Ceritinib and brigatinib have also demonstrated efficacy in crizotinib-resistant patients and superiority over platinum-containing drug and crizotinib in the first-line setting, respectively.^{8–11} In the ESMO guideline for lung cancer treatment, crizotinib, alectinib and ceritinib are recommended as the first-line treatment for *ALK* fusion gene-positive lung cancer over cytotoxic agents.¹²

Lorlatinib has been shown to be active against almost all *ALK* secondary mutations, including the G1202R mutation.¹³ In addition, the results of a phase I study showed that the mean ratio of the cerebrospinal fluid concentration to the plasma concentration of lorlatinib was 0.75, indicating a high rate of penetration of lorlatinib to the CNS.¹⁴

In patients with *ALK*-positive NSCLC, CNS metastases are frequently seen (approximately 20%–70% of cases). The intracranial response rates of crizotinib, ceritinib, alectinib and brigatinib are reported to be 18%, 35%–59%, 55%–68% and 50%–67%, respectively, but many cases inevitably experience relapse of CNS metastases.¹⁵ The intracranial response rates of lorlatinib are 87% in patients treated with

only crizotinib, 56% in patients treated with only one prior second-generation ALKi, and 56% in patients treated with two to four prior ALKis.¹⁶ Furthermore, Felip et al. reported that duration of intracranial objective response was 12.4 months (95% confidence interval, 6.0–16.7) in patients treated with lorlatinib after the failure of two or three ALKis, suggesting that the use of multiple ALKis favors a better outcome.¹⁷ Although there are many reports regarding cases with CNS metastases in which lorlatinib responded after up to four ALKis, in the present case, lorlatinib was shown to be effective for CNS metastases even after five ALKis. As a result of the treatment with multiple ALKis, the overall time from the start of crizotinib to lorlatinib has been 89.5 months (Graphical abstract).

In conclusion, this case suggests that the sequential administration of all ALKis available may provide a long-term survival in *ALK*-positive lung cancer, even in patients with deadly metastases, such as CNS metastases.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with this study.

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