

Crizotinib resistance overcome by ceritinib in an ALK-positive non-small cell lung cancer patient with brain metastases

A case report

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Abstract

Rationale: The treatment of non-small cell lung cancer (NSCLC) has now changed dramatically in recent years and anaplastic lymphoma receptor tyrosine kinase (ALK) inhibitors are developing rapidly.

Patient concerns: Here we reported a 57-year-old ALK-positive NSCLC man with brain metastases.

Diagnoses: A case of lung adenocarcinoma with brain metastases.

Interventions: Crizotinib was administered orally at a dose of 250mg twice a day until the brain metastases were found. Treatment with orally administered ceritinib at a dose of 450mg/d was initiated after crizotinib treatment.

Outcomes: The patient is currently receiving maintenance ceritinib treatment, with no evidence of extracranial or intracranial tumor progression for 25 months.

Lessons: Ceritinib may be a good choice for ALK-positive NSCLC patients with brain metastases who acquire resistance to crizotinib.

Abbreviations: ALK = anaplastic lymphoma kinase, CNS = central nervous system, CT = computed tomography, EGFR = epidermal growth factor receptor, NSCLC = non-small cell lung cancer.

Keywords: anaplastic lymphoma kinase, brain metastases, ceritinib, crizotinib, non-small cell lung cancer

1. Introduction

Cancers are the leading causes of death worldwide, over 20% of which are related to lung cancer.^[1] The most common extrapulmonary sites of distant metastases in non-small cell lung cancer (NSCLC) patients are the brain, bone, adrenal gland, and liver. The treatment of NSCLC has now changed dramatically in recent years and the targeted inhibition of oncogenic driver mutations with molecular therapies, epidermal growth factor receptor (EGFR), and ALK as the most studied targets have dramatic improvements in outcome.^[2] Due to the longer Progression-Free-Survival of targeted therapy, compared with the platinum-based chemotherapy, targeted therapy is

considered to be the standard treatment for patients with specific mutations.

In particular, ALK gene rearrangement is found in approximately 5% of patients with NSCLC and is a therapeutic target in advanced NSCLC.^[3] The ALK inhibitor crizotinib was the first targeted drug approved for the treatment of ALK gene rearranged NSCLC. Despite the excellent efficacy of crizotinib, relapse and resistance to the drug were inevitably encountered in most ALK-rearranged patients within 12 months.^[4] The central nervous system (CNS) is a frequent site of disease progression during treatment with crizotinib.^[5]

Ceritinib is a selective second-generation ALK inhibitor, 20-fold more potent than crizotinib in terms of ALK selectivity.^[6] In April 2014, the FDA granted accelerated approval to ceritinib for the treatment of patients with ALK-positive metastatic NSCLC with disease progression or the patients who were intolerant to crizotinib. The ASCEND-1 study provided evidence that ceritinib had activity and efficacy in the treatment of the CNS metastatic disease. In this case report, the patient responded to crizotinib but ultimately gained brain metastases during crizotinib treatment. Then ceritinib treatment was taken, and it led to a good response. The patient is currently receiving maintenance ceritinib treatment and has been partial remission for 25 months.

2. Case report

In March 2011, a 57-year-old asymptomatic male smoker was admitted to our hospital because of a left lung mass (Fig. 1A and B). After obtaining the patient's informed consent, a radical resection of left upper pulmonary carcinoma and mediastinal

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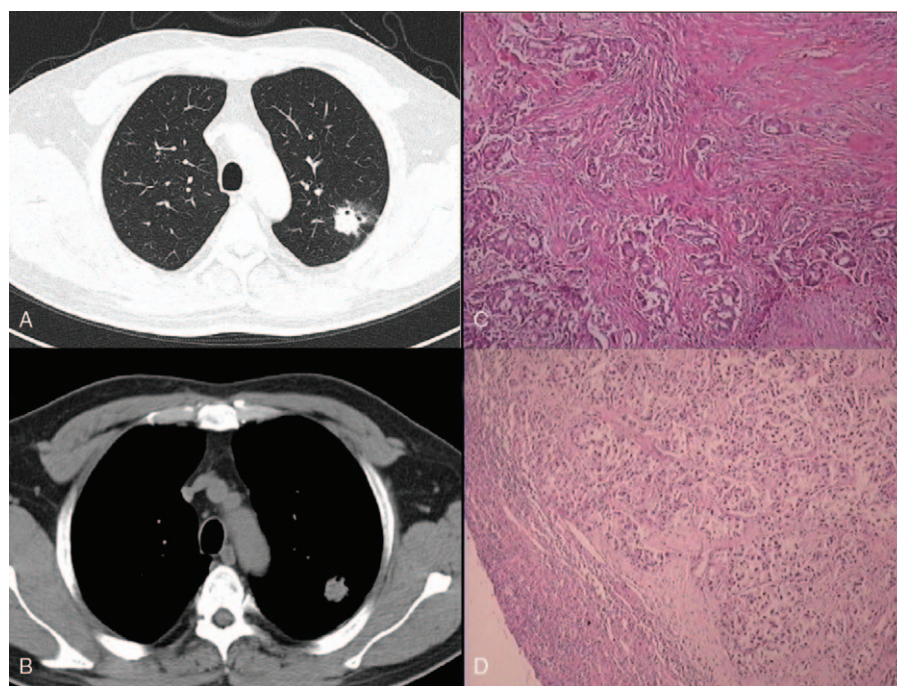


Figure 1. Histology and computed tomographic scan of the primary lung cancer. (A and B) Computed tomographic scan showed an irregularly shaped lesion in the left upper lobe that measured 2.0×1.5 cm. (C) Histopathologic examination of the left upper lobe lesion showed middle to well differentiated adenocarcinoma. (D) Histopathologic examination of the enlarged left axillary lymph node showed metastatic poorly differentiated adenocarcinoma.

lymph node dissection by thoracotomy were performed. Histopathologic examination showed a 2.0×1.5 cm middle to well differentiated adenocarcinoma in left upper lobe (Fig. 1C). Eighteen resected lymph nodes were detected and were all negative. The patient did not undergo postoperative chemotherapy. However, in November 2012, B ultrasound revealed a left axillary lymph node enlargement and the chest computed tomography (CT) scan revealed multiple nodules on the left pleural, both were considered to be metastases at first. After obtaining the patient's informed consent, a resection of the enlarged left axillary lymph node was performed. Histopathologic examination showed a metastatic poorly differentiated adenocarcinoma (Fig. 1D). The patient was initially treated with cisplatin, pemetrexed disodium, and bevacizumab with good response. In March 2013, molecular (EGFR/ALK) testing using FISH was carried out on tissue procured from the enlarged left axillary lymph node. The patient was found to be ALK-positive with EGFR wild-type and crizotinib was therefore administered orally at a dose of 250 mg twice a day. The treatment was well tolerated and CT of the thorax revealed a good response that the number and the size of all the lesions did not increase. After 2 years of crizotinib therapy, however, the patient got a headache and cranial magnetic resonance imaging revealed multiple lesions in the brain which were considered to be metastases at first (Fig. 2A and C). Considering the disease progressed, the treatment of crizotinib was eventually discontinued. Treatment with orally administered ceritinib at a dose of 450 mg/d was initiated after crizotinib treatment. The patient responded well to ceritinib as demonstrated by cranial MRI that the lesions in the brain decreased significantly (Fig. 2B and D). Considering the interesting results, a free molecular testing using FISH was carried out on tissue procured from the resected left upper lobe lesion after obtaining the patient's informed consent. The lesion was found to be both ALK-positive and EGFR mutation. The patient

is currently receiving maintenance ceritinib treatment, with no evidence of extracranial or intracranial tumor progression for 25 months.

3. Discussion

In this case study, crizotinib treatment showed a good response to the ALK-positive NSCLC patient at the initial treatment for 2 years until ultimately gained brain metastases. The patient eventually discontinued crizotinib due to progressive disease and therapy was switched to second-line ceritinib. Interestingly, ceritinib treatment had a good response that the size and number of metastatic lesions in the brain decreased and no evidence of extracranial or intracranial tumor progression is found up to now.

The CNS is a frequent site of disease progression for ALK-positive NSCLC patients, approximately 35% to 50% of ALK-positive NSCLC patients suffering CNS metastases.^[3,4,7] It is not clear whether the higher risk may be related to treatment with ALK inhibitors, or ALK-positive patients have an increased risk of developing CNS metastases independently from the therapy received. Crizotinib appeared no better at staving off progression than chemotherapy in the CNS.^[8] But some clinical trials like ASCEND-1 mentioned that ceritinib had activity and efficacy in the treatment of CNS metastatic disease. However, no prospective research has been finished. In addition, the curative effect of ceritinib to ALK-positive NSCLC patients with brain metastases who have received crizotinib is not definite. Further prospective research is ongoing for patients with ALK-positive NSCLC metastatic to the brain (ClinicalTrials.gov identifier: NCT02336451).

In addition, the patient had different molecular testing results between the primary lesion and the metastatic lesion that the primary lesion was found to be EGFR-positive while the metastases were EGFR-negative, which means the genes of

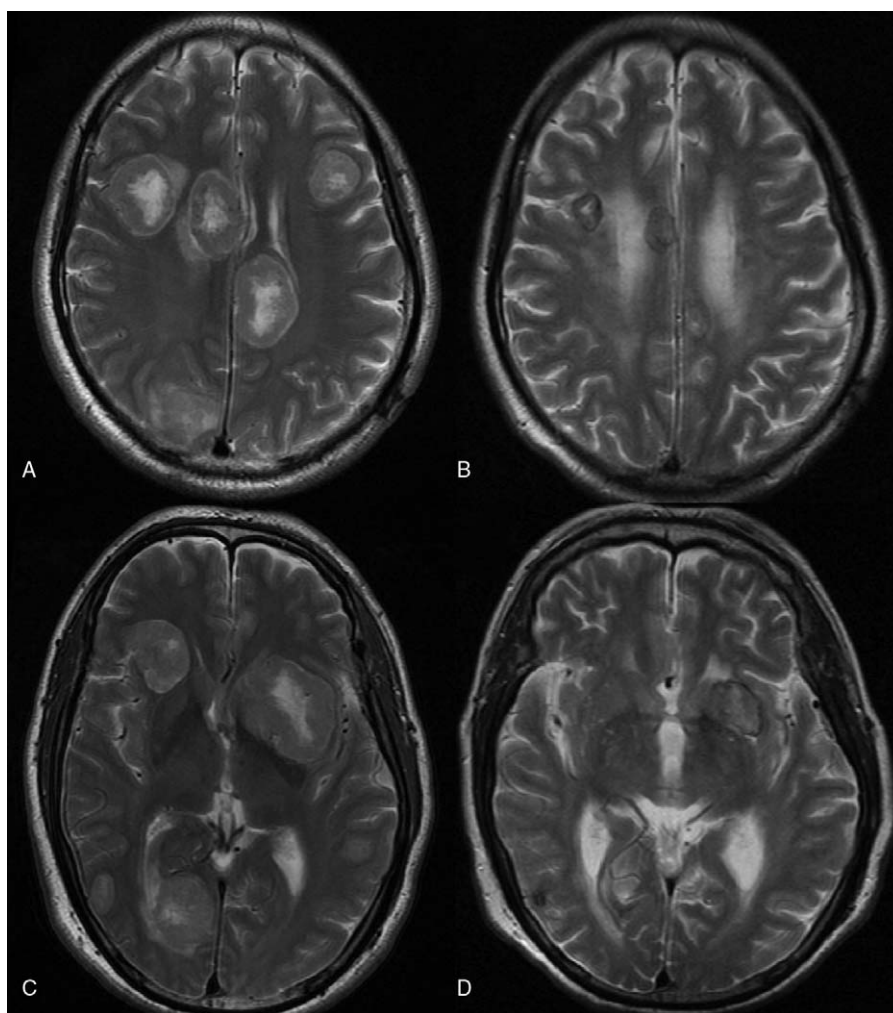


Figure 2. Cranial MRI scans of patient on ceritinib treatment. (A and C) Cranial MRI scan prior to ceritinib treatment revealed multiple lesions in the brain. (B and D) Cranial MRI scan post ceritinib treatment revealed the lesions in the brain decreased significantly.

metastases lesion may be different from the primary lesion's. Doctors should pay more attention to this phenomenon.

This case demonstrated the curative effect of ceritinib for the ALK-positive NSCLC patients with brain metastases who acquire resistance to crizotinib. We consider this strategy appears to be a promising therapeutic approach for these patients. Further studies are warranted.

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