

Successful treatment with crizotinib after alectinib-induced interstitial lung disease

SAGE Open Medical Case Reports
Volume 9: 1–4
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DOI: 10.1177/2050313X211042991
journals.sagepub.com/home/sco



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Abstract

Although alectinib is a well-tolerated and highly effective inhibitor of a second-generation anaplastic lymphoma kinase, special attention should be paid to the possibility of potentially severe and fatal adverse events such as interstitial pneumonia. We report a case of a patient with advanced non-small cell lung cancer treated with alectinib who developed immunohistochemically positive anaplastic lymphoma kinase (ALK(IHC +)). However, due to the rapid emergence of drug-induced interstitial lung disease, alectinib treatment was halted. Once the interstitial lung disease had been successfully treated, we reluctantly chose crizotinib as a second-line treatment for ALK + NSCLC in this patient as he refused all other available treatments. Contrary to expectation, crizotinib performed well both in terms of its safety and efficacy. Our results suggest that crizotinib may provide a promising therapy option for patients with ALK + NSCLC accompanied by alectinib-induced interstitial lung disease. To our knowledge, this is a rare report of successful treatment of ALK + NSCLC with crizotinib after alectinib-induced interstitial lung disease.

Keywords

Non-small-cell lung cancer, anaplastic lymphoma kinase, molecular target drug, crizotinib, alectinib, drug-induced interstitial lung disease

Date received: 24 February 2021; accepted: 12 August 2021

Introduction

Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for 85% of all lung cancers.¹ Anaplastic lymphoma kinase positive (ALK+) NSCLC accounts for about 3%–7% of the incidence of NSCLC.² Crizotinib is a first-generation ALK inhibitor, whereas alectinib belongs to the second generation. The PROFILE 1014³ trial confirmed that crizotinib was significantly superior to standard platinum-containing chemotherapy as a first-line treatment for patients with advanced ALK + NSCLC. Subsequently, the global multicenter, randomized, head-to-head clinical phase III ALEX study⁴ showed that the median progression-free survival (PFS) of alectinib in ALK + NSCLC patients reached 34.8 months, which was 2 years longer than the 10.9 months PFS with crizotinib. Furthermore, alectinib more effectively delayed the occurrence and progression of brain metastasis. This study also confirmed the superior safety of alectinib over crizotinib. Alectinib is commonly associated with grade 1–2 adverse events, with a lower incidence of grade 3–4 adverse events than crizotinib (26% vs 52%). Alectinib also showed a better

response than crizotinib after drug resistance.⁵ Therefore, the US National Comprehensive Cancer Network (NCCN) Guidelines (2021 edition) recommend alectinib as the preferred first-line treatment for ALK + NSCLC.⁶

Hereby, we report a case of advanced NSCLC patient with ALK(+) who was successfully treated with crizotinib after alectinib-induced interstitial lung disease.

Case report

A 65-year-old man with a long history of smoking had a semi-lunar tubercle around the right lower lung on physical

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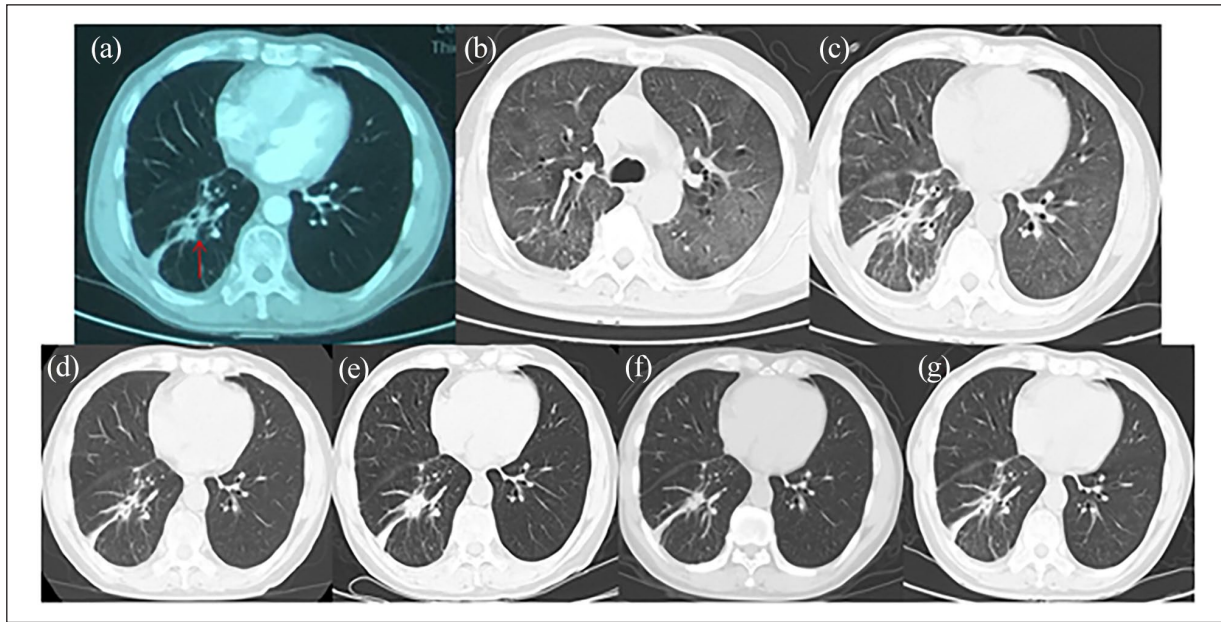


Figure 1. Chest computed tomography before and after treatment with anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs). (a) Changes after right lower lung adenocarcinoma surgery (arrow). (b) and (c) CT scan after 27 days of alectinib treatment showed bilateral interstitial changes, presenting as diffuse ground-glass shadows. (d) After corticosteroid treatment, the ground-glass shadows in both lungs disappeared. (e) One month after the withdrawal of targeted drug therapy, the tumor recurred in the right lower lung, presenting an enlarged tumor. (f) The tumor shrank after 6 weeks of crizotinib treatment. G: Crizotinib was administered for 6 months, followed up and found to be stable in the right lower lung with no ILD recurrence.

examination. Surgical intervention was performed considering the possibility of lung malignancy after thorough evaluation. Biopsy specimens were analyzed using the Ventana immunohistochemical method and were found to be positive for ALK. The final diagnosis of ALK+NSCLC was reported as: “right lower lobe onset peripheral adenocarcinoma, dirty wall of pleural biopsy+right pulmonary pleura biopsy, sp=T1cN2M1a (pleura), IVa period, ALK (IHC +), sp=1.” After being discharged, the patient was placed on oral alectinib therapy (150 mg twice a day) for postoperative treatment of AK+NSCLC of the right lower lobe. A chest computer tomography scan (CT) was performed (Figure 1(a)) after 27 days, as the patient complained of gradually worsening breathing difficulties. The patient was again hospitalized for treatment, and pulse oximetry indicated a decrease in the oxygen saturation of breath from 93% to 88% compared to room air. This easily fell below 85% on coughing. The arterial blood gas analysis showed that oxygen partial pressure was lower than normal (60 mmHg). Chest CT examination showed diffuse ground-glass opacity in both lungs (Figure 1(b) and (c)). Echocardiography, sputum tests, and other laboratory tests ruled out heart failure and infection. The diagnosis of grade 3 ILD induced by alectinib was confirmed by imaging and clinical findings. Alectinib treatment was immediately stopped and methylprednisolone (80 mg/day) was injected intravenously for 3 days. This was reduced to 40 mg/day for the next 7 days, after which the patient’s symptoms gradually disappeared and the CT images gradually returned to their postoperative

appearance (Figure 1(d)). As a result, oral prednisolone was administered at 20 mg/day. This treatment was gradually reduced and discontinued after 2 weeks. The patient strongly resisted further chemotherapy, immunotherapy, or other intravenous therapy due to concerns over their side effects.

One month later he developed a cough accompanied by right chest discomfort and CT revealed an enlarged right lower lung lesion (Figure 1(e)). Considering the lack of alternative therapies, the patient, although fully aware of the associated risk of ILD, agreed to try oral crizotinib. Subsequently, crizotinib was administered at 250 mg/day for 2 weeks. The dosage was then increased to 500 mg/day for 4 weeks, at which point a chest CT was performed indicating a reduction in the lung tumor with no recurrence of ILD (Figure 1(f)). At the most recent follow-up (6 months later), CT showed no further improvement (Figure 1(g)) and the patient experienced no change in exercise tolerance.

Discussion

In recent years, the prognosis for patients with ALK + NSCLC has significantly improved, and the median survival of advanced patients has exceeded 5 years.⁷ To date, several anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs) have been developed and approved by the Food and Drug Administration (FDA), including first-generation ALK-TKIs (crizotinib), second-generation ALK-TKIs (ceritinib, alectinib, and brigatinib), and third-generation ALK-TKIs

(lorlatinib). In previous clinical practice, these targeted drugs were mainly used in intergenerational order according to drug resistance. However, current evidence suggests that first-line treatment of ALK + NSCLC with alectinib offers a better survival benefit.

ALK-TKI-induced ILD has a low overall probability of severe adverse reactions, and, in nearly half of the cases, these occurred within 1 month of administration. In a phase 1–2 clinical trial, alectinib-induced ILD was found in 1 of 70 patients.⁸ In fact, only three of the 149 patients experienced grade 3 or grade 4 crizotinib-induced ILD,^{9,10} and 2 of the 173 patients died of crizotinib-induced ILD in a phase 3 trial.¹¹

In the present case, the patient developed ILD after taking alectinib orally for 27 days. Fortunately, this form of ILD was corticosteroid-sensitive and responded to treatment. However, the lung tumor progressed after the withdrawal of targeted drug therapy. In addition to palliative care, the treatment regimen for the occurrence of a drug-induced ILD emergency involves reactivation or initiation of an alternative medication. In general, the use of a secondary pathogenesis-causing drug would lead to a recurrent ILD and should be avoided.¹² However, this patient resisted intravenous therapy such as chemotherapy and immunotherapy, but was willing to try other types of oral ALK-TKIs. In addition, epidermal growth factor receptor TKI (EGFR-TKI) studies have shown successful treatment of ILD with erlotinib, induced by gefitinib.^{13,14} Another report showed that the same TKI could be safely administered to ALK-TKI-induced ILD patients.¹⁵ Crizotinib has also been used to successfully treat ILD caused by alectinib in the absence of prednisolone.¹⁶ Considering these reports and the fact that crizotinib and alectinib are the only two ALK-TKIs available in China, and after fully notifying the patient and his family of the risks, and obtaining their consent, we cautiously administered a small dose of crizotinib (without prednisolone) as the initial treatment, before gradually increasing it to the therapeutic dose. Fortunately, we found that the tumor gradually shrank as treatment progressed, and there was no evidence of ILD in the long-term follow-up.

Alectinib is a novel oral ALK-TKI with high selectivity. Crizotinib was the first oral small-molecule multi-target tyrosine kinase inhibitor acting on ALK, tyrosine protein and receptor tyrosine kinases (eg c-met and ros-1).¹⁷ We speculate that these differences in drug selectivity may contribute to the successful treatment of this patient with crizotinib. In addition, individual differences may also play a role, since drugs in the same class may not necessarily all cause the same adverse events.

For ALK-rearranged patients who progress on Crizotinib, the current guidelines recommend treatment with next-generation ALK TKIs, including Alectinib, Ceritinib, Brigatinib or Lorlatinib.¹⁸ Brigatinib is a second-generation ALK inhibitor which is active against various mutations that

might occur in the ALK kinase domain, and it has been developed to overcome the majority of the resistance mechanisms that arise as a result of treatment with first-generation ALK inhibitors. The trial¹⁹ studying Brigatinib showed it could also induce severe lung toxicity, typically within 24 to 48 hours from the beginning of treatment, and it could develop as dyspnea with ground-glass or interstitial opacity on CT scan. This effect was observed in 3% to 6% of patients, and seems to be more frequent in those patients pre-treated with Crizotinib, and it is dose-related. Although the patient is still being followed up and is in stable condition, given the clinical studies in the literature above, we believe that we need to be more careful when trying to use the new generation ALK-TKIs if the patient progresses.

Conclusion

In summary, although alectinib is a well-tolerated and highly effective inhibitor of ALK, special attention should be paid to the possibility of potentially severe and fatal adverse events such as interstitial pneumonia. This case suggests that crizotinib may be an important therapeutic option for non-fatal alectinib-induced ALK rearrangement of ILD in NSCLC patients. Cumulative case reports are needed to confirm our results. It is expected that under the guidance of the principles of precise targeted therapy, ALK + patients with advanced NSCLC may receive more efficient and safer treatments, improving their quality of life, and extending their survival times.

Acknowledgements

The authors thank Enago (<https://www.enago.cn/>) for English language editing.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Science and Technology Innovation 2025 Major Project of Ningbo (2019B10037).

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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