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Successful alectinib treatment after crizotinib-induced interstitial lung disease

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Abstract

A 70-year-old woman with lung adenocarcinoma, harbouring anaplastic lymphoma kinase gene rearrangement, was treated with crizotinib as third-line chemotherapy. After 2 months, crizotinib was discontinued because of the development of crizotinib-induced interstitial lung disease (ILD). Steroid treatment was then introduced and tapered off. Following complete resolution of the interstitial shadow, cytotoxic chemotherapy was initiated, and continued for over 2 years, until new intrapulmonary lesions developed. Although there was a risk of drug-induced interstitial pneumonia, alectinib was initiated as the fifth-line therapy, without steroid supplementation, as there was no alternative treatment. No recurrence of ILD was noted at 10 months. To our knowledge, this is the first report of successful alectinib treatment after the development of crizotinib-induced ILD without the use of prednisolone.

Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangement is a driver mutation for lung cancer and is found in approximately 4% of adenocarcinoma cases. In these cases, the ALK receptor tyrosine kinase is constitutively activated as a result of ALK gene rearrangement. Moreover, ALK-tyrosine kinase inhibitors (TKIs) have been reported to show excellent antitumor activity for ALK-positive lung cancer. However, 2% of patients treated with ALK-TKIs reportedly develop life-threatening drug-induced interstitial lung disease (ILD) [1]. In the present report, we describe a case of successful alectinib treatment after crizotinib-induced ILD.

Case Report

We here report the case of a 70-year-old non-smoking Japanese woman diagnosed with advanced lung adenocarcinoma who was successfully treated with alectinib following crizotinib-induced ILD. The patient was referred to our hospital in January 2012 after a chest radiograph revealed an abnormal shadow in her left lung. Systemic study indicated stage IIIA pulmonary squamous cell carcinoma (cT3N2M0). Combination chemotherapy of cisplatin plus gemcitabine was initiated. In May 2012, a bronchoscopic tumor biopsy was performed after the disease progressed (Fig. 1A); at this time, the histological diagnosis was revised to adenocarcinoma. Fluorescence in situ hybridization, as well as immunohistochemical staining, revealed ALK gene rearrangement in the tumor cells. Treatment with the ALK inhibitor crizotinib (500 mg twice a day [BID]) was initiated mid-July 2012. Concomitant administration of crizotinib, sodium risedronate hydrate (17.5 mg once a week [QW]), amlodipine besylate (5 mg once daily [QD]), famotidine (10 mg QD), and levocetirizine hydrochloride (5 mg QD) had been continued since 2010.

Although the radiological findings began to improve 3 weeks later, she presented with progressive dyspnoea, fever, and coughing mid-September 2012. Her vital signs revealed a temperature of 38.6 °C, blood pressure of 128/66, pulse rate of 92 beats/min, and respiratory rate of 23 breaths/min. No oedema was observed, whereas fine crackles were heard in the bilateral lower lung fields. Arterial blood gas analysis revealed an arterial oxygen pressure of 54.2 torr, a carbon dioxide arterial pressure of 35.0 torr, and a pH of 7.44. Chest X-ray showed a bilateral diffuse interstitial shadow, while

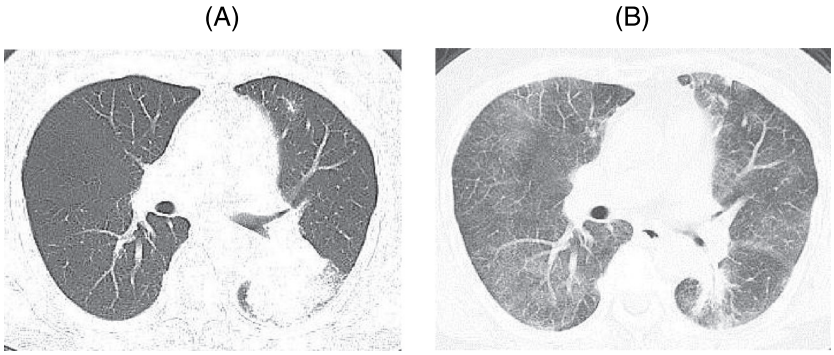

Figure 1. Chest computed tomography scans of the 70-year-old female patient. Initially, a large tumor was observed in the left lung on presentation (A). The lower lobe tumor decreased in size, however, a bilateral diffuse ground-glass opacity occurred 60 days after initiating crizotinib treatment (B).

chest computed tomography revealed a diffuse ground-glass opacity (Fig. 1B). She presented a small amount of mucinous sputum production; however, the bacterial, mycological, and mycobacterial cultures were all negative. The blood analysis showed a white blood cell count of 8200/μL (73% neutrophils, 19% lymphocytes, 5% monocytes, and 3% eosinophils) and hemoglobin of 8.7 g/dL. Although the serum levels of aspartate transaminase (31 IU/L) and alanine transaminase (21 IU/L) were in the normal ranges, the lactate dehydrogenase (316 IU/L), C-reactive protein (3.76 mg/dL; normal <0.3 mg/dL), Krebs von den Lungen-6 (1439 U/mL; normal <500 U/mL), and surfactant protein-D (225.0 ng/mL; normal <110 ng/mL) levels were all elevated. Most auto-antibodies related to collagen diseases were negative, except for an increased anti-nuclear antigen titre (1:160) with a proliferating cell nuclear antigen pattern. The samples were negative for galactomannan antigen, candida antigen, influenza antigen, mycoplasma antibody, and cytomegalovirus antibody. Electrocardiography and echocardiography showed no abnormal findings. Hence, because there was no evidence of infection, cardiac dysfunction, or collagen disease, the patient was diagnosed with crizotinib-induced ILD.

As a result, crizotinib was immediately discontinued, and intravenous high-dose methylprednisolone (1000 mg/day) was administered for 3 days. This was followed by oral prednisolone (40 mg/day), after which the symptoms and radiographic findings showed improvement. Consequently, the prednisolone was gradually tapered off and discontinued at 10 weeks. After complete disappearance of the ground-glass opacity in the lung, carboplatin–pemetrexed–bevacizumab was initiated as third-line chemotherapy at the end of October 2012; this was followed by pemetrexed–bevacizumab maintenance therapy. However, new intrapulmonary lesions developed after 25 cycles; therefore, retreatment with an ALK inhibitor was considered. The patient agreed to undergo alectinib treatment despite full awareness of the risk of ILD. Alectinib was initiated at 160 mg/day mid-March 2015, 3 days later alectinib was increased to 320 mg/day and 4 days after that to 600 mg/day. Partial tumor remission was achieved 3 weeks later. At the latest follow-up (10 months later), no recurrence of the ILD was noted (Fig. 2).

Discussion

Anaplastic lymphoma kinase-tyrosine kinase inhibitor are recommended for patients with advanced non-small-cell lung cancer with EML4-ALK rearrangement. To date, two ALK-TKIs, namely, crizotinib and alectinib, are available in Japan. While it has been established that fatal adverse events of crizotinib are relatively rare, similar to that for other molecular targeted drugs, crizotinib can, however, cause life threatening ILD in approximately 2% of patients [1] .

Approximately 50% of ALK-TKI-induced ILD cases occur within 1 month of treatment; however, our patient developed ILD 2 months after crizotinib initiation. Crequit *et al.* reported that there are two types of crizotinib-associated ILD [2]. The first type presents as severe and usually fatal ILD, generally occurring within a month of crizotinib initiation. The second type is less severe and occurs later in time, with predominant ground-glass opacities on computed tomography. Based on our findings, our case was considered to be the latter, less severe type of crizotinib-associated ILD.

Although the mechanism of TKI-induced ILD is uncertain, it has been suggested that, with regards to epidermal growth factor receptor (EGFR)-TKIs, inhibition of the EGFR signaling pathway impairs the repair of the lung epithelium [3]. In turn, this signaling alteration may cause EGFR-TKI-induced ILD. On the other hand, little is known about the mechanism of ALK-TKI-induced ILD. Kitajima *et al.* reported that surfactant protein (SP)-D may be indicators of gefitinib-induced ILD and that KL-6 is a predictor of outcome [4]. They concluded that using a combination of these markers may help to establish a differential prognosis in patients with gefitinib-induced ILD. This case report also indicated that

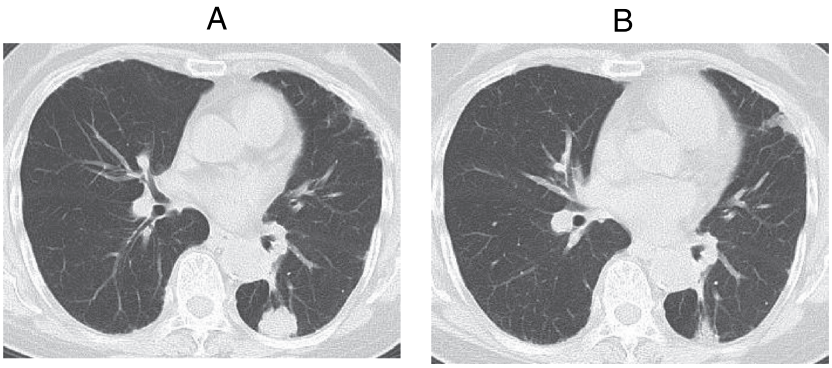

Figure 2. Chest computed tomography scans before and after alectinib treatment. After new lesions developed following 2 years of cytotoxic chemotherapy, alectinib treatment was initiated (A). Two months later, the tumor sizes were markedly reduced; moreover, no interstitial lung disease was detected (B).

the values of KL-6 and surfactant protein D measurements might be useful to diagnose the drug induced ILD.

Once drug-induced ILD occurs, the causative drug must be discontinued immediately. After recovery from the ILD, the subsequent treatment has to be carefully considered. A report described that retreatment with the same TKI could be safely performed in the presence of steroid administration in a patient with ALK-TKI-induced ILD [5]. However, it remains unclear whether alectinib treatment can cause lung injury in patients with crizotinib-induced ILD. As there is no effective alternative therapy for such cases, in the present case, we considered treatment with alectinib, which we administered without prednisolone, despite the known risks. In this case, because the patient was afraid of initiation of full dose of alectinib, we escalated the dosage step by step.

Ten months after the initiation of alectinib treatment, there were no signs of ILD in this patient. The reason for the different risks of ILD development between the different ALK-TKIs is unclear, but we speculate that it may be owing to the different inhibitory pathway of the drugs. Recently, Chino *et al.* reported successful alectinib treatment after crizotinib-induced ILD, and, to our knowledge, the present case is the first report of successful alectinib treatment after crizotinib-induced ILD without prednisolone [6]. This case report therefore indicates that it is possible to proceed to alectinib treatment in a patient with crizotinib-induced ILD, subsequent to recovery from ILD.

Finally, a progression-free survival of 30 months with alectinib has been reported, which is an excellent benefit for patients with ALK rearrangement. In addition, from a phase I/II study, alectinib presented an effective response as salvage therapy for crizotinib-resistant non-small-cell lung cancer. Therefore, we conclude that alectinib treatment ought to be considered, under careful monitoring, even in patients with prior crizotinib-induced ILD.

Disclosure Statements

No conflict of interested declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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