Ceritinib-related interstitial lung disease improving after treatment cessation without recurrence under either crizotinib or brigatinib: a case report

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Abstract: Anaplastic lymphoma kinase inhibitors (ALKi) like ceritinib are considered standard for front-line treatment of non-small cell lung cancers (NSCLC) harboring a translocation of the anaplastic lymphoma kinase (ALK) gene. We report herein a case of interstitial lung disease (ILD) that developed following a 7-month ceritinib treatment without recurrence under either crizotinib or brigatinib, two others ALKi.

Keywords: Anaplastic lymphoma kinase rearrangement (ALK rearrangement); ceritinib; diffuse interstitial pneumonitis; non-small cell lung cancer (NSCLC)

Submitted Sep 12, 2018. Accepted for publication Dec 12, 2018.
doi: 10.21037/atm.2019.01.24
View this article at: http://dx.doi.org/10.21037/atm.2019.01.24

Introduction

Lung cancer is the first cause of mortality by cancer worldwide (1), with an estimated 1.8 million new cases (12.9% of all cases) and 1.6 million deaths (19.4% of the total) worldwide in 2012 (1). Non-small cell lung cancer (NSCLC) accounts for around 85% of cases, with adenocarcinoma being currently the most common histological subtype (38.5%) (2). Since the beginning of the 21st century, several driver mutations have been detected in non-squamous cell carcinoma (NSqCC), first including adenocarcinoma and undifferentiated large-cell carcinoma epidermal growth factor receptor (*EGFR*) activating mutations, then followed by anaplastic lymphoma kinase (*ALK*) translocations (3). These oncogenic driver mutations like *EFGR* activating mutations and *ALK* rearrangements are more common in never smokers (4). Indeed, 44% *EGFR* activating mutations and 12% *ALK* rearrangements are found in NSqCC of never smokers, as compared to 11% *EGFR* activating mutations and 5% *ALK* rearrangements in overall NSqCC (4).

These driver mutations or rearrangements that are targetable have led to a new revolution in cancer treatment with significantly better patient outcomes, namely response rates of about 70%, progression free survival (PFS) between 9 to 11 months, as well as median survival time between 16.5 to 27 months (4,5) as compared to a maximum of 12 months under platinum-based chemotherapy (6). In 2014, crizotinib, a first-generation ALK inhibitor (ALKi), proved its superiority in comparison with pemetrexed-plus-platinum chemotherapy as first-line agent for ALK-positive lung cancer patients (7). However, over time, most patients develop resistance to crizotinib, which new-generation ALKi can overcome. Ceritinib, a second-generation ALKi, demonstrated significant clinical efficacy in crizotinib-refractory ALK-rearranged NSCLC patients (8). Brigatinib, another second-generation ALKi, has proven its clinical efficacy in patients who progressed under crizotinib therapy, especially in those with brain metastases (9).

Case presentation

In December 2014, an ALK-positive adenocarcinoma of the left lower pulmonary lobe staged cT4N3M1b (7th edition) was diagnosed in a 53-year-old woman, never smoker and without previous medical history. The present case had distant metastases (pulmonary, pericardial, bone, and adrenal

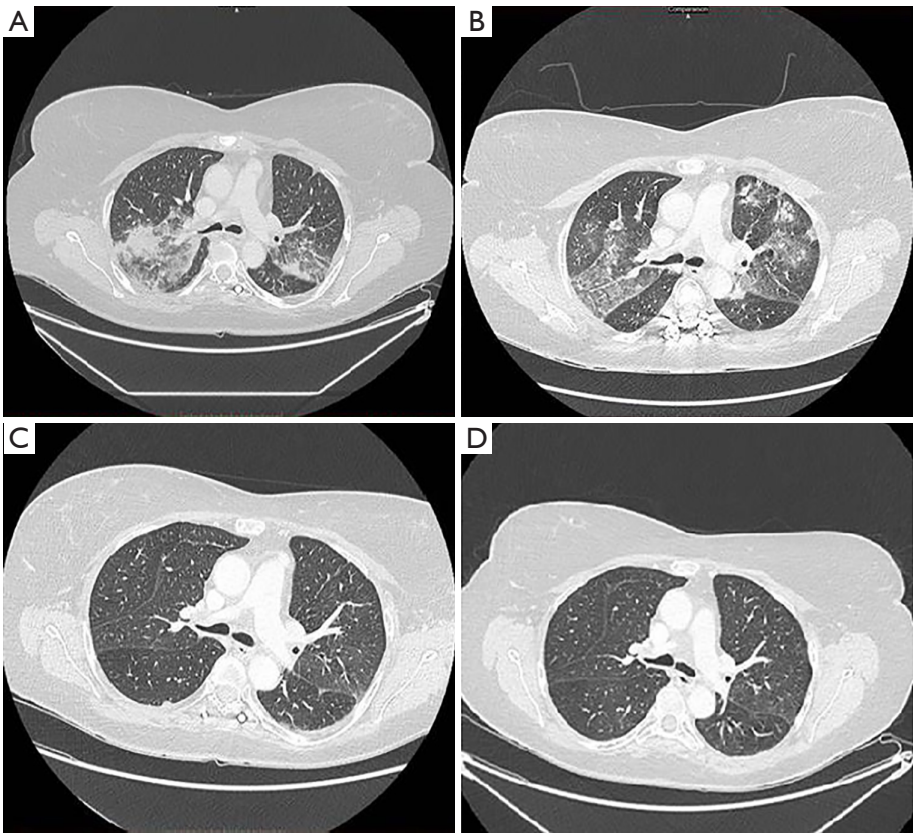

Figure 1 Thoracic CT-scan images, axial section. (A) Diffuse interstitial pneumonitis after 7 months of ceritinib; (B) three months after ceritinib interruption and corticosteroid therapy, partial regression of alveolar condensation and ground-glass opacities; (C) no diffuse interstitial pneumonitis recurrence after 3 months of brigatinib; (D) no diffuse interstitial pneumonitis recurrence after 5 months of brigatinib.

lesions). The patient was included in a clinical trial with ceritinib, with treatment initiated in February 2015. After 7 months of treatment, the patient developed progressive dyspnea with a dry cough leading to hospitalization in September 2015. A thoracic computed tomography (CT)-scan revealed alveolar condensations and ground-glass opacities of the two upper lobes, along with a thickening of the inter-lobular septa of both apexes (*Figure 1A*). Upon arterial blood gas analysis, there was a P_aO_2 of 73.2 mmHg, P_aCO_2 of 35.1 mmHg, and pH of 7.46. Blood analysis displayed a leucocyte count at 10.88×10^9/L (9.14×10^9/L neutrophils, 0.95×10^9/L lymphocytes, and 0.11×10^9/L eosinophils), hemoglobin level at 13.5 g/dL, and platelet count at 354×10^9/L. Serum C-reactive protein level was elevated at 119.3 mg/L. A bronchial fibroscopy with bronchioloalveolar lavage (BAL) was performed, with 110 mL fluid instilled and 40 mL fluid collected. BAL fluid analysis revealed 1,440,000/mL leucocytes (90% lymphocytes with a TCD4/TCD8 ratio of 1.4, 5% neutrophils, 1% eosinophils, and 4% macrophages). Bacteriological and parasitological cultures were negative. No other etiology of interstitial lung disease (ILD) was found, namely no concomitant medications, no infection, and no progressive disease. Treatment with ceritinib was immediately discontinued. After one week without ceritinib administration, along with high-dose corticosteroid therapy consisting of 1.5 mg/kg daily for 5 days, respiratory symptoms had completely regressed with normalization of blood biology, especially a serum C-reactive protein level decreased at 6.1 mg/L. The thoracic CT-scan showed a significant regression of alveolar and interstitial images (*Figure 1B*). In November 2015, crizotinib was initiated without relapse of ILD (*Figure 1C*). After 1-year crizotinib treatment, the patient developed multiple brain metastases. Thus, brigatinib was introduced in January 2017. Fourteen months after treatment initiation, there were no signs of relapse of ILD (*Figure 1D*).

Discussion

In clinical trials with ceritinib, drug-related ILD was reported to occur with a frequency of 1.1% (10). This serious adverse event has been described with all ALKi, independent of their generation, and especially with brigatinib (7%) (10). Our case described ceritinib-related ILD without recurring under two different ALKi. Our patient had no known ILD risk factors (mainly previous ILD or interstitial pulmonary fibrosis) (11). Doménech *et al.* reported a similar case of a patient with ALK-rearranged NSCLC who developed crizotinib-induced ILD without ILD relapse with brigatinib (12). On the other hand, Pellegrino *et al.* reported a case of a patient who developed brigatinib-induced ILD and lung toxicity relapse with ceritinib (10). Management of these drug-related pulmonary adverse events secondary has proven to be a challenge in current practice in thoracic oncology. Generally speaking, after eliminating all other etiological diagnoses of ILD, mainly infection, lymphangitic carcinomatosis, and other concomitant medication, the concerned drug must be stopped and corticosteroids be administered for a few weeks, whilst gradually tapering their dosages (10,13). Whereas the evolution after drug discontinuation is favorable in the majority of cases, it may be fatal in about 9% of cases (10). Ceritinib-related ILD was reversible upon discontinuation of ceritinib and steroid treatment in our patient. The introduction of another ALKi treatment did not induce ILD relapse. This observation suggests that ALK-positive NSCLC patients treated by ALKi therapy who develop ILD could continue treatment, though with a different ALKi. Several hypotheses have been proposed to identify the mechanism responsible for ALKi-related ILD in NSCLC patients. Créquit *et al.* suggested that crizotinib-related ILD could be considered as a hypersensitivity pneumonitis. Indeed, the long delay before respiratory symptoms occur, which is accounted for by a phase of drug sensitization, along with symptom resolution after treatment cessation and high-dose corticosteroid administration, as well as the relapse after drug re-introduction, which was however not attempted in our case, are all in favor of a hypersensitivity mechanism (14). Moreover, BAL fluid in our patient revealed a majority of lymphocytes with a low CD4/CD8 ratio, which likewise suggested a hypersensitivity reaction. These authors proposed a second theory, given that in their view, crizotinib-related ILD could result from an immune antitumor response. Indeed, the authors reported the case of five patients who developed ILD occurring a long time after crizotinib introduction, all patients exhibiting a favorable tumor response. In addition, PFS proved to be longer in these patients versus patients without lung toxicity (19.9 versus 6.2 months, respectively) (14). Moreover, while all ALKi may be at the origin of ILD, its incidence is apparently not identical among the different ALKi treatments. It should, however, be stressed that other studies are necessary to fully explain the pathophysiological mechanism of ALKi-related ILD. To conclude, this case suggests that the occurrence of an ALKi-related ILD should not be considered to be an absolute contraindication to use another ALK tyrosine kinase inhibitor. Indeed, while all ALKi may be responsible for ILD, lung toxicity relapse does not systematically occur under a different ALKi therapy. However, re-challenge of another ALKi to patients with previous history of ALKi-related ILD and with ILD risk factors must be approved in a collegial decision. Moreover, patients must be informed about the potential risk of ILD-relapse in order to obtain their consent. Physicians should exercise caution when re-challenging of another anti-cancer therapy to patients with previous ALKi-related ILD, especially patients with ILD risk factors. Indeed, those patients could develop severe or lethal ILD. We propose that regularly follow-up be implemented for patients who developed an ILD over the past and were then switched to another ALK tyrosine kinase inhibitor, and this in an effort to promptly detect pulmonary toxicity recurrence and discontinue treatment as necessary.

Acknowledgements

None.

Footnote

Conflicts of Interest: B Mennecier and E Quoix were investigators of clinical trials regarding crizotinib, ceritinib, brigatinib and lorlatinib. The other authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

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Cite this article as: Bender L, Meyer G, Quoix E, Mennecier B. Ceritinib-related interstitial lung disease improving after treatment cessation without recurrence under either crizotinib or brigatinib: a case report. Ann Transl Med 2019;7(5):106. doi: 10.21037/atm.2019.01.24

