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Successful treatment with brigatinib in a patient with *ALK*-rearranged lung adenocarcinoma who developed crizotinib-induced interstitial lung disease

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ABSTRACT

We present a 45-year-old patient diagnosed with anaplastic lymphoma kinase (ALK)-rearranged metastatic lung cancer who developed grade 4 interstitial lung disease (ILD) while on crizotinib treatment and was lately treated with brigatinib with no reappearance of ILD. To our knowledge, this is the first case report of successful treatment with brigatinib after crizotinib-induced ILD. Even though ILD secondary to brigatinib has been reported in clinical trials, no pulmonary toxicity has been seen in our patient, suggesting no crosslink lung toxicity between crizotinib and brigatinib.

1. Case report

A 45-year-old, non-smoker woman with a previous medical history of allergic asthma presented with progressive dyspnea in October 2015. The chest X-ray and computed tomography (CT) showed bilateral reticulonodular opacities, an opacification on the right inferior lobe and ipsilateral malignant pleural effusion confirmed by thoracocentesis (Fig. 1A–C). A bronchial biopsy showed lung adenocarcinoma with anaplastic lymphoma kinase (ALK) rearrangement by fluorescence *in situ* hybridization. The patient started front-line crizotinib 250 mg twice daily (bid) and nine days later, she went to the emergency unit complaining of worsening dyspnea and fever, with no other respiratory or heart failure symptoms. A chest X-ray showed new bilateral interstitial pulmonary infiltrates and right hydroneumothorax secondary to a prior pleural tap (Fig. 1D). The pleural fluid supported the diagnosis of empyema. Pleural fluid was macroscopically serohematic and cytobiochemical fluid analysis showed an exudate with predominance of neutrophils and low glucose levels (0.4 mmol/L), but pH could not be processed. Gram stain was positive and pleural effusion culture was positive for streptococcus gordonii sensible to penicillin. Therefore, antibiotic treatment with piperacilline-tazobactam was started and a chest tube inserted. However, the patient condition seriously deteriorated with severe dyspnea and hypoxemia and she was transferred to the intensive care unit for non-invasive ventilation. The bronchoalveolar lavage showed predominance of macrophages (89%) with only 11% of lymphocytes (mainly CD8) and bronchoalveolar lavage microbiologic culture was negative. A chest CT scan showed left pleural effusion and novel bilateral ground-glass opacities; however, an improvement of the reticulonodular infiltrates in both lungs indicated response to the treatment (Fig. 1E and F). As crizotinib-induced interstitial lung disease (ILD) was suspected, crizotinib was permanently discontinued and high-dose corticosteroid therapy was initiated. The patient experienced rapid clinical improvement and was discharged from intensive care unit 14 days later to continue treatment with antibiotics and steroids on the oncology ward. She completed 15 days of piperacillin-tazobactam that was switched to amoxicillin clavulanic acid and received steroids at 1 mg/kg. There was no fever recurrence and further cultures were negative. Patient was discharged from hospital with mild shortness of breath and continued receiving oral steroids that were progressively tapered during 45 days. However, the chest X-ray before hospital discharge revealed enlargement of the reticulonodular infiltrates, suggesting disease progression within days of stopping crizotinib. Second-line therapy with single-agent pemetrexed was started, but the tumor progressed after 3 cycles. Third-line treatment with carboplatin and paclitaxel was administered up to 6 cycles since a partial response was obtained. Five months after the last chemotherapy cycle, the patient reported headache, nausea and vomiting; brain magnetic resonance imaging (MRI) showed multiple intracranial metastases. The patient received whole-brain radiotherapy at 30 Gy in 10 fractions. A chest X-ray and CT scan showed disease progression, with significant increase of the reticulonodular infiltrates and consolidations in the lower lobes (Fig. 2A and B, respectively). The patient experienced severe dyspnea with oxygen saturation (O_2Sat) of 92–94% in room air. Brigatinib, a second-generation ALK tyrosine kinase

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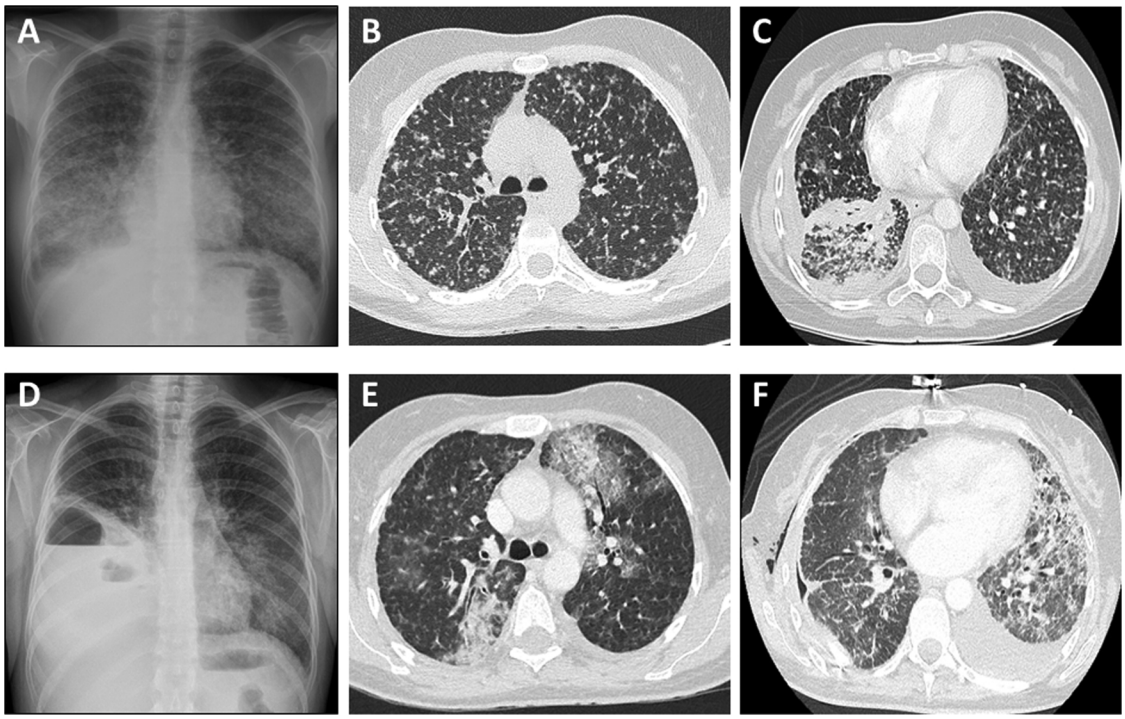

Fig. 1. Chest X-ray (A) and chest computed tomography (CT) scan performed at diagnosis showing reticulonodular infiltrates, right lung opacification and ipsilateral pleural effusion in the upper lobes (B) and lower lobes (C). Chest X-ray (D) with bilateral infiltrates and a larger pleural effusion after 9 days on crizotinib. Chest CT scan showing upper lobes (E) and lower lobes (F) revealed a left pleural effusion, bilateral ground-glass opacities as well as improvement in reticulonodular infiltrates in both lungs after 9 days on crizotinib.

inhibitor, was made available within the expanded access program and the patient was admitted to the hospital to monitor respiratory symptoms and oxygen saturation during the first week of brigatinib. Forty-eight hours after starting brigatinib 90 mg once daily (qd), the patient had significant symptomatic relief and, likewise, chest X-rays demonstrated improvement of lung opacities (Fig. 2C). One week later, the brigatinib dose was increased to 180 mg qd and she was uneventfully discharged. A chest CT scan performed 8 weeks later showed a partial response that continued to improve, with a nearly complete response in the latest chest CT scan (Fig. 2D). Moreover, a reduction in the size and number of brain metastases was observed. After 10 months of brigatinib therapy, the patient remains on treatment with no symptoms or signs of pulmonary toxicity and maintains a near-complete response.

2. Discussion

Crizotinib was approved by the European Medicines Agency (EMA) in November 2015 as first-line treatment for ALK-rearranged non-small cell lung cancer. ILD has been described in all crizotinib trials as a rare but potentially life-threatening adverse event [1,2]. An independent review of 1,669 patients treated with crizotinib in clinical trials showed an incidence of 1.2% of crizotinib-related ILD, with a median onset of 23 days after treatment initiation [1]. Symptoms were subacute and included dyspnea, cough and fever, with a rapid progression to hypoxemia and bilateral ground-glass opacities on the chest CT scan of most patients. All patients required hospitalization and 50% died due to ILD [1]. In another retrospective study of patients receiving crizotinib, six out of 26 patients developed ILD. Among the six patients with pulmonary toxicity, two clinical patterns for crizotinib ILD were described: one with severe presentation, irreversible evolution and usually fatal outcome, and a second one with less severe and reversible symptoms that might not need crizotinib withdrawal. Bronchoscopy was performed in four patients showing T-lymphocytic alveolitis with a predominant CD4 cell subset [3]. In our patient, the shortness of breath occurred as an early presentation, and the chest CT scan showed diffuse ground-glass opacity, suggesting a diagnosis of ILD. Although our patient had a predominance of macrophages and CD8 lymphocytes in the bronchoalveolar lavage, the clinical and radiological patterns suggested a diagnosis of crizotinib-related ILD that was supported by the quick improvement after crizotinib withdrawal and corticosteroid therapy. Grade 4 early crizotinib ILD is generally associated with poor outcome and a high rate of mortality [4,5]. We are unsure if the pleural effusion infection could have played a role on the onset of ILD as a previous inflammatory environment.

Clinical presentation of ILD due to crizotinib is well described in the literature [4,5]. Histopathological characteristics of ALK inhibitor-related ILD have also been described in the post-mortem analysis of a patient who exhibited juvenile fibroblast hyperplasia, nuclear swelling of aberrant alveolar cells and mild infiltration of inflammatory small round cells and neutrophils [6]. However, predisposing factors remain unclear and management of crizotinib-related ILD consists of interrupting the drug, corticosteroid treatment and oxygen therapy if needed. Reintroduction of crizotinib should be considered only in less severe cases of ILD [7,8].

One question that remains unsolved is whether to retreat the patient with the same drug (rechallenge) or to switch to another ALK inhibitor. In case studies reporting rechallenge with crizotinib in Asian patients who had crizotinib-related ILD, recurrence of lung toxicity was not reported [9,10]. Likewise, reports of patients with crizotinib-related ILD and posterior switch to alectinib, a potent and selective ALK inhibitor, have been described without ILD recurrence [11,12]. However, to our knowledge, no cases have previously been reported of treatment with brigatinib after crizotinib-related lung toxicity.

Brigatinib (AP26113) is a novel potent ALK and ROS1 inhibitor that has demonstrated activity against a large spectrum of *ALK* resistance mutations [13,14]. In the phase I/II trial, pulmonary events such as dyspnea, cough, hypoxia and pulmonary infiltrates or pneumonitis occurred within 7 days from starting brigatinib, usually within 24–48 h [13]. As the incidence of such toxicities, termed early onset pulmonary adverse events (EOPEs), was higher when starting at higher doses, a 7-day lead-in at 90 mg qd followed by a dose-escalation to 180 mg qd was evaluated, with no occurrence of respiratory events during 180 mg qd