Crizotinib-induced acute interstitial lung disease in a patient with EML4-ALK positive non-small cell lung cancer and chronic interstitial pneumonia

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To the Editor,

Recently, as the number of patients receiving new generations of anticancer agents increases, associated interstitial lung disease (ILD) is being more commonly seen. Preexisting interstitial pneumonia (IP) is considered to be one of the risk factors for development of ILD during anticancer treatment. In a prospective large cohort study of Japanese NSCLC patients, preexisting IP was an independent risk factor for development of acute ILD, regardless of whether they received gefitinib therapy or other chemotherapy [1].

Crizotinib is an orally active, small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK) that is efficacious against non-small cell lung cancer (NSCLC) with echinoderm microtubule-associated protein-like 4 (EML4)-ALK rearrangements. In recent trials, crizotinib showed marked antitumor activity with few instances of major toxicity in patients with advanced ALK-positive NSCLC [2,3]. ILD was reported as one of the most serious adverse events in these trials. However, predictive risk factors for developing crizotinib-induced ILD remain uncertain. Here, we describe an EML4-ALK positive NSCLC patient with preexisting IP who developed fatal acute ILD induced by crizotinib.

Case presentation

A 77-year-old male never-smoker of Japanese descent was diagnosed with Stage II a (T1aN1M0) lung adenocarcinoma. The patient's medical history was significant for an 11-year history of treatment for IP. He had been diagnosed with non-specific interstitial pneumonia (NSIP) at the age of 65 years based on surgical lung biopsy. He then received immunosuppressive therapy comprised of low-dose prednisolone and other immunosuppressant. He also developed myalgia and was diagnosed with polymyositis (PM) at the age of 73 years.

His first-line treatment for NSCLC was concurrent chemoradiotherapy with carboplatin and paclitaxel, and second-line treatment was pemetrexed. After a total of 11 cycles of chemotherapy with pemetrexed, treatment was withdrawn because of disease progression. Mutation analysis of a biopsied tumor specimen showed that the tumor was wild type for epidermal growth factor receptor (EGFR) mutations and revealed the presence of an EML4-ALK gene translocation. Immunohistochemical (IHC) staining for ALK protein was positive, and fluorescence in situ hybridization (FISH) analysis revealed the presence of ALK translocation. Therefore, as third-line treatment, crizotinib was administered orally at a dose of 250 mg twice daily. A chest computed tomography (CT) scan obtained prior to crizotinib administration showed a moderate amount of right sided pleural effusion and left sided reticular opacity with a predominantly peripheral distribution (Figure 1A). On the seventh day, he experienced abrupt onset of high fever, chills, and hemoptysis with low oxygen saturation. PaO_2 while breathing oxygen at a flow

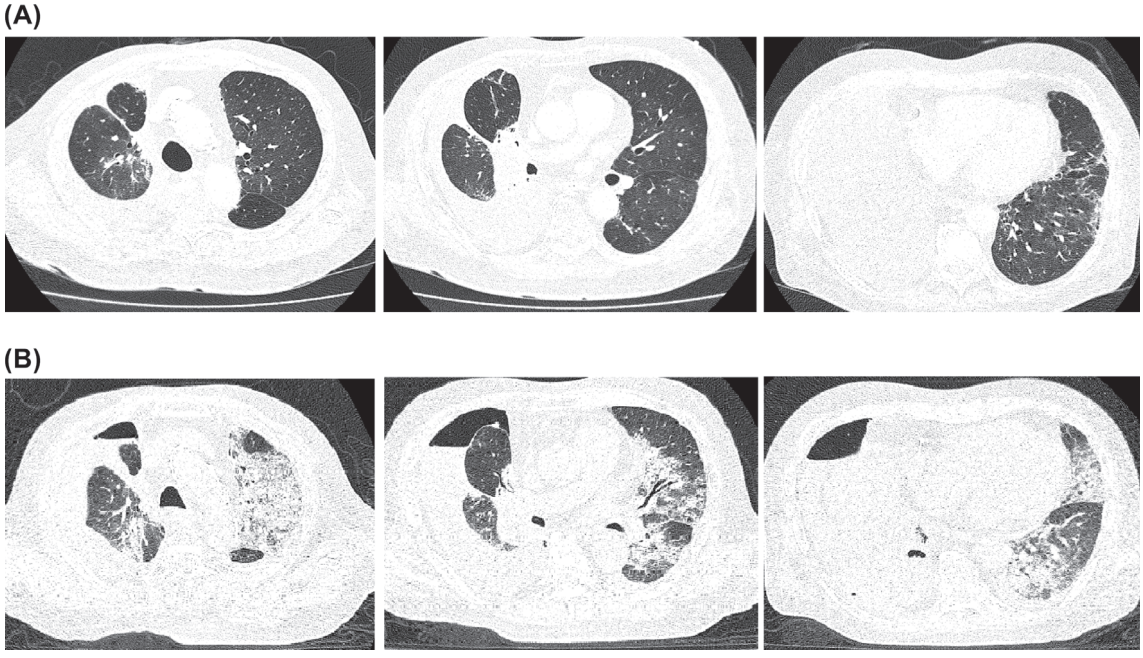

Figure 1. (A) Chest computed tomography (CT) scan obtained prior to crizotinib administration shows a moderate amount of right sided pleural effusion and reticular opacity with a predominantly peripheral distribution. (B) Chest CT scan performed on seventh day of crizotinib therapy showed new extensive bilateral ground-glass opacities and patchy consolidation associated with traction bronchiectasis.

rate of 10 L/min via reservoir mask was 70.7 mmHg. His body temperature was 38.8°C, pulse rate was 72 beats/min, respiratory rate was 30 breaths/min and blood pressure was 99/60 mmHg. On auscultation, breath sounds were decreased with crackles bilaterally. No pathologic microorganism was isolated from sputum or blood cultures, and serology test results for atypical pathogens were all negative. There was no evidence of left heart failure by echocardiography. A chest CT scan revealed new extensive bilateral ground-glass opacities and patchy consolidation associated with traction bronchiectasis (Figure 1B). Based on rapid development after the initiation of crizotinib and lack of an alternative explanation for respiratory failure and imaging results, the most probable diagnosis was considered to be crizotinib-induced ILD [4]. Crizotinib therapy was immediately discontinued, and methylprednisolone pulse therapy was initiated under non-invasive positive pressure ventilation support. Despite this therapy, he gradually deteriorated and died due to progressive respiratory failure on day 16 after the first administration of crizotinib. No postmortem autopsy was performed due to family request.

Discussion

To our knowledge, this is the first case of fatal crizotinib-induced ILD in a patient with EML4-ALK positive NSCLC and preexisting IP. Crizotinib-induced ILD is a rare event, with only three of 149 patients experiencing grade 3 or 4 ILD (no grade 5 ILD) in a recent phase 1 clinical trial [2,3]. Tamiya et al. previously reported a patient who developed fatal acute ILD after crizotinib therapy, however, there was no preexisting pulmonary fibrosis in that patient [5].

This case highlights the potential for crizotinib to induce fatal ILD and the possible association of this complication with the presence of preexisting IP. However, crizotinib may still be a treatment option for advanced ALK-positive NSCLC patients with IP for reasons as follows. First, from the results of previous trials, marked response with good tolerability is expected for crizotinib in ALK-positive NSCLC patients [2,3]. Second, it remains uncertain whether preexisting IP is a risk factor of crizotinib-induced ILD as in patients receiving other tyrosine kinase inhibitors (e.g. gefitinib or erlotinib) and cytotoxic drugs [1,6]. Third, there are no established chemotherapeutic regimens for advanced NSCLC patients with IP, although a few small studies have indicated the clinical efficacy and safety of several regimens [7,8]. Given this background, it will be necessary to investigate the feasibility of crizotinib for advanced ALK-positive NSCLC patients with preexisting IP by assessing both the efficacy and toxicity profile of crizotimib in the future.

In conclusion, ALK-positive NSCLC patients with preexisting IP may be at particular risk for crizotinib-induced ILD. Therefore, greater care is required when administrating crizotinib for NSCLC patients with IP as occurrence of ILD can be serious and potentially fatal.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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