Successful Crizotinib Retreatment after Crizotinib-Induced Interstitial Lung Disease

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CASE REPORT

We report the case of a 53-year-old Japanese woman with no smoking history, who suffered general fatigue for 2 months. Radiological screening showed a right lower lung (RLL) mass (Fig. 1), and she was diagnosed with stage IV lung adenocarcinoma (cT4N3M1b) with pulmonary, bone, and brain metastases. Fluorescence in situ hybridization revealed anaplastic lymphoma kinase (ALK) gene rearrangement. Crizotinib (ALK inhibitor, 250 mg twice daily) was initiated as first-line chemotherapy in May 2012. Symptoms and chest radiological findings improved until day 10, when she developed a non-productive cough. Despite levofloxacin treatment, the dry cough and dyspnea progressively worsened. On day 14, chest computed tomography revealed partial remission of the RLL tumor, although new bilateral ground-glass opacities were noted (Fig. 2A). Because of hypoxemia (oxygen saturation in room air was 90%), further diagnostic studies could not be performed. No pulmonary pathogens were identified and we considered the lesions to be consistent with crizotinib-induced interstitial lung disease (ILD). Crizotinib was immediately discontinued, and intravenous high-dose methylprednisolone (1000 mg daily for 3 days) was initiated, which improved her symptoms and lung shadow, although the RLL mass grew larger (Fig. 2B). As the disease progressed, we tried various regimens of conventional chemotherapy, such as carboplatin/pemetrexed, S-1, and docetaxel; all of which were ineffective. The patient and her family expressed their wish to retry the crizotinib treatment, even after the risk of recurrent ILD was explained. Crizotinib treatment was recommenced in January 2013 (250 mg twice daily), with intravenous dexamethasone (6.6 mg daily). The general condition of the patient gradually stabilized, and oxygen supplementation became unnecessary. No pulmonary toxicity recurred, and partial tumor remission was achieved (Fig. 3). The steroid dosage was tapered gradually on a weekly basis, until it was 2 mg daily. She was discharged on day 20, and at 2 months there was neither disease progression nor recurrence of ILD.

DISCUSSION

Echinoderm microtubule-associated protein-like 4 (EML4)-ALK rearrangement occurs in approximately 5% of patients with non–small-cell lung carcinoma, especially those with adenocarcinoma. Crizotinib is recommended as first-line therapy for patients with EML4-ALK–mutant lung cancer. Although its adverse effects are relatively mild, ILD is an infrequent, but life-threatening pulmonary toxicity. With crizotinib-induced ILD, permanent drug withdrawal is inevitable, although there is currently no effective alternative therapy. Drug-induced ILD has also been reported with other tyrosine kinase inhibitors (TKIs), such as epidermal growth factor receptor–TKIs (EGFR-TKIs). Recent reports describe the safety and efficacy of EGFR-TKI retreatment, even after EGFR-TKI-induced ILD, and imply the need for steroid pretreatment to reduce ILD recurrence. In case of crizotinib, there have not been any previous reports on the retreatment after crizotinib-induced ILD. Thus, dexamethasone was used in our case after the example of EGFR-TKI retreatment. In addition, a relatively long inpatient follow-up may be reasonable, as most cases of crizotinib-induced ILD are reported in the first 3 weeks.

In conclusion, this is, to our knowledge, the first report of a successful crizotinib retreatment after crizotinib-induced ILD. In selected patients with EML4-ALK–mutant lung cancer, crizotinib retreatment might be considered with careful monitoring.

REFERENCES

2. Wong DW, Leung EL, So KK, et al.; University of Hong Kong Lung Cancer Study Group. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723–1733.
FIGURE 1. PET and CT of a 53-year-old woman. Both PET scan (A) and CT scan (B) showed a mass in the right lower lobe with bilateral, multiple pulmonary nodules. PET, positron emission tomography; CT, computed tomography.

FIGURE 2. Crizotinib-induced interstitial lung disease. A, A chest CT scan performed 14 days after initiation of crizotinib treatment showing a decrease in size of the main tumor, but visible bilateral ground-glass opacities. B, CT scan 5 days after cessation of crizotinib and initiation of corticosteroid, showed improvement of air space consolidations, despite the right lower lobe tumor enlargement. CT, computed tomography.

FIGURE 3. Chest computed tomography scan before and after crizotinib retreatment. A, Before treatment with crizotinib, the scan showed the right lower mass and bilateral lung metastases. B, Two months after the initiation of crizotinib, the scan showed a partial remission of the right lower lung tumor without recurrence of interstitial lung disease.