Abstract:
A 75-year-old man with stage IV lung adenocarcinoma was treated with osimertinib due to disease progression despite having been administered erlotinib. Both an epidermal growth factor receptor (EGFR) L858R mutation on exon 21 and a T790M mutation on exon 20 were detected in a specimen from a recurrent primary tumor. Five weeks after osimertinib initiation, he developed general fatigue and dyspnea. Chest computed tomography scan revealed diffuse ground glass opacities and consolidation on both lungs. An analysis of the bronchoalveolar lavage fluid revealed marked lymphocytosis, and a transbronchial lung biopsy specimen showed a thickened interstitium with fibrosis and prominent lymphocytic infiltration. We diagnosed the patient to have interstitial lung disease induced by osimertinib.

Key words: epidermal growth factor receptor, T790M resistance mutation, osimertinib, non-small cell lung cancer, interstitial lung disease, transbronchial lung biopsy

Introduction
Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) provides dramatic antitumor activity in patients with advanced non-small cell lung cancer with active EGFR mutations. However, the majority of patients treated with EGFR-TKI frequently acquire resistance within 1 to 2 years (1-4). The most common mechanism for EGFR-TKI resistance is a T790M mutation, which has been reported to be present in approximately 50-60% (5, 6). Osimertinib was developed to overcome resistance due to a T790M mutation, with clinical response rates ranging from 59-71% (7-10). Based on these results, osimertinib has been approved for use in Japan since May 25, 2016. We herein report a case of interstitial lung disease (ILD) induced by osimertinib, which was given to treat disease progression of EGFR T790M-positive, erlotinib-resistant non-small cell lung cancer.

Case Report
A 75-year-old Japanese man, never-smoker, was diagnosed to have stage IV lung adenocarcinoma (cT3N3M1b) with brain metastasis in March 2015. A genomic analysis of the left lower lung tumor revealed an EGFR L858R mutation on exon 21. He was given erlotinib as the first-line treatment, which achieved a partial response on both the lungs and brain. After 7 months, a follow-up computed tomography (CT) scan showed the regrowth of the primary lung tumor; in this case, erlotinib was continued beyond disease progression (11).
In May 2016, re-biopsy of the primary lesion revealed both an EGFR L858R mutation on exon 21 and T790M mutation on exon 20, for which osimertinib was started as a second-line treatment. During a routine visit at 20 days after the start of osimertinib administration, lactate dehydrogenase (160 U/L) was within normal limits, but C-reactive protein (10.1 mg/dL) and white blood cell count (9,000/μL: 77.9% neutrophils, 8.4% lymphocytes, 6.3% eosinophils) were elevated on laboratory examinations. The white blood cell count (4,200/μL: 60.5% neutrophils, 24.5% lymphocytes, and 3.8% eosinophils) was normal before using the drug. At this time, he was asymptomatic and his chest X-ray and CT findings showed no evidence of pneumonitis. With a suspicion of adverse drug reaction, we discontinued osimertinib treatment and monitored his condition carefully. Two weeks later, he developed generalized weakness and dyspnea, and was then admitted to our hospital.

On examination, his body temperature was 36.0°C, but the respiratory rate was 24/min, oxygen saturation was 90% at room air; there were inspiratory fine crackles on both lung fields. A chest CT scan revealed diffuse ground glass opacities and areas of patchy consolidation on both upper
Osimertinib is an oral, potent, irreversible EGFR-TKI that is selective for both EGFR-TKI-sensitizing mutations and T790M resistance mutation (12). Compared with previous EGFR-TKIs, osimertinib shows significantly less in vitro activity against wild-type EGFR (12), and it is supposed to be less toxic than the first- and second-generation EGFR-TKIs. However, in clinical trials of osimertinib, which excluded patients with a past history of ILD, pneumonitis/ILD occurred in 2-4% of patients (grade 1-2: 1.0-3.2%, grade 3-4: 0-1.5%, fatal: 0.4-0.5%) (8-10), an incidence that was not much different from that of the previous EGFR-TKIs. In this case, grade 3 ILD developed about 5 weeks after osimertinib administration, although the patient had experienced no pulmonary side effects during the prior erlotinib treatment.

In our case, DLST for osimertinib was negative. The test, which can only detect the presence of sensitization, had been widely used in Japan for the diagnosis of drug-induced ILD. DLST has been reported to only be slightly helpful in detecting the causative agents (13), and a negative test result does not rule out causation between the suspected drug and ILD. The mechanism of osimertinib-induced ILD remains unclear. Given the fact that osimertinib induced ILD in patients who had no pulmonary toxicities during a prior treatment with first- or second-generation EGFR-TKI, the mechanism of ILD may be different for third-generation EGFR-TKIs.

There have been several studies that focused on the CT patterns of drug-induced ILD. According to a retrospective analysis on gefitinib-induced ILD by the West Japan Thoracic Oncology Group, the CT findings were classified into four patterns: (A) a nonspecific area with ground glass attenuation; (B) multifocal areas of airspace consolidation; (C) patchy distribution of ground glass attenuation accompanied by interlobar septal thickening; and (D) extensive bilateral ground glass attenuation or airspace consolidation with traction bronchiectasis (14). Of 51 ILD cases in this report, 24, 7, 1, and 12 cases had CT patterns A, B, C, and D, and the mortality rate in each pattern was 31.0%, 28.6%, 0%, and 75.0%, respectively. Based on this classification, our case presented with predominantly pattern A and partially pattern B, which was confirmed by the histology of the TBLB specimen as non-specific interstitial pneumonia. Pronounced lymphocytosis on a BAL fluid analysis was likewise supportive of this diagnosis, as well as indicative of a good response to steroid therapy.

During the publication process of this case report, there have been a few reports published on ILD associated with osimertinib. Mamesaya et al. reported a case of osimertinib-induced mild symptomatic ILD after treatment with anti-PD1 antibody, in which the CT pattern was compatible with hypersensitivity pneumonitis (15). Noonan et al. reported transient asymptomatic pulmonary opacities, including ground-glass opacities, peribronchial nodules, and subpleural nodules, developed in 7 of 20 patients during osimertinib treatment (16). Interestingly, these reports suggest that osimertinib-induced ILD has various radiological patterns including unrecognized patterns shown in previous EGFR-
TKIs and steroid therapy might not be needed if the severity is below grade 2. In our case, however, the patient had symptomatic ILD requiring oxygen supplementation, and the early use of steroids was thought to be effective considering the mortality rate of the CT patterns described above.

The onset of ILD induced by osimertinib therefore cannot be predicted based on the current data (10, 15, 16). The chest condition of patients treated with osimertinib should be carefully monitored, considering the possibility of interstitial pneumonitis, even without a prior history of pulmonary toxicity to the same drug class. The continued accumulation of detailed information and further analysis of radiologic and histologic patterns of osimertinib-associated ILD are therefore needed.

The authors state that they have no Conflict of Interest (COI).

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