Title

Successful re-administration of osimertinib in osimertinib-induced interstitial lung disease with organized pneumonia pattern: a case report and literature review

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Abstract

Osimertinib is the standard therapy for epidermal-growth-factor-receptor (EGFR)-mutant lung cancers. Herein, we report a case of osimertinib-induced interstitial lung disease (OsiILD) with organizing pneumonia (OP) pattern and provide a literature-based review. Six months after osimertinib administration, a 75-year-old woman with right pleural carcinomatosis developed ILD with OP pattern. After salvage chemotherapy, osimertinib with corticosteroid was successfully re-administered. Literature review suggested that 1) OsiILD with OP pattern was rare but should be recognized, 2) re-administration of osimertinib in OsiILD was successful in selected patients. A criterion that determines whether a patient would benefit from re-administration is warranted.

Key words

Osimertinib; drug-induced ILD; reversed halo sign; organizing pneumonia pattern; re-administration

Introduction

The discovery of driver mutations has drastically changed clinical practice in patients with lung tumors. The management of lung cancer with appropriate oncoprotein inhibitors is vital for patient survival (1). Osimertinib is a third-generation irreversible epidermal-growth-factor-receptor (EGFR)-tyrosine kinase inhibitor (TKI) that has positively changed the standard treatment for non-small-cell lung cancer harboring EGFR T790M mutation (2-4). Therefore, continued treatment with osimertinib is crucial for patients with EGFR-mutant lung cancer.

Unfortunately, some patients discontinue the use of EGFR-TKIs due to toxicities. Drug-induced interstitial lung disease (ILD) is the most common serious adverse event that occurs during EGFR-TKI treatment. Previous clinical trials have reported that osimertinib-induced ILD (OsiILD) occurred in 2–4 % of patients (2-4). However, only few case reports describing OsiILD have been published, and the specific clinical features are not fully understood. Notably, some cases reported successful re-challenge of patients with osimertinib, even after suffering from OsiILD. Herein, we report the case of a patient having OsiILD with OP pattern, re-challenged with osimertinib and provide a literature-based review.

Case

A 75-year-old woman with no history of smoking or allergies had a postoperative recurrence of lung adenocarcinoma harboring the EGFR exon 19

deletion. She developed cancer-related pleural effusion, which disseminated to the right lung. The patient's Eastern Cooperative Group Performance Status (PS) was grade 1; thus erlotinib was administered. Three months after initiation of erlotinib, pleural dissemination and effusion were reduced. (Fig 1A, B). However, pleural dissemination and effusion increased 1 year after beginning the erlotinib treatment. Genetic testing of the pleural fluid revealed EGFR exon 19 deletion and EGFR T790M mutation in cancer cells. The patient's PS maintained at grade 1. Thus, osimertinib was provided, and pleural dissemination to the right lung almost disappeared 3 months after the initiation (Fig.1C, D); however, the patient complained of cough 6 months after starting osimertinib administration. A chest high-resolution computed tomography (HRCT) scan revealed patchy consolidation with a reversed halo sign in the left lower lung lobe (Fig.2A, B). We suspected that the ILD with an OP pattern was induced by osimertinib; therefore, the anti-cancer drug was immediately discontinued, and she was admitted to our hospital for diagnosis and treatment. At that time, her oxygen saturation was 98 % in room air. Therefore, we thought the lung injury was mild based on "Consensus statement for the diagnosis and treatment of drug-induced lung injuries" edited by the Japanese respiratory lung society (5).

A bronchoscopy was performed on day 2 following hospitalization. We performed a transbronchial lung biopsy from the right posterior segment (S2). The pathological examination did not detect specific findings, including the existence of malignant cells or granuloma. The cellular composition of the bronchoalveolar lavage (BAL) fluid was the following: lymphocytes, 58.5 %;

eosinophils, 0.5 %; neutrophils, 0 %; monocytes, 3.0 %, and macrophages, 38.0 %. The CD4/CD8 ratio was 0.20. Cytology and polymerase chain reaction test for *Pneumocystis jirovecii* of the BAL fluid was negative. The screening of general bacterial culture and acid-fast *Bacillus* smear and culture were all negative. Blood tests to rule out infections were performed, and the results were follows; procalcitonin ＜0.05 ng/mL; (1,3)-beta-D-glucan ＜6.0 pg/mL; cryptococcal antigenemia: negative; Interferon-gamma release assay （T-SPOT.TB ®): negative, cytomegalovirus viral antigen (pp65.C7-HRP): negative, and anti-mycoplasma pneumoniae IgM antibody: negative. The concentrations of serum Krebs von den Lungen-6 and surfactant protein-D were 1011 U/mL (reference range, 0-500 U/mL) and 77.3 ng/mL (reference range, 0-110 U/mL), respectively. Therefore, the patient was diagnosed with OsiILD. As expected, the consolidation shadows gradually improved with 0.6 mg/kg prednisolone (30 mg) (Fig. 2C). Prednisolone was tapered as follows: 30 mg daily for 1 week, 20 mg daily for 1 week, 15 mg daily for 4 weeks, 10 mg daily for 2 weeks. After that, 5 mg of prednisolone was continued. Fortunately, ILD did not recur during the tapering. After tapering the prednisolone dose, the patient was treated with cytotoxic chemotherapy consisting of carboplatin, paclitaxel, and bevacizumab; however, her treatment was discontinued due to the onset of grade 3 peripheral neuropathy. Additionally, the right plural effusion gradually increased again during the drug holiday (Fig.2D). Her Eastern Cooperative Group PS was grade 1. The patient and her family had strong will to continue the treatment and provided informed consent to re-administer osimertinib with a

maintenance dose of 5 mg prednisolone daily. As a result, the patient has been successfully treated with osimertinib without recurrence of ILD for 7 months (Fig.2E).

Discussion

Herein, we reported a case of a patient with OsiILD with OP pattern who was successfully re-administered with osimertinib. Table 1 shows previous case reports of OsiILD (6-13). Our literature-based review suggested that ground-glass opacity was the most common HRCT finding, but some cases evidenced OP pattern. Our case presented patchy consolidation with a reversed halo sign, indicating an OP pattern. The frequency of OP pattern in OsiILD is unclear. Currently, few cases of osimerinib-induced ILD with OP pattern have been reported, although it was reported as a characteristic pattern of first generation TKIs-induced ILD (14-16) (Table 2).

Interestingly, the re-administration of osimertinib was successful in 83 % of the cases (5 in 6 cases) in the literature-based review. In general, ILD induced by EGFR-TKIs such as gefitinib or erlotinib is severe, and approximately one-third of these cases are fatal (17, 18). Similarly, fatal cases have been reported in clinical trials for osimertinib (4). To date, there is no consensus regarding the safety and efficacy of re-administering EGFR-TKIs in patients with EGFR-TKI-induced ILD. However, even though the literature shows a high success rate with re-administration of osimertinib, we must be cautious. The high success rate may be due to positive publication bias. In contrast, considering that osimertinib has different biological features such as

considerably lesser activity against wild-type EGFR than other EGFR-TKIs (19), disease severity, mortality, and biology of OsiILD might be different from those of EGFR-TKI-induced ILDs. Recently, several groups reported that osimertinib could induce transient asymptomatic pulmonary opacities (TAPOs) in 20-35 % of the patients (20-22). The radiological patterns of TAPOs included ground-glass opacity, peribronchial and subpleural nodules, and cryptogenic organizing pneumonia and/or simple eosinophilic pneumonia. According to the reports, these patients with TAPOs could be treated with continuous osimertinib therapy or a transient drug holiday followed by osimertinib re-administration (20-22). One explanation for the high success rates of osimertinib re-administration in our review might be that some patients may have developed TAPOs and not OsiILD. Thus far, there are no definitive ways to confirm whether pulmonary opacities are drug-induced ILD or TAPOs. Further assessments of the radiological patterns and BAL data are required to investigate this clinical issue.

In conclusion, re-administration of osimertinib for OsiILD might be feasible in selected cases. Further studies are required to identify the clinical features or specific biomarkers of OsiILD to select which ILD patterns or patients can be treated or safely re-administered with osimertinib.

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Figure legend

Figure 1. The effect of epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI). Black arrow indicates plural dissemination. (A, B) Chest high-resolution computed tomography (HRCT) image 3 months after the initiation of erlotinib treatment. Right pleural dissemination and effusion were reduced. (C, D) Chest HRCT images 3 months after the initiation of osimertinib treatment. Right pleural dissemination and effusion were once again reduced.

Figure 2. The clinical course of osimertinib-induced interstitial lung disease with an organizing pneumonia (OP) pattern. (A) Chest HRCT image 3 months after the initiation of osimertinib treatment. No evidence of lung tumor was detected in the lungs. (B) Chest HRCT image 6 months after starting osimertinib treatment, showing patchy consolidation (arrow). Some of the consolidation accompanied a reversed halo sign (arrow head). Red arrow indicates lung lesion on which lung biopsy was performed. Lung cancer cells were not detected. (C) Chest HRCT image after 46 days of corticosteroid treatment, showing improvement in the abnormal shadow. (D) Chest HRCT image after cytotoxic chemotherapy, indicating an increased right plural effusion. (E) Chest HRCT image after 4 months of osimertinib re-administration, presenting decreased right pleural effusion without recurrence of ILD.