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SHORT COMMUNICATION

Successful rechallenge with erlotinib in a patient with EGFR-mutant lung adenocarcinoma who developed gefitinib-related interstitial lung disease

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Abstract Small-molecule tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (*EGFR*) pathways are used clinically for patients with non-small cell lung cancer (NSCLC). It is well established that somatic mutations in the kinase domain of the *EGFR* (Lynch et al. in N Engl J Med 350:2129–2139, 2004; Paez et al. in Science 304:1497–1500, 2004) are strongly associated with the tumor response and clinical outcomes in patients with NSCLC receiving EGFR-TKIs (Mitsudomi and Yatabe in Cancer Sci 98:1817–1824, 2007). Although the most common adverse events are skin rash and diarrhea, the most serious adverse effect reported is drug-related interstitial lung disease (ILD) (Inoue et al. in Lancet 361:137–139, 2003; Ando et al. in J Clin Oncol 24:2549–2556, 2006). The precise mechanism underlying the development of drug-related ILD remains unknown. Here, we describe a case of *EGFR*-mutant NSCLC who was rechallenged with the small-molecule *EGFR* antagonist erlotinib after developing gefitinib-related ILD.

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Case report

A 28-year-old woman who had never smoked, but had been detected to have multiple lung nodules on radiological screening was admitted to our hospital in May 2008. A transbronchial lung biopsy revealed the diagnosis of well-differentiated adenocarcinoma. Soon after admission to the hospital, the physical condition of the patient worsened. She had moderate respiratory distress on effort. Chest computed tomography (CT) demonstrated multifocal alveolar consolidations consistent with the diagnosis of bronchioloalveolar carcinoma, together with the interstitial shadows of carcinomatous lymphangitis. She was started on treatment with gefitinib at the dose of 250 mg daily, as the first line chemotherapy, in May 2008. On day 3 after the start of gefitinib, the symptoms began to improve, as also the chest radiological findings. The gefitinib therapy was well tolerated, except for the development of a grade 2 acne-like skin rash. Examination of a lung biopsy specimen revealed the diagnosis of adenocarcinoma with an in-frame deletion in exon 19 of *EGFR* [1–3].

On day 28 after the initiation of gefitinib, the patient developed generalized fatigue and low-grade fever. She also had moderate respiratory distress on effort. She needed nasal oxygen supplementation (1.0 L/min). A chest CT showed bilateral diffuse ground-glass infiltrates and some areas of patchy consolidation (see Fig. 1). We could not perform bronchoscopy to confirm the diagnosis of the interstitial opacity with a chest CT, because the patient did not agree with this examination. We considered these

lesions to be consistent with gefitinib-related ILD [4, 5], both clinically and radiographically. Gefitinib therapy was immediately discontinued, and the patient was administered intravenous high-dose methylprednisolone (1,000 mg daily for 3 days). Her symptoms and chest radiological findings improved. The steroid dose was tapered from day 4 to day 33 (oral prednisolone, 30 to 15 mg daily). In the drug-induced lymphocyte stimulating test (DLST), the stimulation index (SI) is defined as the counts per minute obtained with the allergen divided by the counts per minute of the negative control. The DLST is considered positive if the SI is 180% or greater. In this case, the SI was 193% for gefitinib, and the DLST yielded a positive test result in July 2008.

On day 34 after the start of steroid therapy, in August 2008, she was started on conventional chemotherapy, consisting of carboplatin (AUC 6) and paclitaxel (200 mg/m^2), as second-line chemotherapy, in combination with oral prednisolone (10 mg daily). Subsequently, she developed grade 3 neutropenia and respiratory distress, and radiological evaluation showed progressive disease (PD). Consequently, docetaxel (60 mg/m^2) administration was attempted as third-line treatment in September 2008. She, however, again developed grade 3 neutropenia, grade 2 nausea and vomiting and grade 2 peripheral neuropathy, and also radiological evidence of PD. Her respiratory distress on effort became worse, and she needed nasal oxygen supplementation (3.0 L/min). Although the patient had developed ILD during the gefitinib therapy, it appeared that the EGFR-TKI was certainly effective against the cancer cells. Therefore, erlotinib, another EGFR-TKI, began to be administered as the patient and her family expressed their wish to receive the treatment even after being explained thoroughly the risk of recurrent ILD.

The patient was given oral erlotinib (50 mg daily, which is one-third of the currently approved dose) concurrently with oral prednisolone (0.5 mg per kg; 30 mg daily) in October 2008. After the start of this treatment, the general condition of the patient began to stabilize gradually. She experienced grade 2 skin rash and grade 1 diarrhea, but no other significant adverse effects. Partial response to erlotinib therapy was noted (see Fig. 2). The therapy was well tolerated and led to a prolonged stable disease phase without the development of erlotinib-related ILD. The steroid dose could be tapered until 5 mg daily on a monthly basis. In late June 2009, the tumor tended to get worse radiographically. Therefore, erlotinib was increased to 75 mg daily. Although she had been administrated erlotinib for life, she was dead in August 2009. The patient had received treatment with erlotinib during ten months in total.

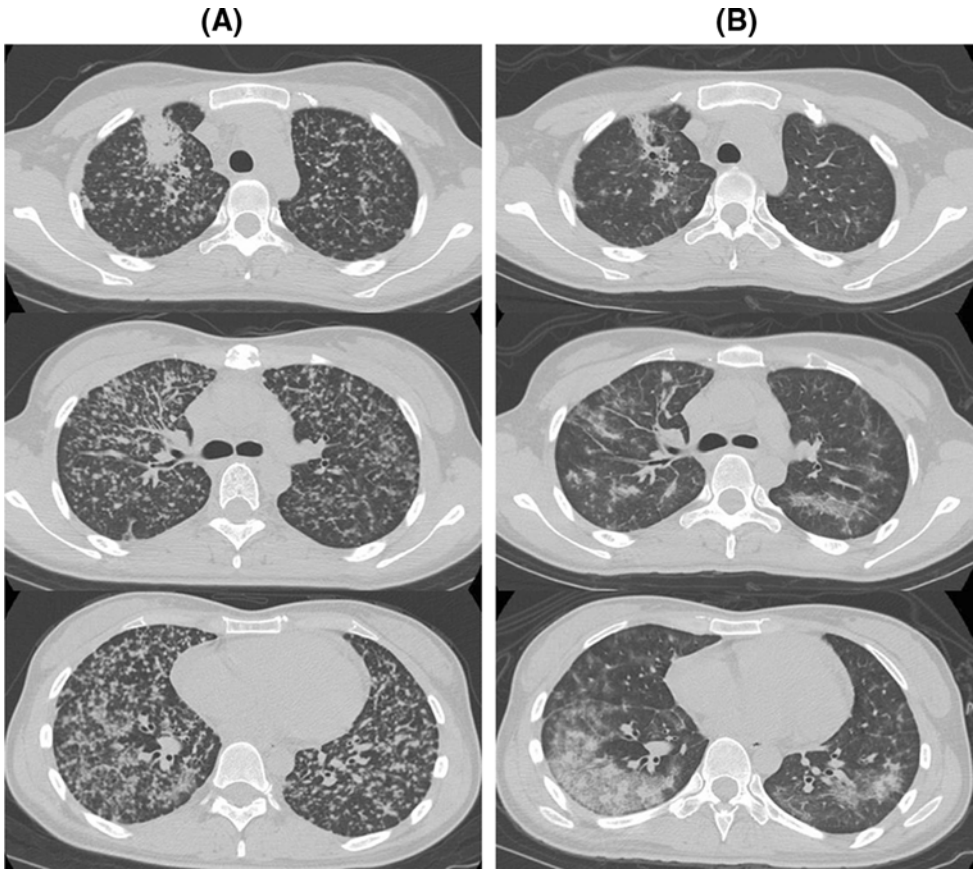

Fig. 1 Chest CT image of the patient before (**a**) and after (**b**) gefitinib therapy. Although gefitinib was certainly effective against the tumor, on day 28 after the initiation of gefitinib, the patient showed evidence of development of drug-related ILD

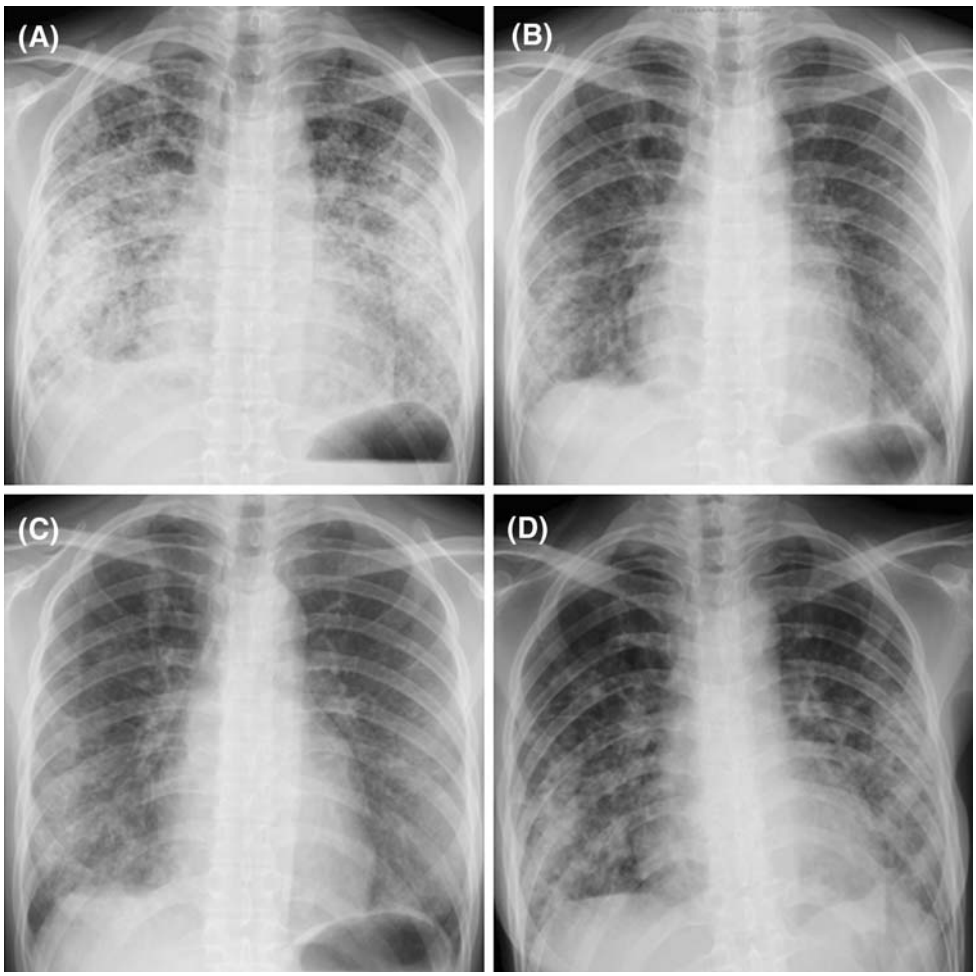

Fig. 2 Chest radiological images during the course of erlotinib therapy; before erlotinib initiation (**a**), on day 9 (**b**), 4 months (**c**) and 8.5 months (**d**) after the initiation of erlotinib. These chest X-rays showed marked radiological response and long stable disease to erlotinib therapy

Discussion

Both gefitinib and erlotinib are adenosine triphosphate-competitive inhibitors of *EGFR* and share the same chemical structure. In a phase I trial of gefitinib, the maximum tolerated dose was 800 mg daily, and antitumor activity was observed at all doses [6]. The currently approved dose of gefitinib was determined based on the data from a large phase II trial (IDEAL 1 [7] and 2 [8]); consequently, 250 mg daily has been the recommended dose. On the other hand, the approved dose of erlotinib used for the patient with NSCLC was the maximum tolerated dose, that is, 150 mg daily, identified in phase I trials [9]. Therefore, it was considered that there may be some differences in the antitumor activity and the frequency of adverse effects between the two drugs. In patients with *EGFR*-mutant NSCLC, the optimum dose of EGFR-TKIs was not investigated after the approval of gefitinib and erlotinib. Autophosphorylation of the mutant *EGFR* protein is inhibited by gefitinib at 10- to 100-fold lower concentrations than those that are necessary to inhibit wild-type *EGFR* [2, 10]. It might therefore be unnecessary to use a dose based on the maximum tolerated dose of EGFR-TKI in patients with *EGFR*-mutant NSCLC.

ILD has not been reported to occur more frequently with erlotinib than with gefitinib. The worldwide incidence of gefitinib- or erlotinib-related ILD is about 1%, and gefitinib-related ILD was reported a prevalence of 3.5% and mortality of 1.6% in Japanese population [5]. There has been no evidence of dose dependency or allergic reaction in relation to the development of drug-related ILD. In our present patient, erlotinib was administered at a reduced dose and in combination with prednisolone, because the tumor had an active *EGFR* mutation in exon 19 and the DLST was positive for gefitinib. It is difficult to find the next effective treatment for patients with NSCLC developing ILD in response to EGFR-TKIs, even if the patients have active *EGFR* mutations. A reduced dose of erlotinib administered in combination with steroid therapy seems to be a potential therapeutic option for the treatment of selected patients with advanced NSCLC with *EGFR* mutations who develop gefitinib-related ILD, although it is necessary to pay attention to the possible of development of recurrent ILD.

In this case, we used erlotinib with concurrent steroid therapy in a patient with active *EGFR* mutation who developed gefitinib-related ILD. Thus, erlotinib may be considered as a potential therapeutic option in patients with *EGFR*-mutant NSCLC who develop gefitinib-related ILD. EGFR-TKIs are key drugs with clinical benefit in patients with *EGFR* mutations. Failure of gefitinib is generally believed to be associated with cross-resistance to erlotinib. However, the optimal treatment after failure of EGFR-TKI therapy is still unknown. Further studies are needed to elucidate the mechanism to the strategy of NSCLC treatment in classification of the corresponding mutational status of *EGFR*.

Conflict of interest statement The authors indicated no potential conflicts of interest.

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