Successful erlotinib rechallenge after both gefitinib- and erlotinib-induced interstitial lung diseases

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Abstract
Epidermal growth factor receptor tyrosine kinase inhibitors, gefitinib and erlotinib, are effective for advanced nonsmall-cell lung cancer with epidermal growth factor receptor gene mutation. However, interstitial lung disease induced by these drugs is sometimes fatal, and discontinuation of the medication is the principle approach once this occurs. There are, however, some reports of cases in which rechallenge of gefitinib or erlotinib was successful, and it remains unclear when or how rechallenge should be attempted. We report the first successful case of erlotinib rechallenge after both gefitinib- and erlotinib-induced interstitial lung diseases. Our case suggests that, in interstitial lung disease induced by an epidermal growth factor receptor tyrosine kinase inhibitor, rechallenge with concurrent glucocorticoid administration and gradual increase of dosage could be a clinical option if imaging does not show a diffuse alveolar damage pattern, and if no alternative therapy is available.

Introduction
Progression-free survival time of advanced non-small cell lung cancer with epidermal growth factor receptor (EGFR) gene mutation has been improved by EGFR tyrosine kinase inhibitors (EGFR-TKI), such as gefitinib [1] and erlotinib.

However, interstitial lung disease (ILD) is a fatal complication requiring immediate discontinuation of the drug. After discontinuation, because no better alternative therapy is available, prognosis might be poor. Cases of EGFR-TKI rechallenge after EGFR-TKI-induced ILD have been reported since 2005 [2], but it is still unclear when or how to rechallenge EGFR-TKI.

Here, we present a successful case of erlotinib rechallenge after both gefitinib- and erlotinib-induced ILDs. To our knowledge, this is the first case of successful control of recurring ILDs induced by both gefitinib and erlotinib.

Case Report
A 62-year-old nonsmoking Japanese woman who had a slight cough for 2 months was referred to our hospital because of scattered lung nodules found on her chest X-ray. Radiological examinations revealed a dominant left upper lung mass, multiple pulmonary nodules (Fig. 1A), and adrenal and brain metastases. Transbronchial examination gave a diagnosis of stage IV lung adenocarcinoma. She was started on conventional chemotherapy of carboplatin and paclitaxel as first-line chemotherapy, followed by 35 Gy of whole-brain irradiation. Radiological evaluation of the carboplatin and paclitaxel showed stable disease.

Because an EGFR gene exon 19 deletion was detected when whole-brain irradiation was finished, 250 mg/day gefitinib, an EGFR-TKI, was started. A week later, cough and chest radiology began to improve with no major adverse effects. On day 29 of gefitinib treatment, nonproductive cough and dyspnea were observed. Her oxyhemoglobin saturation was 95% under room air. Although chest computed tomography showed drastic improvement, diffuse ground glass opacity appeared (Fig. 1B). Because the study showed no signs of infection, gefitinib-induced ILD was likely. Gefitinib was discontinued immediately, and 10 mg/day oral prednisolone was administered for a week, which resulted in improvement of her symptoms and ground glass opacity. 7 weeks after gefitinib discontinuation, the lesions regrew (Fig. 1C). After strict informed consent for ILD recurrence risk, erlotinib,
another EGFR-TKI, was started. The dose was increased from 25 mg every other day, then 25 mg/day, to 50 mg/day. No glucocorticoid was administered concurrently. The disease responded until dry cough and diffuse ground glass opacity recurred on day 282 (Fig. 1D). Because there were neither signs of infection nor administration of additional drugs, erlotinib-induced ILD was highly suspected. Erlotinib was stopped, and 20 mg/day oral prednisolone was administered for 2 weeks and 10 mg/day was then maintained.

Thirty-three days after stopping erlotinib, the disease worsened (Fig. 1E). At her request, erlotinib was rechallenged with concurrent 10 mg/day oral prednisolone after strict informed consent. The dose was increased from 25 mg every other day to 25 mg/day. After 2 months, the tumor responded (Fig. 1F). However, malignant pleural effusion appeared 5 months after rechallenge, and the dosage was increased to 50, 75, and 100 mg/day. Erlotinib rechallenge lasted 258 days without ILD recurrence until 2 days before death. The total clinical period was 25 months.

**Discussion**

The principal approach for drug-induced ILD is discontinuation of the drug. Rechallenge of the drug should be
avoided because it would provoke extended lung toxicity. EGFR–TKI-induced ILD is not an exception. However, because a better regimen besides EGFR-TKI is often not available, some exceptional cases of EGFR-TKI rechallenge after EGFR-TKI-induced ILD have been reported since 2005 [2]. Among such exceptional cases, this is the first successful case of erlotinib rechallenge after both gefitinib- and erlotinib-induced ILDs.

EGFR–TKI-induced ILDs have a variety of radiological shadows. Some have diffuse alveolar damage (DAD) pattern, and others have non-DAD pattern such as organizing pneumonia and hypersensitive pneumonia. DAD pattern shows extensive bilateral ground glass opacity or airspace consolidation with traction bronchiectasis. In an imaging study of gefitinib-induced ILDs [3], 70 ILD cases were found, among which only 20 had DAD pattern. While the average mortality rate of all 70 cases was 44.3%, that of 20 DAD pattern cases was 75%. DAD pattern was never seen in radiological images reported in successful EGFR-TKI rechallenge [4]. Both ILDs in the present case also have diffuse ground glass opacity suggesting non-DAD pattern. EGFR-TKI rechallenge is an option if the ILD image does not show DAD pattern.

Because allergic or immunological reaction can cause ILD [5], concurrent glucocorticoid administration can be effective in EGFR-TKI rechallenge. In a literature review of EGFR-TKI rechallenge [4], rechallenges with glucocorticoid never produced recurrence of ILD, while recurrence was observed without glucocorticoid. In our case, ILDs also occurred without glucocorticoid in gefitinib treatment and in the first erlotinib treatment. Under concurrent glucocorticoid administration, ILD did not occur during erlotinib rechallenge, and erlotinib dose was increased to 100 mg/day.

In a case of EGFR-TKI rechallenge, gradual increase of dosage, as in our case, can be clinically safer to confirm absence of immunological reaction. In previous reports of EGFR-TKI rechallenge, rechallenge was started with a regular dose, and gradual increase of dosage was not attempted. There is no evidence proving that gradual increase of dosage is safer; however, dosing up seems to be a careful choice in actual clinical situations.

In conclusion, we experienced the first successful case of erlotinib rechallenge after both gefitinib- and erlotinib-induced ILDs. In a case of EGFR-TKI-induced ILD, if the imaging does not show DAD pattern, and if no alternative option is available, EGFR-TKI rechallenge with concurrent glucocorticoid administration and gradual increase of dosage, under strict informed consent, has the potential to achieve better survival.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

1. Mitsudomi T, Morita S, Yatabe Y, et al. 2010. Gefitinib versus cisplatin plus docetaxel in patients with non-small cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTGO3405): an open label, randomised phase 3 trial. Lancet Oncol. 11:121-128.

2. Yano S, Nakataki E, Ohtsuka S, et al. 2005. Retreatment of lung adenocarcinoma patients with gefitinib who had experienced favorable results from their initial treatment with this selective epidermal growth factor receptor inhibitor: a report of three cases. Oncol. Res. 15:107-111.

3. Endo M, Johkoh T, Kimura K, et al. 2006. Imaging of gefitinib-related interstitial lung disease: multi-institutional analysis by the West Japan Thoracic Oncology Group. Lung Cancer 52:135-140.

4. Togashi Y, Masago K, Hamatani Y, et al. 2012. Successful erlotinib rechallenge for leptomeningeal metastases of lung adenocarcinoma after erlotinib-induced interstitial lung disease: A case report and review of the literature. Lung Cancer 77:464-468.

5. Camus P, Kudoh S, Ebina M. 2004. Interstitial lung disease associated with drug therapy. Br. J. Cancer 91:S18-S23.