Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5435-20
Intern Med 60: 591-594, 2021
http://internmed.jp

【 CASE REPORT 】

Successful Treatment with Afatinib after Osimertinib-induced Interstitial Lung Disease in a Patient with EGFR-mutant Non-small-cell Lung Cancer

Shunichi Nishima[1], Akihiko Miyanaga[1], Sho Saito[1], Mizuki Yuasa[1], Satoshi Takahashi[1], Takeru Kashiwada[1], Teppei Sugano[1], Rintaro Noro[1], Yuji Minegishi[1], Yasuhiro Terasaki[2], Yoshinobu Saito[1], Kaoru Kubota[1], Masahiro Seike[1] and Akihiko Gemma[1]

Abstract:
Osimertinib is the standard treatment for epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancer. However, drug-induced interstitial lung disease (ILD) is recognized as a serious adverse event associated with EGFR-tyrosine kinase inhibitors (TKIs). We herein report a 78-year-old woman with stage IV lung adenocarcinoma harboring an EGFR L858R mutation on exon 21 who received rechallenge treatment with afatinib after osimertinib-induced ILD with an organizing pneumonia pattern. This is the first report of successful rechallenge with afatinib after osimertinib-induced ILD. Treatment with other EGFR-TKIs after osimertinib-induced ILD may be an option for subsequent therapy.

Key words: lung cancer, osimertinib, afatinib, drug-induced ILD, interstitial lung disease

(Intern Med 60: 591-594, 2021)
(DOI: 10.2169/internalmedicine.5435-20)

Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are extremely effective for the treatment of EGFR-mutant non-small-cell lung cancer (NSCLC), improving the patient prognosis. However, EGFR-TKIs can cause a variety of drug-induced interstitial lung disease (ILD), which are occasionally fatal. Osimertinib is a third-generation EGFR-TKI; the incidence of osimertinib-induced ILD is approximately 2-4% and the mortality rate is <1.0% (1-3). Thus far, the effectiveness and safety of EGFR-TKI rechallenge after osimertinib-induced ILD has been reported in a few cases (4-8). However, there have been no case reports of rechallenge with afatinib after osimertinib-induced ILDs. We herein report a case of successful switching to afatinib after osimertinib-induced ILD in a patient with lung adenocarcinoma harboring an EGFR L858R mutation on exon 21.

Case Report

A 78-year-old woman who had never smoked, was diagnosed with stage IV lung adenocarcinoma with multiple lung and bone metastases (cT4N3M1c). A specimen obtained from a transbronchial lung biopsy (TBLB) revealed the presence of the EGFR exon 21 L858R mutation.

Chest computed tomography (CT) showed carcinomatous lymphangiosis and absence of interstitial changes in the lung field (Fig. 1A). The performance status (PS) was 2. Based on these findings, osimertinib (80 mg once daily) was administered as first-line treatment.

After two months of therapy, the lung primary, metastases, and pleural effusion were reduced (Fig. 1B). However, 4.5 months after the initiation of osimertinib, she complained of cough and dyspnea on effort. Although treatment with osimertinib had been continued with a good response, chest CT revealed the presence of new bilateral multiple

[1]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Japan and [2]Department of Analytic Human Pathology, Graduate School of Medicine, Nippon Medical School, Japan
Received: May 25, 2020; Accepted: August 2, 2020; Advance Publication by J-STAGE: September 30, 2020
Correspondence to Dr. Akihiko Miyanaga, a-miyanaga@nms.ac.jp

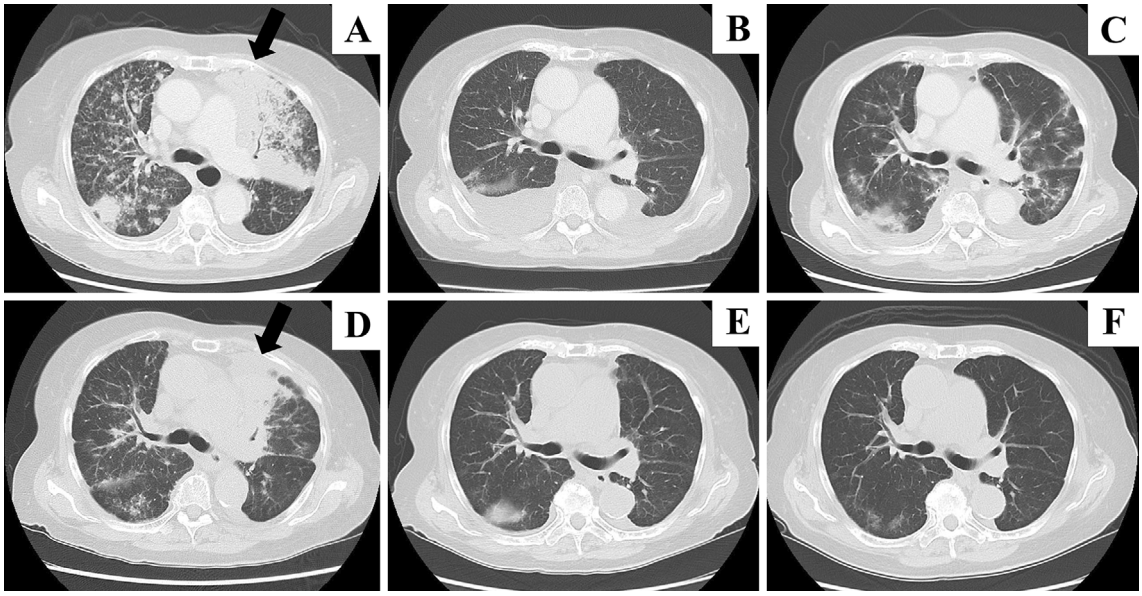

Figure 1. **The clinical course according to chest computed tomography findings. (A) Prior to treatment with osimertinib, a primary tumor was observed at the left upper lobe (arrow) with multiple lung metastases in the bilateral lung fields and no evidence of interstitial pneumonia. (B) Remarkable shrinkage of the tumors two months after initiation of treatment with osimertinib. (C) Patchy consolidations in the bilateral lung fields 4.5 months after initiation of treatment with osimertinib. (D) Improvement of the bilateral patchy consolidation and growth of the primary tumor (arrow) two months after initiation of steroid therapy. (E, F) Examinations at two and six months after the initiation of treatment with afatinib showing continuous effectiveness without recurrence of ILD. ILD: interstitial lung disease**

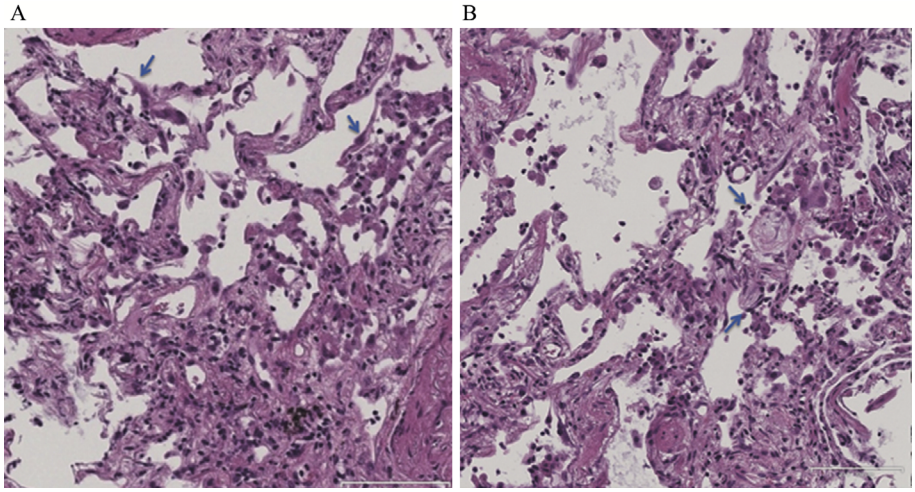

Figure 2. **A transbronchial lung biopsy specimen. (A) The alveolar walls show lymphocytic inflammatory cell infiltration and focal findings of desquamative damaged pneumocytes (arrows). (B) Polypoid plugs indicating organizing pneumonia (arrows). Scale bar=100 μm (Hematoxylin and Eosin staining).**

patchy consolidations (Fig. 1C). A blood examination showed an increase in the serum levels of Krebs von den Lungen-6 (1,064.8 U/mL) and surfactant protein-D (251.1 ng/mL) and a decrease in the levels of carcinoembryonic antigen (4.0 ng/mL).

Osimertinib-induced ILD was suspected, and we performed bronchoalveolar lavage (BAL) and a TBLB through the right middle lobe bronchus (B5) and S8, respectively. An analysis of the BAL fluid (72 mL/130 mL) showed pronounced lymphocytosis (total cell count of 950 cells/μL: 1.0% neutrophils, 90.0% lymphocytes, 0% eosinophils, 0% monocytes, and 9.0% alveolar macrophages). Bacterial cultures from the BAL fluid were negative. The CD4/CD8 ratio was 1.3. The TBLB specimen showed lymphocytic cellular alveolitis with some desquamative damaged pneumocytes and typical organizeing pneumonia findings (Fig. 2). Based

Table. Literature Review of Rechallenge with EGFR-TKIs after Osimertinib-induced ILD.

Case	Age	Sex	EGFR status	Cause of ILD	CTCAE Grade	Onset of ILD	Re-challenge	Corticosteroid during rechallenge	Recurrence of ILD	Effect of EGFR-TKI (Initial/ Rechallenge)	References
1	75	F	Exon19 deletion	Osimertinib 80 mg	2	64 days	Osimeritnib 40 mg	Yes	No	PR/PR	4
2	38	F	L858R, T790M	Osimertinib 80 mg	2	31 days	Osimeritnib 80 mg	No	Yes	PR/PR	5
3	82	M	Exon19 deletion	Osimertinib 80 mg	4	8 months	Osimertinib 80 mg	YES→off	No	PR/PR	6
4	60	M	Exon19 deletion, T790M	Osimertinib 80 mg	3	6 weeks	Osimeritnib	YES→off	Yes	NE/PR	6
5	62	M	Exon19 deletion, T790M	Osimertinib 80 mg	2	82 days	Osimertinib 40 mg	Yes	No	NA/SD	7
6	75	F	Exon19 deletion, T790M	Osimertinib 80 mg	2	6 months	Osimertinib 80 mg	Yes	No	PR/SD	8
7	78	F	L858R	Osimertinib 80 mg	2	4.5 months	Afatinib 30 mg	No	No	PR/PR	Present case

EGFR-TKIs: epidermal growth factor receptor-tyrosine kinase inhibitors, ILD: interstitial lung disease, CTCAE: Common Terminology Criteria for Adverse Events (version 5.0), F: female, M: male, PR: partial response, NE: Not Evaluable, SD: stable disease

on the clinical and histologic findings, we diagnosed the patient with grade 2 osimertinib-induced ILD with an organizing pneumonia pattern.

Osimertinib was immediately discontinued, and oral prednisolone (0.5 mg/kg) was administered. This change in treatment improved her symptoms and oxygenation, gradually reduced the number of bilateral lung consolidations, and led to the gradual reduction of oral steroid therapy. Two months after the initiation of treatment, prednisolone was discontinued.

Although there was no recurrence of ILD for one month after discontinuation, the lung primary tumor progressed (Fig. 1D). Due to her PS of 2, cytotoxic chemotherapy was considered a high-risk treatment, and there were no other recommended conventional chemotherapy regimens. A switch to EGFR-TKI therapy was therefore performed. Informed consent regarding the risk of ILD recurrence was given by the patient and her family. Therefore, afatinib (30 mg once daily) was administered.

After two months, partial tumor remission had been achieved without pulmonary toxicity (Fig. 1E). The patient has been receiving treatment with afatinib for eight months without disease progression or recurrence of ILD (Fig. 1F).

Disscussion

We herein report the case of a patient who developed ILD after treatment with osimertinib and subsequently successfully switched to afatinib. Osimertinib is an irreversible EGFR-TKI recently approved for the first-line treatment of patients with EGFR-mutant NSCLC. In clinical practice, there are two potential scenarios available for the treatment of patients with EGFR-mutant NSCLC: 1) osimertinib (first-line treatment) followed by other non-EGFR-TKI agents (second-line treatment); or 2) first-/second-generation TKIs followed by osimertinib only in *EGFR* T790M-positive patients. However, which EGFR-TKI should be selected for rechallenge after osimertinib-induced ILD as first-line therapy is unclear.

Several cases of drug rechallenge after ILD induced by first-generation EGFR-TKIs have been reported. This is because EGFR-TKIs are key drugs for patients with NSCLC harboring EGFR mutations (9, 10). Table shows previous reports of rechallenges with EGFR-TKIs after osimertinib-induced ILD (4-8). Recently, some reports have suggested that rechallenge with osimertinib in combination with steroids can be considered after carefully assessing the potential risks and benefits (4, 7). There are two ways to perform a rechallenge with EGFR-TKI: 1) using the same EGFR-TKI with/without steroids or 2) switching to other EGFR-TKIs. In our case, the general condition of the patient did not permit the use of chemotherapy, and relapse occurred rapidly after discontinuing the initial treatment. We selected another EGFR-TKI (afatinib) for second-line therapy, considering the risk of ILD relapse due to the rechallenge.

In the AURA3 study, 7% of the Japanese patients in the osimertinib group developed an ILD, and all patients recovered (11). Among the Japanese subset of the FLAURA study, the frequency of grade 1-2 ILD and pneumonitis was higher in the osimertinib group (12.3%) than in the gefitinib group (1.8%). However, the frequency of grade ≥3 ILD and pneumonitis was the same in both groups (2% each) (12). In most cases of grade 1-2 ILD, there were no symptoms reported, and these were the only radiological findings (12). Recently, frequent transient asymptomatic pulmonary opacities (TAPOs), which are different from ILDs, were noted in patients during treatment with osimertinib. The incidence of TAPOs ranges from 20% to 35% (13, 14). In most cases, these opacities are asymptomatic, localized, and spontaneously disappear. It has been shown that TAPOs may be mis-

taken for isolated pulmonary progression or drug-induced ILD. Nevertheless, these lesions should be distinguished from differential diagnoses of ILD, such as pneumonia, disease progression, pulmonary edema, hemorrhaging, radiation pneumonitis, and prior interstitial pneumonitis. In the present case, the patient had symptomatic pulmonary opacities and was diagnosed with ILD with an organizing pneumonia pattern through the assessment of BAL and TBLB data.

However, afatinib is also associated with side effects (e.g., pneumonitis and ILD), with an incidence ranging from 1.3% to 4.4% (15, 16). In a large observational study involving the real-world treatment of 1,600 Japanese patients with afatinib, risk factors for ILD were men, age >65 years old, PS 2-4, bone metastasis, presence of contralateral lung metastases, and previous radiotherapy session within 1 year (16). Therefore, it is necessary to determine whether or not to rechallenge with EGFR-TKIs while considering those risks and benefits. In the present case, the patient had some of these risk factors, such as PS 2 and an advanced age. However, her general condition was less severe before the second treatment than before the initial treatment. We therefore considered her capable of tolerating EGFR-TKI treatment. In addition, we expected second-generation EGFR-TKIs to be more effective in this patient than first-generation EGFR-TKIs. We selected another EGFR-TKI (afatinib) in order to avoid using osimertinib (associated with ILD). Moreover, considering the therapeutic effect, osimertinib was not expected to be effective because the patient demonstrated an early relapse.

In conclusion, we herein report the radiological and pathological findings of successful rechallenge with afatinib after osimertinib-induced ILD. This is the first report of switching to an EGFR-TKI other than osimertinib after osimertinib-induced ILD. Treatment with other EGFR-TKIs after osimertinib-induced ILD may be an option for subsequent therapy. Careful monitoring of the patient's clinical course for any relevant symptoms of ILD may be important to ensure the early detection and prevent the development of life-threatening ILD. Additional case reports are needed to address this issue.

Author's disclosure of potential Conflicts of Interest (COI).
Yoshinobu Saito: Honoraria, AstraZeneca and Boehringer Ingelheim. Kaoru Kubota: Honoraria, AstraZeneca; Research funding, Boehringer Ingelheim. Masahiro Seike: Honoraria, AstraZeneca and Boehringer Ingelheim; Research funding, AstraZeneca and Boehringer Ingelheim. Akihiko Gemma: Honoraria, AstraZeneca and Boehringer Ingelheim.

Acknowledgement

We thank the patient and her family for letting us present her case in this report.

References

1. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med **372**: 1689-1699, 2015.
2. Yang JC, Ahn MJ, Kim DW, et al. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. J Clin Oncol **35**: 1288-1296, 2017.
3. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med **376**: 629-640, 2017.
4. Miyauchi E, Ichinose M, Inoue A. Successful osimertinib rechallenge in a patient with T790M-mutant non-small cell lung cancer after osimertinib-induced interstitial lung disease. J Thorac Oncol **12**: e59-e61, 2017.
5. Mamesaya N, Kenmotsu H, Katsumata M, Nakajima T, Endo M, Takahashi T. Osimertinib-induced interstitial lung disease after treatment with anti-PD1 antibody. Invest New Drugs **35**: 105-107, 2017.
6. Nagasaka M, Gadgeel SM. Retreatment with osimertinib following pneumonitis. Clin Lung Cancer **19**: e53-e55, 2018.
7. Kiriu T, Tamura D, Tachihara M, et al. Successful osimertinib rechallenge with steroid therapy after osimertinib-induced interstitial lung disease. Intern Med **57**: 91-95, 2018.
8. Itano J, Higo H, Ohashi K, et al. Successful re-administration of osimertinib in osimertinib-induced interstitial lung disease with an organizing pneumonia pattern: a case report and literature review. Intern Med **59**: 823-828, 2019.
9. Togashi Y, Masago K, Hamatani Y, et al. 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, 2012.
10. Takamochi K, Suzuki K, Bashar AH, et al. Readministration of gefitinib in a responder after treatment discontinuation due to gefinitib-related interstitial lung disease: a case report. J Med Case Rep **1**: 138, 2007.
11. Akamatsu H, Katakami N, Okamoto I, et al. Osimertinib in Japanese patients with EGFR T790M mutation-positive advanced non-small-cell lung cancer: AURA3 trial. Cancer Sci **109**: 1930-1938, 2018.
12. Ohe Y, Imamura F, Nogami N, et al. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. Jpn J Clin Oncol **49**: 29-36, 2019.
13. Noonan SA, Sachs PB, Camidge DR. Transient asymptomatic pulmonary opacities occurring during osimertinib treatment. J Thorac Oncol **11**: 2253-2258, 2016.
14. Lee H, Lee HY, Sun JM, et al. Transient asymptomatic pulmonary opacities during osimertinib treatment and its clinical implication. J Thorac Oncol **13**: 1106-1112, 2018.
15. Ding PN, Lord SJ, Gebski V, et al. Risk of treatment-related toxicities from EGFR tyrosine kinase inhibitors: a meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-Mutated non-small cell lung cancer. J Thorac Oncol **12**: 633-643, 2017.
16. Tamura K, Nukiwa T, Gemma A, et al. Real-world treatment of over 1600 Japanese patients with EGFR mutation-positive non-small cell lung cancer with daily afatinib. Int J Clin Oncol **24**: 917-926, 2019.