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Successful Use of Afatinib After Erlotinib-induced Pneumonitis in a Patient With Epidermal Growth Factor Receptor-mutant Lung Cancer

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Keywords

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Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are the first-line treatment of choice for patients with EGFR-mutant lung cancer. Interstitial lung disease (ILD) is an infrequent, yet significant, adverse effect of EGFR-TKI therapy. Erlotinib-induced ILD occurs in approximately 1% of patients treated.^{1,2} The clinical manifestations of pneumonitis can vary but include acute-onset dyspnea, cough, and fever. The radiologic presentation often consists of diffuse, multifocal, ground-glass and confluent opacities with intralobular interstitial thickening.³ The histologic presentation varies but can present as diffuse alveolar damage, interstitial pneumonia, interstitial fibrosis, eosinophilic pneumonia, or bronchiolitis obliterans organizing pneumonia.⁴ Because drug-induced pneumonitis can be progressive and fatal, early recognition of the symptoms and discontinuation of the offending drug are critical. Corticosteroids can sometimes be used to hasten resolution of the symptoms.

After the development of drug-induced pneumonitis, clinicians are often hesitant to readminister the offending agent or a similar medication in the same class. If pneumonitis occurs with a specific EGFR-TKI, 1 option is to consider rechallenge with another EGFR-TKI. Several case reports have described this, most often using a different EGFR-TKI at a

lower dose with concurrent corticosteroids (Table 1). No cases of afatinib rechallenge after erlotinib-induced ILD have been reported.

Case Report

A 61-year-old woman who had never smoked was diagnosed with stage IV EGFR-mutant lung adenocarcinoma that was metastatic to the lymph nodes, contralateral lung, and pleura (Figure 1A). She began treatment with erlotinib after her diagnosis. The initial scans demonstrated a response to treatment. Five months later, she had developed night sweats and a dry productive cough. Repeat computed tomography (CT) of her chest revealed her disease to be decreased but new patchy ground glass opacities were present throughout the right lung and left upper lobe (Figure 1B). She underwent bronchoscopy, and pathologic examination indicated an organizing pneumonia with focal non-necrotizing granulomas and chronic interstitial pneumonitis (Figure 2). All infectious cultures were negative, and the biopsy results were consistent with drug-induced pneumonitis.

The patient subsequently stopped erlotinib and started prednisone 40 mg daily. She experienced an initial improvement in her clinical symptoms and on her CT scan (Figure 1C). She was then weaned off steroids because of side effects. A repeat CT scan, approximately 1 year after the diagnosis, demonstrated worsening left lower lobe opacities and bilateral enlarging pulmonary nodules, consistent with disease progression (Figure 1D). She was then started on afatinib 40 mg daily. After starting afatinib, she felt better, with resolution of her cough and dyspnea on exertion occurring almost immediately. A repeat CT scan after 4 weeks showed a disease response to the treatment, with no recurrence of the inflammatory infiltrates (Figure 1E). At the last follow-up examination, she has continued afatinib with stable disease almost 3 years after her diagnosis of metastatic disease. The patient agreed to the description of her case in our report.

Conclusion

We have reported a case of a patient with biopsy-proven erlotinib-induced ILD who symptomatically improved after discontinuation of erlotinib and the initiation of corticosteroids. She subsequently received afatinib with good control of her disease and no recurrence of pneumonitis. We present a single case report, which limits any definitive conclusions. Because pneumonitis is seen as an idiopathic inflammatory response to a specific drug, it does not always recur with retreatment of a similar agent, such as described in the present report and in further examples in Table 1, or the original offending agent. Dasatinib and erlotinib have been successfully reintroduced after pneumonitis at a lower dose.^{8,10} The risk of pneumonitis varies among the EGFR-TKIs, ranging from 0.8% with erlotinib to 2.4% with osimertinib and should be considered when choosing a subsequent drug for retreatment.^{11,12} For patients with EGFR-TKI-induced pneumonitis, a retreatment of a different EGFR-TKI might be warranted in the setting of close supervision and follow-up protocols. Prospective data are needed to establish the safety of this clinical practice.

References

1. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012; 13:239–46. [PubMed: 22285168]
2. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005; 353:123–32. [PubMed: 16014882]
3. Akira M, Ishikawa H, Yamamoto S. Drug-induced pneumonitis: thin-section CT findings in 60 patients. *Radiology.* 2002; 224:852–60. [PubMed: 12202725]
4. Schwaiblmair M, Behr W, Haeckel T, Märkl B, Foerg W, Berghaus T. Drug induced interstitial lung disease. *Open Respir Med J.* 2012; 6:63–74. [PubMed: 22896776]
5. Chang S-C, Chang C-Y, Chen C-Y, Yu C-J. Successful erlotinib rechallenge after gefitinib-induced acute interstitial pneumonia. *J Thorac Oncol.* 2010; 5:1105–6. [PubMed: 20581580]
6. Fukui T, Otani S, Hataishi R, et al. Successful rechallenge with erlotinib in a patient with EGFR-mutant lung adenocarcinoma who developed gefitinib-related interstitial lung disease. *Cancer Chemother Pharmacol.* 2010; 65:803–6. [PubMed: 20035424]
7. Tian Q, Chen L. Erlotinib achieved partial response in a non-small cell lung cancer patient with gefitinib-induced interstitial lung disease. *Case Rep Oncol.* 2011; 4:464–6. [PubMed: 22114570]
8. Dallas JL, Jantz MA, Lightsey JL, Sonntag C, Kaye FJ. Successful erlotinib rechallenge after erlotinib-induced interstitial lung disease. *J Thorac Oncol.* 2011; 6:1142–3. [PubMed: 21623280]
9. Takeda M, Okamoto I, Makimura C, Fukuoka M, Nakagawa K. Successful treatment with erlotinib after gefitinib-induced severe interstitial lung disease. *J Thorac Oncol.* 2010; 5:1103–4. [PubMed: 20581579]
10. Bergeron A, Réa D, Levy V, et al. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. *Am J Respir Crit Care Med.* 2007; 176:814–8. [PubMed: 17600277]
11. Yoneda KY, Shelton DK, Beckett LA, Gandara DR. Independent review of interstitial lung disease associated with death in TRIBUTE (paclitaxel and carboplatin with or without concurrent erlotinib) in advanced non-small cell lung cancer. *J Thorac Oncol.* 2007; 2:537–43. [PubMed: 17545850]
12. Jänne PA, Yang JC-H, Kim D-W, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med.* 2015; 372:1689–99. [PubMed: 25923549]

Clinical Practice Points

- Pneumonitis is a uncommon but serious complication of treatment with EGFR tyrosine kinase inhibitors.
- This is a case report of a successful rechallenge using afatinib after erlotinib-induced pneumonitis.
- A retrial of the same or an alternate EGFR-TKI under careful observation may be warranted.

Figure 1.

(A) Chest Computed Tomography (CT) Scan Showing Left Lower Lobe Mass-Like Consolidation With Tumoral Components (Black Arrows) and Atelectasis at Diagnosis. A Small Adjacent Effusion (Star) and Numerous Punctuate Nodules Scattered Throughout the Lungs Are Present. (B) Chest CT Scan After 5 Months of Treatment With Erlotinib Showing Improvement in the Tumor Mass, Resolution of the Punctuate Nodules, and an Unchanged Pleural Effusion (Star). Drug-Induced Pneumonitis With Bilateral Areas of Confluent and Ground Glass Opacity (White Arrows) Has Developed. (C) Chest CT Scan 2 Months After Patient Discontinued Erlotinib and Started Prednisone Showing Improvement in Pneumonitis, With Residual Left Basilar Confluent Opacity (White Arrow) and Unchanged Mass-Like Consolidation (Black Arrow) and Decreased Pleural Effusion (Star). (D) Chest CT Scan 4 Months After Patient Stopped Erlotinib Showing Worsening of Tumor Burden, With Increased Left Lower Lobe Mass-Like Consolidation (Short Black Arrow), Numerous New Small Pulmonary Nodules (Long Black Arrows), and an Unchanged Small Pleural Effusion (Star). (E) Chest CT Scan 1 Month After the Start of Afatinib Showing Improvement in Tumor Burden, With a Decreased Left Lower Lobe Mass-Like Opacity and Resolved Pulmonary Nodules. No Pneumonitis Had Development. The Small Pleural Effusion (Star) Was Unchanged

Figure 2.
(Left) Hematoxylin and Eosin Sections at Medium Magnification Showing Alveolar Parenchyma With Chronic Interstitial Pneumonitis, Organizing Pneumonia (Black Arrows), and Focal Reactive Pneumocyte Hyperplasia (White Arrow). (Right) Hematoxylin and Eosin Sections at Higher Magnification Showing the Presence of Focal Non-Necrotizing Granulomas (Black Arrow)

Table 1

Details of Several Cases of EGFR-TKI Rechallenge After Drug-Induced Pneumonitis

Initial TKI	Symptoms	Pneumonitis Treatment	TKI Used for Rechallenge	Outcome
Gefitinib 250 mg ⁵	Fever, dry cough, dyspnea	Methylprednisolone	Erlotinib 150 mg with steroid therapy	Partial response, no pneumonitis
Gefitinib 250 mg ⁵	Dry cough, progressive dyspnea	Methylprednisolone	Erlotinib 100 mg with prednisolone	Partial response, no pneumonitis
Gefitinib 250 mg ⁶	Fatigue, fever, respiratory distress	Methylprednisolone	Erlotinib 50 mg with prednisolone	Partial response, no pneumonitis
Gefitinib 250 mg ⁷	High fever, respiratory distress	Methylprednisolone and mechanical ventilation	Erlotinib 75 mg with prednisolone	Partial response, no pneumonitis
Erlotinib 150 mg ⁸	Fever, skin rash, nonproductive cough, dyspnea	Prednisone and doxycycline	Erlotinib 100 mg with prednisone and doxycycline	Partial response, no pneumonitis
Gefitinib 250 mg ⁹	Dyspnea with fever and cough	Methylprednisolone	Erlotinib 150 mg	Partial response, no pneumonitis

Abbreviation: TKI = tyrosine kinase inhibitor.