CASE REPORT

Severe Drug-Induced Interstitial Lung Disease After Administration of Osimertinib as Adjuvant Treatment for Resected EGFR-Mutated NSCLC: A Case Report

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ABSTRACT

Osimertinib administration has been approved as an adjuvant treatment after complete surgical resection in patients with EGFR-mutated NSCLC. This article presents the first report of life-threatening postoperative osimertinib-induced interstitial lung disease. An 83-year-old male patient underwent right upper lobectomy (pathologic stage IIA) and osimertinib (80 mg/d) was initiated on postoperative day 75. On day 44 of osimertinib administration, chest computed tomography revealed diffuse ground-glass opacities; accordingly, osimertinib-induced interstitial lung disease was diagnosed. Steroid pulse therapy was initiated using a high-flow nasal cannula to treat dyspnea and hypoxemia, rapidly improving the respiratory status and imaging findings; moreover, the patient's clinical course was excellent. This case report suggests that the postoperative occurrence of severe osimertinib-induced interstitial lung disease is a crucial factor that must be considered in patient decision-making regarding perioperative treatment.

Keywords: EGFR tyrosine kinase inhibitor; Osimertinib; Drug-induced interstitial lung disease; Case report

Introduction

The phase 3 randomized ADAURA (ClinicalTrials.gov identifier: NCT02511106) trial evaluated the efficacy and safety of osimertinib as adjuvant therapy after surgical resection of EGFR-mutated stage IB to IIIA NSCLC.[1–3] The study found that osimertinib markedly prolonged disease-free survival; accordingly, it was approved as a standard adjuvant treatment option. However, there has been a high prevalence of severe drug-induced interstitial lung disease (DI-ILD) associated with osimertinib, especially in Japan.[4] Nevertheless, the ADAURA trial did not report any cases of severe or life-threatening DI-ILD events. Notably, there have been limited real-world data regarding the incidence of DI-ILD associated with osimertinib. This article describes a case of severe DI-ILD

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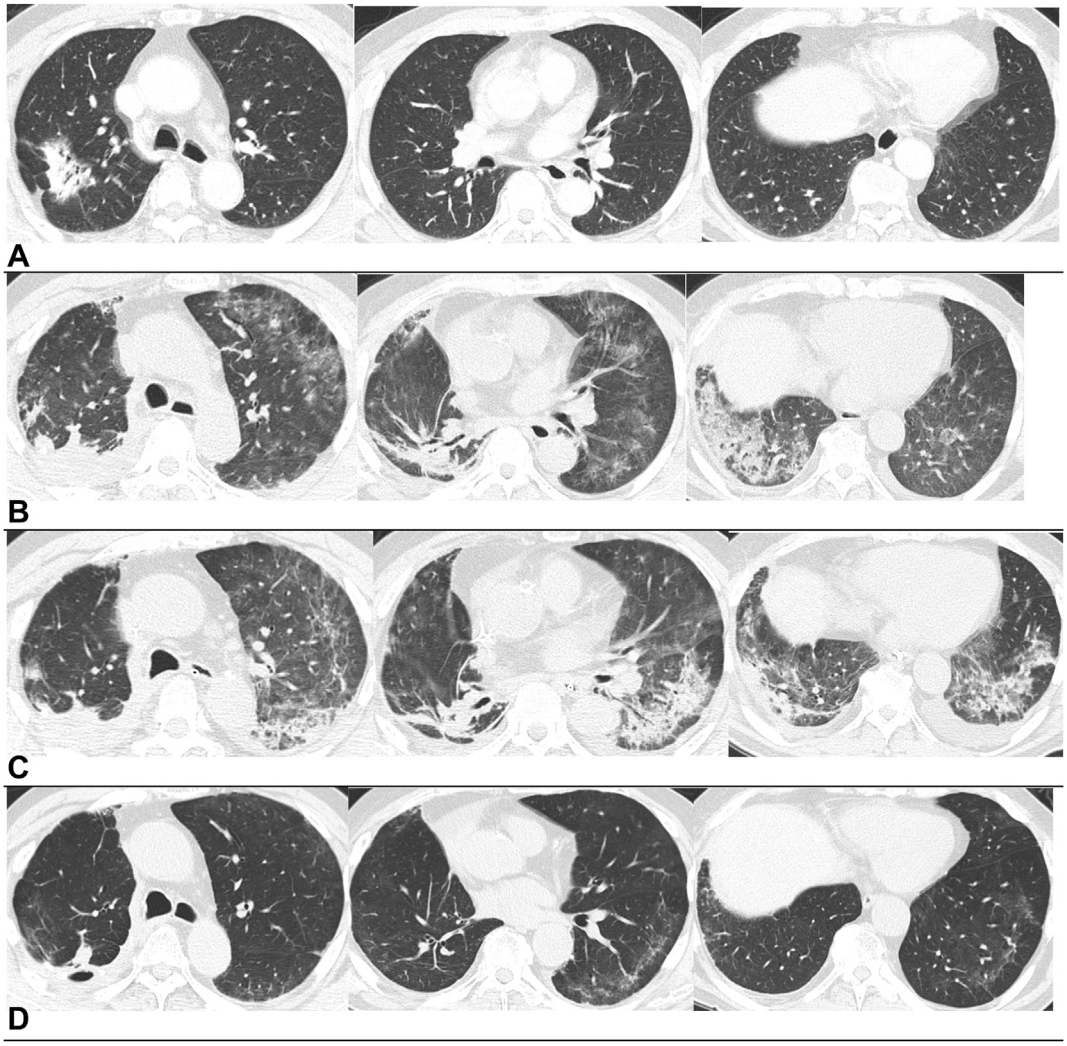

Figure 1. Chest CT scans obtained from before the administration of osimertinib to discharge. (*A*) A preoperative CT scan (day 103) revealed no evidence of interstitial shadowing. (*B*) The CT scan obtained on day 44 of admission revealed light pleural effusion, diffuse ground-glass opacities in the left lobe, and consolidation in the right lower lobe. Traction bronchiectasis was observed, and the subpleural area was preserved. Given the widespread ground-glass opacities and consolidation, along with partial bronchiolar dilation and architectural changes, a DAD pattern was diagnosed. (*C*) Images obtained on day 51 revealed bilateral pleural effusion, extensive consolidation, and ground-glass opacities. (*D*) On day 92, the consolidation disappeared, leaving only residual linear shadows. CT, computed tomography; DAD, diffuse alveolar damage.

after osimertinib treatment in a patient with EGFR-positive NSCLC who had previously undergone lung surgery. This case highlights the potential adverse effects of osimertinib and illustrates the need for vigilance while monitoring patients receiving this therapy.

Case Presentation

An 83-year-old male patient presented with exertional dyspnea that had persisted for 6 months. Chest computed tomography (CT) revealed right upper lobe lung cancer. The patient underwent right upper lobe resection and was diagnosed with stage IIA right upper lobe pulmonary adenocarcinoma (pT2bN0M0) with an EGFR exon 21 L858R mutation. He had a smoking history of 20 cigarettes per day for 45 years and a performance status of 1. His only relevant medical history included paroxysmal atrial fibrillation. Furthermore, he had no history of interstitial pneumonia (Fig. 1*A*). On postoperative day 75, the patient was started on oral osimertinib at a dose of 80 mg/d. However, on day 44 of osimertinib administration, the patient developed cough and dyspnea (Fig. 2). In addition, he presented oxygen desaturation with a peripheral capillary oxyhemoglobin saturation (SpO2) of 95% on supplemental oxygen by nasal cannula at 3 L/minute. Chest CT revealed bilateral diffuse ground-glass opacities; consequently, DI-ILD was diagnosed (Fig. 1*B*). The patient was admitted to our hospital on the same day, and osimertinib therapy was discontinued. On admission, laboratory test results

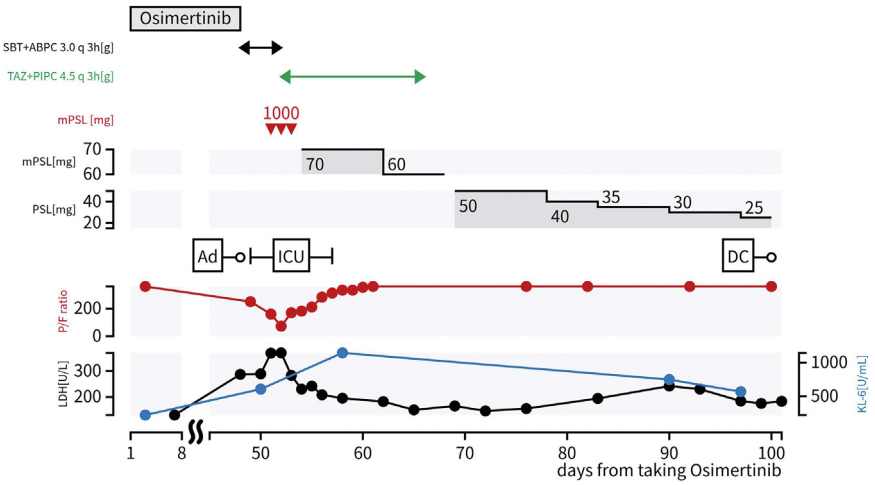

Figure 2. Clinical course and management of DI-ILD. This figure illustrates the clinical course after initiation of osimertinib treatment on day 1. The patient was admitted on day 44. Despite receiving sulbactam and ampicillin 3.0 g at 8-hourly intervals, the lactate dehydrogenase levels revealed an upward trend and the PaO2/FiO2 ratio decreased, suggesting worsening DI-ILD. Osimertinib therapy was discontinued (day 44), and methylprednisolone (1000 mg/d) was administered for 3 days. The antibiotic regimen was changed to tazobactam and piperacillin 4.5 g at 8-hour intervals, whereas the steroid dosage was tapered to prednisolone 70 mg/d and gradually reduced as the respiratory status improved. On day 102, the prednisolone dose was decreased to 25 mg/d, and the patient was discharged with confirmed respiratory improvement. Readministration of osimertinib was not performed. Ad, Admission; DC, discharge; DI-ILD drug-induced interstitial lung disease; FiO2, fraction of inspired oxygen; ICU, intensive care unit; mPSL, methylprednisolone; P/F, PaO2/FiO2; PaO2, the partial pressure of oxygen in the arterial blood; PSL, prednisolone; SBT+ABPC, sulbactam and ampicillin; TAZ+PIPC, tazobactam and piperacillin.

revealed elevated levels of Krebs von den Lungen-6 (608 U/mL) and lactate dehydrogenase (289 U/L); however, autoimmune test results were unremarkable. Accordingly, sulbactam and ampicillin treatment was initiated, along with steroid pulse therapy. However, after 3 days, the patient exhibited decreased oxygenation and required a high-flow nasal cannula with a fraction of inspired oxygen level of 70% and a flow rate of 45 L/minute to maintain a peripheral capillary oxyhemoglobin saturation of 96%. DI-ILD with grade 4 severity was subsequently diagnosed according to the Common Terminology Criteria for Adverse Events. CT performed on day 51 revealed left pleural effusion and extensive consolidation (Fig. 1*C*). Subsequently, the patient's respiratory status and interstitial pneumonia marker levels, including Krebs von den Lungen-6, gradually improved. By day 92, the ground-glass opacities and consolidations observed on the CT images had disappeared (Fig. 1*D*). Steroid tapering was initiated, and the patient was discharged on day 102. Osimertinib was not readministered.

Discussion

This report describes the clinical course of a patient who developed DI-ILD after the initiation of osimertinib treatment. This case indicates the need to consider the safety profile of osimertinib and closely monitor patients receiving this therapy. Although the mechanisms underlying DI-ILD associated with osimertinib remain unclear, EGFR tyrosine kinase inhibitors have been associated with ILD.[4] Prompt steroid administration rapidly improves oxygenation and decreases lactate dehydrogenase levels. There are several factors associated with the development of DI-ILD,[5] including age, smoking history, and performance status. In addition, the observed hypoxemia could be attributed to the presence of consolidation with structural changes, which displayed a diffuse alveolar damage pattern on chest CT. The present case illustrates the potential for severe DI-ILD development associated with adjuvant osimertinib treatment. Accordingly, it is important to exercise caution and closely monitor patients receiving osimertinib because severe DI-ILD may occur not only in advanced-stage patients but also in postoperative settings. Finally, we should focus on the clinical challenges of perioperative molecular targeted therapy of lung cancer with curative intent. In our case, readministration of osimertinib was avoided for severe DI-ILD. However, with the increasing use of osimertinib as adjuvant therapy for resected EGFR-mutated NSCLC, the decision to readminister osimertinib during the perioperative period for cases of mild to moderate DI-ILD will require further accumulation of real-world data.

Conclusion

The occurrence of severe DI-ILD after postoperative treatment with osimertinib is a crucial factor that must

be considered in patient decision-making regarding perioperative treatment.

CRediT Authorship Contribution Statement

Sho Mitsuya: Investigation, Data curation, Visualization, Writing - original draft.

Masahiro Arai: Investigation.

Kiyoe Kanaoka: Investigation.

Tomoya Funamoto: Investigation, Data curation.

Hiroyuki Tsuji: Validation, Data Curation.

Kenjiro Tsuruoka: Validation, Data Curation.

Ninso Matsunaga: Validation.

Takahiko Nakamura: Validation, Data curation.

Yosuke Tamura: Visualization.

Masafumi Imanishi: Validation. Visualization.

Soichiro Ikeda: Validation.

Akihisa Imagawa: Supervision.

Yasuhito Fujisaka: Conceptualization, Supervision, Writing - review and editing.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosures

Dr. Mitsuya reports receiving lecture fees from AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Chugai Pharmaceutical Co., Ltd. Dr. Tsuji reports receiving lecture fees from Ono Pharmaceutical Co., Ltd. and Chugai Pharmaceutical Co., Ltd. Dr. Nakamura reports receiving lecture fees from AstraZeneca K.K., Novartis Pharmaceuticals K.K., Nippon Boehringer Ingelheim Co., Ltd., GlaxoSmithKline plc., Sanofi K.K., and KYORIN Pharmaceuticals Co., Ltd. Dr. Tamura reports receiving lecture fees from Merck Sharp & Dohme (Merck & Co., Inc.), AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharmaceuticals K.K., and Chugai Pharmaceutical Co., Ltd. Dr. Ikeda reports receiving lecture fees from AstraZeneca K.K. Dr. Imagawa reports receiving research funding from Taiho Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., Parexel International Inc., and Ono Pharmaceutical Co., Ltd. Dr. Fujisaka reports receiving lecture fees from AstraZeneca K.K., Eli Lilly and Company, Ono Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Pfizer Inc., Takeda Pharmaceuticals Co., Ltd., Novartis Pharmaceuticals K.K., and Chugai Pharmaceutical Co., Ltd.; and research funding from Merck Sharp & Dohme (Merck & Co., Inc.), Taiho Pharmaceutical Co., Ltd., Bristol Myers Squibb K.K., Ono Pharmaceutical Co., Ltd., and Regeneron Pharmaceuticals, Inc. The remaining authors declare no conflict of interest.

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