Early-Onset Pulmonary Events with Combined Brigatinib and Afatinib Treatment of L858/cisT790M/cisC797S NSCLC: A Case Report

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Patient: Female, 54-year-old
Final Diagnosis: Interstitial lung disease
Symptoms: Dyspnea
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Unusual or unexpected effect of treatment
Background: Brigatinib is used for anaplastic lymphoma kinase (ALK)-positive lung cancer treatment, and some research showed it was useful in treating triple-mutant epidermal growth factor receptor lung cancer. Clinical trials have shown some potential pulmonary toxicities of brigatinib. The early-onset pulmonary events (EOPEs) of brigatinib are associated with high dosage and older age. The successful treatment of EOPEs with steroids was reported. We present the case of a patient with epidermal growth factor receptor L858R/cis-T790M/cis-C797S triple mutations who developed EOPEs after using brigatinib together with afatinib, and the patient was successfully treated with high-dose steroids.

Case Report: A 54-year-old woman with underlying stage IV lung adenocarcinoma, ECOG score of 0, was treated with brigatinib and afatinib due to disease progression secondary to L858R/cis-T790M/cis-C797S triple mutations. After starting brigatinib and afatinib, she developed dyspnea and dry cough within 2 days and was intubated due to hypercapnic respiratory failure. The chest X-ray showed bilateral interstitial infiltrates while chest computed tomography (CT) showed bilateral ground-glass opacities. EOPEs were suspected and methylprednisolone was prescribed. The oxygenation of the patient improved and her chest CT showed complete resolution after 2 weeks of steroid treatment.

Conclusions: This is the first reported case in which brigatinib combined with afatinib induced EOPEs in a patient with triple-mutant epidermal growth factor receptors of lung cancer. Use of doubled tyrosine kinase inhibitors may result in increased risk of pulmonary toxicities that require high alertness, and the respiratory symptoms should be monitored closely after prescription. The early treatment of EOPEs with high-dose steroids resulted in remarkable improvement.

Keywords: Brigatinib • Lung Diseases, Interstitial • Afatinib

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Background

Some research showed brigatinib was useful in treating triple-mutant epidermal growth factor receptor lung cancer. In focused drug screening of 30 drugs, including other ALK tyrosine kinase inhibitors, only brigatinib showed growth inhibition of EGFR cis-C797S/T790M/activating-mutation in vitro, with half-maximal inhibitory concentration [IC50] <100 nM of Ba/F3 cells expressing the triple mutant [1]. However, pulmonary toxicities were reported in clinical trials, which were related with higher dose and older patient age [2]. Some patients were rechallenged with brigatinib after symptoms improved with or without steroid treatment [3].

Case Report

We report the case of a 54-year-old non-smoking woman with underlying stage IV lung adenocarcinoma, with brain, liver, and multiple bone metastasis and ECOG score of 0. The initial clinical presentation was chronic cough and the computed tomography (CT)-guided biopsy of the right lung tumor showed L858R-positive lung adenocarcinoma in 2016 with a clinical staging of cT4N3M1b. Disease progression was noted despite the use of erlotinib in 2016 for L858R and osimertinib in 2018 for acquired T790M. Chemotherapy was started in 2019. Disease progression was observed in 2022. Re-biopsy was done at the right middle lobe for genomic profiling by using the ACTDrug next-generation sequencing (NGS)-based assay. The pathology report revealed mutations of L858R/cis-T790M/cis-C797S and no other molecular alterations were found.

The brigatinib was used for triple-mutant EGFR based on published research [2]. The combination with afatinib was suggested since afatinib had not been tried previously. The patient and her family agree to this off-label treatment after explanation of possible pulmonary toxicities. Thus, brigatinib 90 mg once daily and afatinib 30 mg once daily were prescribed in Mar 24, 2022 during admission. However, the patient began to experience exertional dyspnea and dry cough within 2 days. Rapid progression with hypercapnic respiratory failure was observed and intubation was performed on Mar 26, 2022. The blood test showed leukocytosis with neutrophil predominant and carbon dioxide retention. The chest X-ray showed bilateral interstitial infiltrates, of which pneumonia was the first impression. It was treated with broad-spectrum antibiotics. Although her fever has subsided and septic shock status improved, oxygenation remained poor. The chest CT showed bilateral ground-glass opacities and left lower lung consolidation (Figure 1). All microbiology studies showed negative findings. EOPES of doubled tyrosine kinase inhibitors emerged. Thus, intravenous methylprednisolone 40 mg every 8 hours was given. The oxygenation of the patient improved remarkably within the next 48 hours. The following chest X-ray showed improvement of bilateral infiltrates. A chest CT at 2 weeks revealed complete resolution of ground-glass opacities and consolidation (Figure 2). The patient was successfully treated and was transferred to the respiratory care center for weaning after 3 weeks of treatment in the intensive care unit. However, she was transferred to the intensive care unit again after 1 week due to a seizure related to progressive brain metastasis. Brain radiotherapy was performed for 5 days. Progressive septic shock developed despite treatments with broad-spectrum antibiotics and vasopressors. The patient died after 10 days in the Intensive Care Unit.

Discussion

The role of brigatinib in triple-mutant EGFR has become more important in recently published research. Antitumor effects in triple mutations of lung cancers were significant when brigatinib was combined with vorinostat [4]. The brigatinib and cetuximab combination therapy showed an objective response rate of 60% and disease control rate of 100% among 5 patients...
with EGFR 19del/T790M/cis-C797S mutations [5]. A case report showed significant reduction in EGFR mutations and partial remission after a lung cancer patient with EGFR L858R/T790M/cis-C797S mutations was treated with a combination of osimertinib, bevacizumab, and brigatinib [6]. Despite no solid proof of the efficacy of brigatinib combined with afatinib, afatinib was considered since the patient had tried erlotinib and osimertinib before. The patient was informed of the adverse effect of pulmonary toxicities and agreed to the prescription. However, the patient did not respond to the combination therapy and EOPEs within 2 days of prescription, perhaps associated with the cumulative pulmonary toxicities of doubled-TKIs. The patient then died of septic shock despite reversible EOPEs. There are no published papers about cumulative toxicities of brigatinib when combined with other tyrosine kinase inhibitors. In fact, this is the first reported case of double-TKIs-induced pulmonary toxicities in treatment of triple-mutant EGFR lung cancer. Therefore, the anti-neoplastic regimens chosen for off-label use should consider using different categories of regimens rather than the same categories, which can increase risk of cumulative toxicities. Combination therapy with drugs of similar toxicity, including but not limited to pulmonary toxicity, should also be avoided. New therapeutic solutions are needed in some situations despite the lack of evidence, and the ethical dilemmas should be discussed with the patient.

**Conclusions**

We found that the combination of brigatinib and afatinib was not effective for NSCLC with L858R/cisT790M/cisC797S and should not be recommended. The increased risk of cumulative pulmonary toxicities should be kept in mind when using doubled-TKIs, especially brigatinib and afatinib. The different mechanisms of anti-neoplastic agents should be considered first as combination therapy of triple-mutant EGFR to prevent cumulative toxicities. Combining brigatinib and afatinib escalates the risk for pulmonary toxicity, which is usually reversible.

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**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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