



Effectiveness of afatinib in an NSCLC patient with *EGFR* mutation and early progression to osimertinib: a case report

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Abstract: Osimertinib, a third-generation epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI), shows great clinical activity in non-small cell lung cancer (NSCLC) patients with *EGFR* mutations regardless of T790M mutation at first-line chemotherapy. Previous studies demonstrated that there are few patients with initial resistance to osimertinib. Here, we describe a case to report the efficacy of afatinib in an *EGFR*-mutated NSCLC patient with early progression to first-line osimertinib treatment. A 68-year-old Japanese male was diagnosed with stage IVB lung adenocarcinoma with the *EGFR* L858R mutation in exon 21. Two months after the start of osimertinib, his tumor progressed at the initial response evaluation. Because he refused to receive cytotoxic chemotherapy, afatinib treatment was initiated. He was administered afatinib, and the tumor shrank. After five months of afatinib treatment, nevertheless the primary tumor was not enlarged, he experienced disease progression with leptomeningeal metastasis and passed away. To elucidate the resistance mechanisms of osimertinib in this patient, we performed next-generation sequencing (NGS) on tumor samples from pleural effusions after osimertinib failure. NGS revealed no specific gene mutations causing resistance to osimertinib except for the *EGFR* L858R mutation; however, his tumor had a relatively high tumor mutational burden. Afatinib is considered an option for *EGFR*-mutated patients with early progression to osimertinib.

Keywords: Epidermal growth factor receptor (EGFR); non-small cell lung cancer (NSCLC); afatinib; early progression to osimertinib; case report

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Introduction

Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is effective in cases where T790M is detected after resistance to first- or second-generation EGFR-TKIs and shows great clinical activity in non-small cell lung cancer (NSCLC) patients with EGFR mutations regardless of T790M mutation at first-line chemotherapy (1,2). Afatinib, second-generation EGFR-TKI, was reported to be effective for NSCLC

with uncommon EGFR mutations and compound EGFR mutations (3). However, there is no report that Afatinib is effective in EGFR mutation-positive lung cancer without uncommon and compound EGFR mutations that increases early after treatment with osimertinib.

Here, we report a case of EGFR-mutated NSCLC treated with afatinib after early progression to osimertinib. We present the following article in accordance with the CARE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-1850/rc>).

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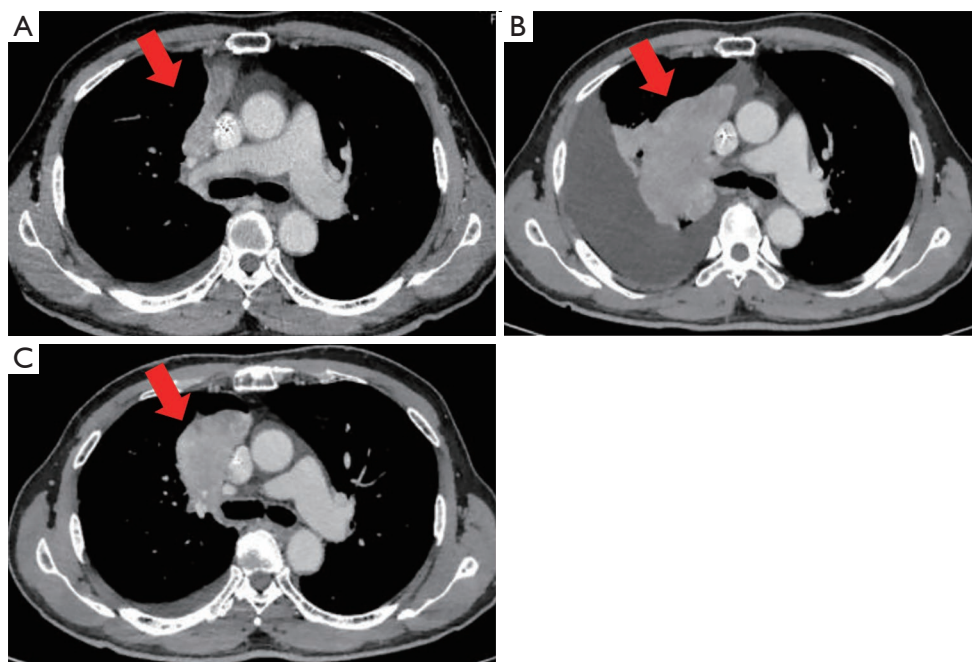


Figure 1 Chest CT images before and after afatinib treatment. The CT showed a primary tumor (red arrow) in the upper lobe of the right lung before osimertinib treatment (A). Two months after osimertinib treatment, rapid progression of primary tumor (red arrow) and pleural effusion were revealed by the CT (B). After one month of afatinib treatment, the CT demonstrated a good response of primary tumor (red arrow) and pleural effusion (C). CT, computed tomography.

Case presentation

A 68-year-old Japanese male with a smoking history was diagnosed with stage IVB lung adenocarcinoma with multiple bone metastases (cT3N1M1c, *Figure 1A*). *EGFR* gene detection showed the L858R mutation in exon 21. The patient started osimertinib treatment as a first-line chemotherapy. Two months after the start of osimertinib, a computed tomography (CT) scan revealed tumor progression (*Figure 1B*). We confirmed that this patient had no financial problems and was taking osimertinib daily. Because he refused to receive cytotoxic chemotherapy, afatinib treatment was initiated. After a month of treatment with afatinib, a CT scan showed a good response of the primary tumor in the upper right lobe (*Figure 1C*). To elucidate the resistance mechanisms of osimertinib in this patient, we performed amplicon sequencing (Ion AmpliSeq Comprehensive Cancer Panel, ThermoFisher Scientific, Waltham, MA) on tumor samples from pleural effusions after osimertinib failure. Amplicon sequencing revealed a high tumor mutational burden (TMB) (8.56 mutations per Mb); however, we found neither compound *EGFR* mutations nor HER-family gene mutations except for

the *EGFR* L858R mutation. After five months of afatinib treatment, nevertheless the primary tumor was not enlarged, he experienced disease progression with leptomeningeal metastasis and passed away.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Previous studies have demonstrated that there are few patients who have early progression to first-line osimertinib treatment. In the phase III FLAURA trial, first-line osimertinib had great treatment responses in *EGFR*-mutated NSCLC patients, and only 1% of patients (3 of 279) showed progressive disease as the best response in the osimertinib arm (2). Although the mechanisms of acquired

resistance to first-line osimertinib have been reported [MET amplification (15%), C797X (7%), PIK3CA mutation (7%), KRAS mutation (3%) and HER2 amplification (2%)] (4), c-Myc modulation (5), CD74 upregulation (6), and structural changes of *EGFR* mutations (7), the mechanisms of intrinsic resistance to osimertinib are largely unknown. Similarly, next-generation sequencing (NGS) analysis of tumor samples from our patient failed to find specific gene mutations or amplifications that caused resistance to osimertinib.

Afatinib was reported to be effective for NSCLC with uncommon *EGFR* mutations and compound *EGFR* mutations (3). In addition, there have been NSCLC patients with compound *EGFR* mutations who respond to afatinib immediately after osimertinib failure (8,9). Although we expected that tumor cells from our patient could have compound *EGFR* mutations and although the tumor showed a response to afatinib, NGS analysis did not demonstrate any uncommon or compound *EGFR* mutations in our patient. A phase I study investigating the safety of the combination of afatinib and osimertinib after failure of osimertinib reported a response rate of 7.7%, suggesting that the efficacy of afatinib combination therapy may be limited, but no predictive biomarkers are known (10). Previous studies observed a higher TMB in patients harboring *EGFR* L858R mutations than in those carrying exon 19 deletions, and a high TMB was correlated with a shorter survival time in patients with *EGFR*-mutated NSCLC receiving *EGFR*-TKIs (11). There is also a report that afatinib treatment decreased TMB (12). These findings indicate that afatinib is more effective for patients with high TMB *EGFR*-mutated NSCLC than other *EGFR*-TKIs. Because our patient had *EGFR*-mutated NSCLC with a high TMB, this could be a reason why afatinib had clinical activity in our patient after resistance to osimertinib. The limitation of this case was that the rebiopsy specimen was a cell block of pleural fluid, not from an enlarging primary tumor. In addition, if liquid biopsy had been performed, we may have found a specific gene mutation involved in *EGFR*-TKI resistance.

To the best of our knowledge, this is the first case to report the effectiveness of afatinib for *EGFR*-mutated NSCLC with early progression to osimertinib. Our findings suggest that the administration of afatinib is a treatment option in *EGFR*-mutated NSCLC patients with initial tolerance to first-line osimertinib.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-1850/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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