Transformation from acquired EGFR 19del/C797S to EGFR 19del/T790M in an advanced non-small cell lung cancer patient: a case report and literature review

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Third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the first-line treatment of choice for patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC). However, patients treated with these inhibitors eventually develop resistance. One of the most common mechanisms is the emergence of the EGFR C797S mutation. Whether first-generation EGFR inhibitors (e.g. icotinib or gefitinib) can sustainably control EGFR-sensitive mutations/C797S NSCLC following third-generation EGFR inhibitor treatment remains insufficiently reported. Our case report discusses a female patient with advanced lung adenocarcinoma carrying an EGFR exon 19 E746_A750delELREA mutation who received almonertinib as first-line treatment and developed C797S resistance during therapy. The patient was subsequently treated with a double dose of icotinib for 8 months until disease progression occurred, along with the development of an EGFR exon 20 T790M point mutation and TP53 mutation. This case provides clinical evidence suggesting that first-generation EGFR-TKIs may be an effective treatment strategy for patients with acquired EGFR 19del/C797S resistance following EGFR TKI therapy. *Anti-Cancer Drugs* 36: 513–517 Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc.

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Background

Third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the preferred first-line treatment for patients with advanced or metastatic non-small cell lung cancer (NSCLC) harboring common EGFR mutations [1]. While EGFR-TKIs have demonstrated significant clinical efficacy and better tolerability compared to chemotherapy, the emergence of acquired resistance during treatment remains a major challenge to their effectiveness. The mechanisms of resistance to EGFR-TKIs include secondary mutations such as T790M and C797S [2,3], alterations in downstream pathways (e.g. K-RAS mutations and PTEN loss) [4,5], activation of alternative signaling pathways (e.g. Met and IGF-1R) [6,7], and disruption of apoptosis pathways mediated by EGFR-TKIs (e.g. BCL2-like 11/BIM deletion polymorphisms) [8]. The EGFR T790M mutation is the most common mechanism of resistance to first-generation and second-generation EGFR-TKIs, but third-generation TKIs are generally effective in overcoming this issue [9]. In contrast, the EGFR C797S mutation, whether in cis (on the same allele as T790M) or trans (on different alleles), is commonly observed in patients with progression following third-generation TKI treatment, with reported incidence rates of 6–24% [10]. The C797S mutation is a late-onset resistance mechanism and is more commonly seen after second-line treatment with third-generation EGFR-TKIs [11]. Preclinical studies have shown that the EGFR C797S mutation may resensitize tumors to first-generation or second-generation EGFR-TKIs [12]. Given the lack of approved targeted therapies for these patients, it has been proposed to use first-generation or second-generation EGFR-TKIs in cases of acquired EGFR C797S mutations, thereby delaying the need for platinum-based chemotherapy [13]. This case is analyzed to provide insights into the clinical management of such scenarios and to serve as a reference for optimizing therapeutic strategies in clinical practice.

Case presentation

The patient is a 55-year-old female, nonsmoker. In April 2023, she presented with symptoms of 'cough and shortness of breath'. Chest CT revealed a 96 mm × 74 mm × 82 mm mass with increased density in the right lower lobe, multiple enlarged mediastinal lymph nodes in regions 1, 2R, 3, and 4R, thickened pericardium with effusion, and arc-shaped effusion in the right pleural cavity. Chest ultrasound revealed pleural and pericardial effusion. Closed chest drainage and pericardial

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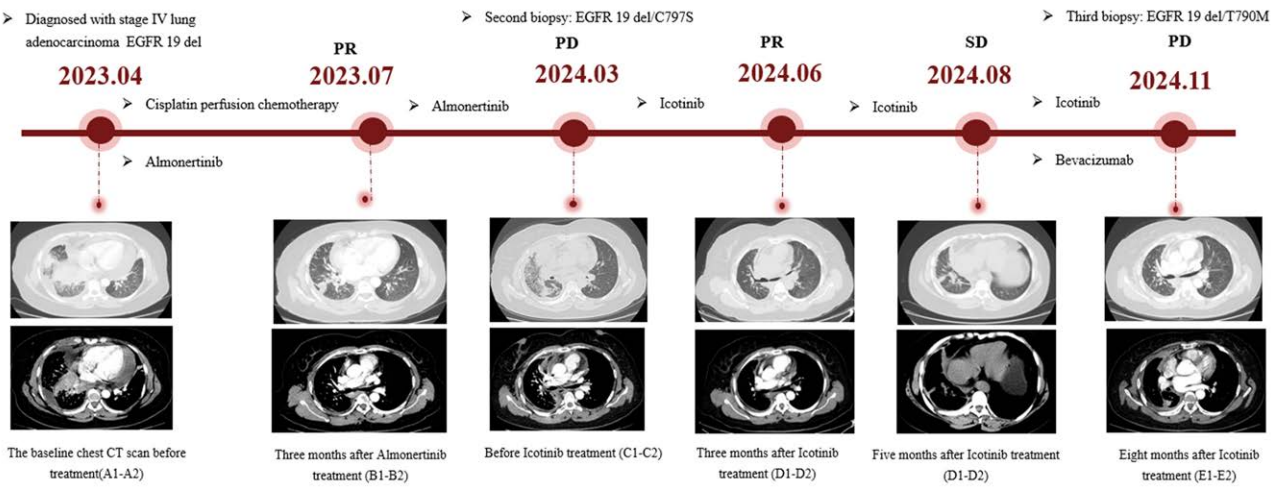
puncture catheterization were performed, and effusion analysis suggested malignant pleural and pericardial effusions. Cisplatin (20 mg) intrapleural chemotherapy was administered. On 28 April 2023, lung cancer genetic testing revealed an EGFR NM-005228 c.2236-2250del15 exon 19 deletion (p.E746-750delELREA), with a mutation frequency of 32.29%. Additional evaluations determined the clinical stage as right lung adenocarcinoma CT4N3M1c (involving pleura, pericardium, brain, and bones), stage IVB, with an EGFR exon 19 deletion.

With the consent of the patient and her family, almonertinib targeted therapy was initiated on 27 April 2023. In July 2023, follow-up indicated a reduction in the right lung lesion, decreased pleural effusion, and reduced intracranial lesions, along with lower tumor markers, suggesting effective treatment. Although some new bone metastases were detected, the patient experienced no pain or mobility issues. Continued almonertinib therapy was recommended, with monitoring of bone metastases and local treatment added if necessary. In October 2023, follow-up showed minimal changes in the right lung lesion compared to July 2023, further reduction in intracranial lesions, and stable tumor markers. Treatment efficacy was assessed as stable. Continued almonertinib therapy and monitoring of bone metastases were recommended, with local treatment added if needed.

In February 2024, follow-up chest CT showed progression of the lung lesion compared to before, suggesting tumor progression (Fig. 1, C1–C2). A second biopsy was recommended, and pathology confirmed adenocarcinoma. On 14 March 2024, genetic testing of lung tissue samples revealed an EGFR NM_005228.5 c.2236_2250del15 exon 19 deletion (p.E746_A750delELREA) with a mutation frequency of 3.91% and an EGFR NM_005228.5 c.2390G>C p.C797S mutation with a frequency of 3.1%. On 18 March 2024, icotinib (250 mg TID) therapy was initiated. A follow-up chest CT on 15 April 2024, showed a reduction in the right lower lung lesion, decreased exudate, and less pericardial effusion, indicating effective icotinib therapy. In June 2024, carcinoembryonic antigen (CEA) levels showed a slight increase compared to 5 March 2024 (Fig. 2). However, chest CT revealed a further reduction in the right lung lesion, decreased pericardial and right pleural effusions, stable bone metastases, and no new intracranial lesions. The tumor was assessed as stable, and icotinib treatment was continued.

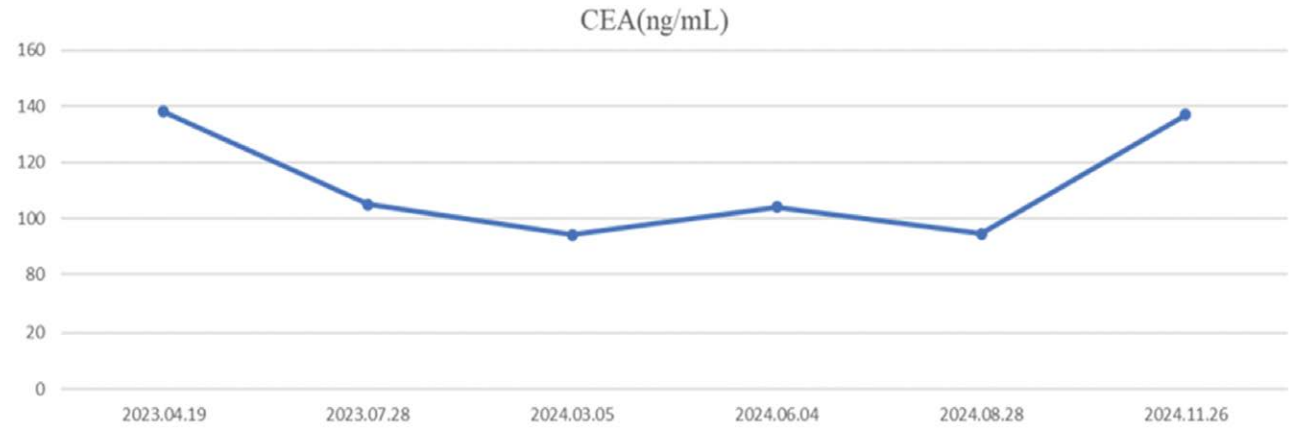
In August 2024, the patient's follow-up CT showed slight enlargement of the right lower lung lesion, with some tumor markers elevated. The recommendation was to administer a combination of icotinib and bevacizumab, along with local radiotherapy. The patient and family were fully informed and agreed to the combination therapy with bevacizumab but declined the local radiotherapy. Bevacizumab (500 mg) was administered intravenously on 29 August 2024 and 28 October 2024, although the patient did not adhere to the scheduled treatment regimen. In November 2024, follow-up indicated pleural effusion, a significant increase in CEA levels, and imaging suggested disease progression. It was recommended to perform a third biopsy and, if necessary, repeat genetic testing for lung cancer. The third biopsy revealed the following genetic mutations: EGFR NM_005228.5 c.2236_2250del p.E746_A750del exon 19 (mutation frequency 0.37%), EGFR NM_005228.5 c.2369C>T p.T790M exon 20 (mutation frequency 0.07%), and TP53 mutation NM_000546.6 c.641A>G p.H214R exon 6 (mutation frequency 0.21%). The patient is currently undergoing treatment with recombinant human vascular endothelial inhibitor combined with bafetinib.

Fig. 1



Timeline of the main events of this case report.

Fig. 2



The detection of CEA in different time periods. CEA, carcinoembryonic antigen.

Discussion

EGFR plays a crucial role in cellular signaling. Its activation promotes cell differentiation, proliferation, invasion, and angiogenesis [14]. EGFR mutation is the most frequently detected oncogenic driver in NSCLC among Asians, with an incidence rate of 38.8–64.0%, higher than that in Caucasians (4.9–17.4%) [15]. EGFR-mutated lung cancer is highly sensitive to EGFR-TKIs, which can significantly induce tumor cell apoptosis or growth inhibition [16]. EGFR-TKIs competitively bind to the ATP-binding site within the receptor. This inhibits the heterodimerization of EGFR with human epidermal growth factor receptor 2 (HER2) and its subsequent autophosphorylation, thereby reducing EGFR tyrosine kinase activity and effectively suppressing tumor growth [17]. Previous studies have shown that specifically blocking the EGFR signaling pathway with EGFR-TKIs can also inhibit tumors that have metastasized to other tissues [18]. In terms of targeted therapy, first-generation, second-generation, and third-generation EGFR-TKIs have all been shown to prolong the median progression-free survival (mPFS) of patients with advanced NSCLC carrying EGFR-sensitive mutations [19,20]. Thus, EGFR-TKIs are considered the standard first-line therapy for these patients. However, over time, patients with advanced NSCLC harboring EGFR-sensitive mutations inevitably face the challenge of resistance to EGFR-TKIs.

C797S mutation is considered a major acquired resistance mechanism to third-generation EGFR-TKIs, but there is no consensus on its management. In 2015, cell studies by Niederst *et al.* [21] demonstrated that in cells where C797S is present in the T790M wild-type background (i.e. without T790M), resistance to third-generation TKIs develops, but sensitivity to first-generation TKIs remains. This provides early experimental evidence that tumors with isolated C797S mutation after third-generation resistance may still respond to first-generation TKIs. Rangachari *et al.* [22] reported a case of a female patient with metastatic lung adenocarcinoma. Initial EGFR testing revealed exon 19 deletion (delE746_T751insV). She received osimertinib 80 mg/day as first-line therapy and developed asymptomatic brain progression after 10 months. The dose was increased to 160 mg/day, but 1 month later, progression in the lung, pleura, and abdomen was observed. Blood gene testing revealed EGFR exon 19 deletion, C797S mutation, and TP53 R174W mutation. Erlotinib was used for maintenance, achieving stable disease for 4 months. However, brain and lung progression occurred at 5 months and 5.5 months, respectively. Post-resistance blood genetic testing showed a triple cis mutation of EGFR exon 19 deletion, C797S, T790M, and TP53 R174W. Fei Cai *et al.* [23] reported a case of a 68-year-old female patient with advanced lung adenocarcinoma carrying an EGFR exon 19 deletion (E746_A750delinsIP). She received osimertinib as first-line therapy and experienced progression after 18 months. Subsequent genetic testing revealed the acquisition of the C797S resistance mutation. The patient, intolerant to chemotherapy, was treated with icotinib and achieved an 8-month progression-free survival (PFS). Paola Muscolino *et al.* [24] reported a 52-year-old female patient with advanced lung adenocarcinoma. At diagnosis, she had an EGFR exon 19 deletion (E746_A750del). After 18 months of first-line osimertinib, she experienced progression in the hilar lymph nodes, and blood testing revealed an additional EGFR C797S mutation. After combining with local radiotherapy, osimertinib was continued for 2 more months, but multiple progressions were observed. Repeat blood testing showed EGFR exon 19 deletion and increased abundance of the EGFR C797S mutation, prompting a switch to erlotinib. Erlotinib achieved a PFS of 5 months. Post-resistance testing revealed a triple mutation of EGFR

exon 19 deletion, C797S, and T790M. Additionally, the phase II INCREASE trial found that high-dose icotinib (250 mg TID) improved mPFS and overall response rate in patients with EGFR-mutated NSCLC, with acceptable tolerability [25]. Collectively, after third-generation EGFR resistance with isolated C797S mutation, treatment with first-generation TKIs may be effective, but overall efficacy can be influenced by various factors, including baseline genetic mutation profile, metastatic sites, tumor burden, local treatments, and individual immune status. There is significant interindividual variability.

Current clinical studies have shown that the combination of anti-EGFR and anti-VEGF drugs significantly prolongs mPFS in patients with advanced EGFR-mutant NSCLC [26]. The mechanism of such combination therapy is based on the shared downstream signaling pathways of EGFR and VEGF, which work to inhibit tumor growth and metastasis [27]. Several randomized clinical trials, including JO25567 [28], NEJ026 [29], ARTEMIS [30], BeTa [31], and RELAY [32], have demonstrated the efficacy of anti-EGFR/VEGF combination therapy in prolonging mPFS in patients. These findings indicate that combination therapy significantly prolongs mPFS in EGFR-mutant NSCLC. Unfortunately, in this case, the patient was unable to complete regular anti-EGFR/VEGF combination therapy due to personal reasons.

Conclusion

Most patients with EGFR mutations develop resistance to EGFR-TKIs, but the sequential development of multiple resistance mechanisms is rare. Third-generation EGFR-TKI therapy inevitably leads to acquired resistance, which limits its efficacy in patients with EGFR-mutant NSCLC. We report a case of an advanced NSCLC female patient with an initial diagnosis of an EGFR mutation. After developing resistance to third-generation EGFR-TKI therapy, retesting revealed EGFR 19del/C797S mutations. Subsequent treatment with a first-generation EGFR-TKI achieved prolonged survival, providing insights into treatment options for patients with C797S resistance.

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Conflicts of interest

There are no conflicts of interest.

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