Dynamic changes of acquired T790M mutation and small cell lung cancer transformation in a patient with EGFR-mutant adenocarcinoma after first- and third-generation EGFR-TKIs: a case report

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Abstract: Epithelial growth factor receptor (EGFR) T790M mutation and small cell lung cancer (SCLC) transformation are well-known resistance mechanisms acquired during treatment with EGFR tyrosine kinase inhibitors (TKIs). Various mechanisms sometimes coexist in patients. Here, we report a 57-year-old female diagnosed with stage IV lung adenocarcinoma, who harbored an EGFR exon 19 deletion mutation. This patient initially received gefitinib and progressed after 14 months. A repeat biopsy was performed, and the original EGFR exon 19 deletion and acquired exon 20 T790M mutation were identified. Then, pemetrexed plus carboplatin was administered as second-line and osimertinib as third-line treatment. Rapid progression and mixed response were observed after 2 months on osimertinib, with stable disease of the primary lung lesion but rapid growth of a right lower chest mass. The progressive chest lesion underwent biopsy, and the SCLC transformation was revealed. Furthermore, the patient was treated with etoposide and cisplatin, and she achieved disease control for 4 months. A fourth biopsy both for the primary lung lesion and the chest mass were finally conducted. Interestingly, the histopathology of the two different lesions showed adenocarcinoma and SCLC, respectively. The patient then rapidly suffered brain metastasis, and no EGFR mutations were detected in her cerebrospinal fluid (CSF). Overall survival (OS) of the patient was 29 months. This patient experienced concomitant resistance mechanisms of T790M mutation and SCLC transformation, which might have resulted from intra-tumor heterogeneity and drug-induced selection. Ultimately, this case reminds us that repeat biopsies are essential for patients receiving EGFR-TKIs in order to make appropriate treatment decisions according to the diverse mechanisms of acquired resistance.

Keywords: Case report; EGFR T790M mutation; osimertinib; small cell lung cancer (SCLC); transformation

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Introduction

Epidermal growth factor receptor (EGFR) inhibitors have revolutionized the treatment of EGFR-mutant non-small cell lung cancer (NSCLC) patients. Unfortunately, all patients will ultimately experience relapse with a median progression-free survival (PFS) of 7 to 16 months during the first- and second-generation EGFR-tyrosine kinase inhibitor (TKI) treatment (1,2). The major resistance mechanism is the EGFR T790M mutation within exon 20, observed in approximately 60% of resistant cases (3,4).

Osimertinib, a third-generation EGFR-TKI, is a pyrimidine-based irreversible inhibitor for both EGFR-activating mutations (e.g., exon 19 deletion or L858R) and T790M mutation. In AURA3, osimertinib was superior to...
platinum plus pemetrexed in patients with T790M-positive NSCLC who progressed during prior EGFR-TKI therapy, achieving a median PFS of 10.1 months (5). However, similar to first- and second-generation EGFR-TKIs, resistance to osimertinib is inevitable. Numerous resistance mechanisms have been discovered to date, of which transformation to small cell lung cancer (SCLC) has been defined as a rare mechanism occurring in approximately 2% of patients (6,7).

Hence, we report a case in which T790M mutation and SCLC transformation appeared sequentially during treatment with first- and third-generation EGFR-TKIs. We present the following case in accordance with the CARE-Guideline (8).

Case presentation

A 57-year-old never-smoking female complaining with intermittent cough presented in February 2015. Her father had been diagnosed with gastric adenocarcinoma and her sister with breast cancer. Physical examination suggested an Eastern Cooperative Oncology Group (ECOG) performance status of 1, and no significant abnormalities were found. Computed tomography (CT) scans of the chest showed a 20 mm × 14 mm mass in the middle lobe of the right lung, and two small nodules in the right middle lung, and right pleura (Figure 1A). Magnetic resonance imaging (MRI) of the brain and emission computed tomography (ECT) of the bone were also performed, and no other metastases were found. Both trans-bronchial biopsy and
pleural lesion biopsy confirmed lung adenocarcinomas (Figure 1B). EGFR exon 19 deletion was identified via the reverse transcription-polymerase chain reaction (RT-PCR) method. So the diagnosis of this patient was stage IV lung adenocarcinoma with an EGFR exon 19 deletion mutation (cT3N0M1a according to TNM version 7).

Gefitinib (250 mg daily) was initiated as first-line treatment from March 2015, and the best response was partial response (PR) according to the Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST 1.1). The disease progressed after 14 months, and repeat chest CT scans showed an enlarged right middle lobe mass (Figure 1C). Laboratory findings showed increased carcinoembryonic antigen (CEA) level of 11.1 ng/mL (normal range, 0 to 3.4 ng/mL) and neuron-specific enolase (NSE) of 15.44 ng/mL (normal range, 0 to 12.5 ng/mL) in the serum. A repeat biopsy of the right middle lung mass was performed and histologic analysis showed adenocarcinoma (Figure 1D). The results of immunohistochemistry (IHC) staining were positive for Napsin A, thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK-7). Next-generation sequencing including 8 genes (EGFR, ALK, KRAS, ROS-1, BRAF, RET, ERBB2, MET) revealed original EGFR exon 19 deletion and acquired exon 20 T790M mutation.

The third-generation EGFR-TKIs including osimertinib was not accessible in China until 2017, so pemetrexed (500 mg/m² intravenously on day 1, every 21 days) and carboplatin (AUC 5 intravenously on day 1, every 21 days) were administrated as second-line treatment. The patient achieved a response of PR and a PFS of 5 months. In October 2016, the chest CT scan showed an enlarged right middle lung mass (Figure 1E).

Then this patient was given osimertinib (80 mg daily) as third-line treatment. Regrettably, a mixed response was observed after 2 months, with stable disease of the lung lesions but a sharply increased right lower chest mass (Figure 1F). No metastases were found on brain MRI. The blood test showed significantly increases of NSE (from 24.9 ng/mL in December 2016 to 159.3 ng/mL in February 2017). Biopsy of the progressive chest lesion showed SCLC transformation (Figure 1G). The IHC staining results also showed a neuroendocrine morphology with CD56 and synaptophysin (SyN) positive, which was not seen in pre-osimertinib tumors, while Napsin A, TTF-1 and CK-7 were negative.

For fourth-line treatment, we chose etoposide (100 mg/m² intravenously on day 1 to 3) plus cisplatin (75 mg/m² intravenously on day 1, every 21 days), which is the standard regimen for advanced SCLCs. The level of NSE in serum was decreased dramatically to 14.97 ng/mL after two cycles of chemotherapy. The patient achieved a response of PR and a PFS of 4 months (Figure 1H). After progression, we did the fourth biopsy both for the right middle lung mass and the chest mass. Interestingly, the chest mass showed SCLC (Figure 1I), while the histopathology of the lung mass showed adenocarcinoma (Figure 1J). This patient rapidly developed brain metastases in July 2017. No EGFR mutations were detected in her cerebrospinal fluid (CSF). The tolerability of this patient was well during treatment. No severe or unanticipated adverse events were reported. She died in September 2017, and the overall survival (OS) of this patient was 29 months.

**Discussion**

SCLC transformation is one of the resistance mechanisms associated with first-generation EGFR-TKIs, accounting for about 10% of all cases (7,9). Resistance to osimertinib is also inevitable and numerous mechanisms have been discovered to date. Acquired EGFR C797S mutation was thought to be the major mechanism (10). Meanwhile, SCLC transformation has also been reported as a rare resistance mechanism, accounting for about 2% of cases (6,7). Until now, fewer than 10 SCLC transformation cases after third-generation EGFR-TKIs have been reported in total (11-14). The durations from third-generation EGFR-TKI initiation to transformation is 6 to 18 months, which suggests that long-term exposure to TKI may be needed for SCLC transformation. Furthermore, genomic analysis has shown that the primary EGFR mutation can be universally maintained and the SCLC and EGFR T790M-positive clonal subpopulations seem to be distinct from each other (15).

In our case, we report another metastatic adenocarcinoma patient harboring activating EGFR mutation who experienced T790M mutation and SCLC transformation dynamically after the treatment of first-generation EGFR-TKI gefitinib and third-generation EGFR-TKI osimertinib. Different from previously reported cases, the patient reported in our study experienced rapid SCLC transformation just 2 months after osimertinib initiation. Moreover, the case in our report lost T790M mutation as well as the primary EGFR exon 19 deletion after transformation, which might be a false test result because of the low sensitivity of CSF detection.

The mechanisms of SCLC transformation remain largely unresolved. Several studies have shown that...
alveolar type II cells may be common precursors of both lung adenocarcinoma and SCLC. Thus, EGFR-mutant lung cancers have the potential to transform into SCLCs during disease progression (16,17). Another hypothesis is that initial tumors consisted of mixed NSCLC and SCLC components. After treatment with EGFR-TKIs, the number of NSCLC decreased and the SCLC became dominant (16). This positive drug selection possibly depends on the tumor microenvironment in lesions in each organ, which results in spatial heterogeneity between lung and chest lesions.

It has been reported that the rapid increase of tumor markers including NSE and pro-gastrin releasing-peptide (pro-GRP) during EGFR-TKI treatment are usually an indication of transformation from NSCLC to SCLC (18-20). In the present case, the remarkably increase in serum levels of NSE highlighted the necessity of repeat biopsy and suggested SCLC transformation (Figure 2).

Recently, a retrospective study examined 58 NSCLC patients diagnosed with adenocarcinoma that transformed to SCLC after one or more EGFR-TKI treatments (21). Median time to transformation was 17.8 months (95% CI, 14.3 to 26.2 months). After transformation, both platinum-etoposide and taxanes yielded high response rates. Median OS after diagnosis was 31.5 months (95% CI, 24.8 to 41.3 months), whereas median survival after the time of SCLC transformation was 10.9 months (95% CI, 8.0 to 13.7 months). In our case, etoposide plus cisplatin chemotherapy yielded considerable response with a response of PR and a PFS of 4 months. The time from diagnosis to transformation was 24 months, and the OS of the patient was 29 months.

In summary, we experienced a case of concomitant mechanisms of drug-resistance via T790M mutation and transformation to SCLC. The dynamic changes among the specific mutations depend on drug-induced selection, which possibly led to drug-resistance. Overall, repeat biopsy is essential for patients whose disease progresses while they are receiving EGFR-TKIs so that appropriate treatment decisions can be made according to the diverse mechanisms of acquired resistance.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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

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Figure 2 Predictive function of NSE for SCLC transformation. After osimertinib therapy was initiated, the levels of NSE in the serum gradually increased. After etoposide plus cisplatin chemotherapy, the levels of NSE sharply decreased. SCLC, small cell lung cancer; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; Pem, pemetrexed; Carbo, carboplatin; VP-16, etoposide.
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