Case Report

Bevacizumab Combined with Icotinib Overcomes Osimertinib Resistance in a Patient of Non-Small-Cell Lung Cancer

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Abstract

A 61-year-old Chinese female patient was diagnosed with primary pulmonary adenocarcinoma of left superior lobe with epidermal growth factor receptor (EGFR) 19 del mutation positive. Treatment with Icotinib was given and her disease progressed after 6 months. CT-guide needle biopsy for the new lesion of inferior lobe of left lung demonstrated metastasis, and EGFR gene panel was test by Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS-PCR) confirmed EGFR T790M mutation. Treatment with Osimertinib was initiated. After 2 months remission, the disease progressed. The biopsy was performed for the new tumor of the inferior lobe of the left lung, and ARMS-PCR demonstrated no other gene mutation except EGFR 19 del. Icotinib was re-challenged, but disease progressed quickly. Bevacizumab was added, and after 2-cycle of combination therapy, partial response was achieved. Patients of non-small-cell lung cancer maintain EGFR activating mutation and loss of EGFR T790M mutation is a genetic change after Osimertinib treatment. This case suggests the re-challenge of first-generation EGFR-TKIs combines with bevacizumab may overcome its resistance and prolong patients' survival.

EPIDERMAL growth factor receptor (EGFR) C797S/G point mutation or loss of EGFR T790M was the most common genetic change in patients with non-small-cell lung cancer (NSCLC) harboring EGFR T790M mutation after resistance to osimertinib.^{1,2} Anti-EGFR antibody combined with EAI045 or Brigatinib could overcome Osimertinib resistance in vitro or in vivo if it was caused by EGFR L858R/C797S/T790M or EGFR del 19/C797S/T790M.^{3,4} But their clinical effects are largely unclear. There has been no standard care for patients who lose EGFR T790M mutation after Osimertinib resistance; re-challenge with first generation EGFR tyrosine kinase inhibitor (TKI) or systemic chemotherapy might be the optimal method.⁵ About 10%-30% Caucasian or 50% eastern Asian patients with NSCLC harbor EGFR mutation, and 60% of them will acquire EGFR T790M mutation after the first generation EGFR-TKI

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treatment with 10–13 months remission.^{6,7} Acquired resistance would happen after a median PFS of 9.6 months in patients receiving Osimertinib treatment (an irreversible third-generation EGFR-TKI).⁸ The resistance mechanism of Osimertinib is complex. To date, several mechanisms about resistance to Osimertinib have been identified, such as secondary EGFR mutation, EGFR amplification, and loss, low expression.^{9–11} Among them, EGFR C797S/G mutation happened in 20%-60% patients.¹² So Re-biopsy to study the resistance mechanisms at the time of disease progression is necessary to direct therapeutic regimens for patients with Osimertinib resistance.^{13,14}

Currently, no drug or therapeutic strategies has been approved for the treatment of Osimertinib resistant patients, especially for patients who are T790M negative or lost. Many strategies are mainly limited *in vitro* or *in vivo*,³ in lack of clinical data. It has been reported cytotoxic chemotherapy or protracted EGFR TKI treatment might be applied after disease progressed, but only a short survival time benefit was reached.^{15–17} We report a patient of NSCLC, who lost EGFR T790M mutation after Osimertinib treatment, was responsive to Icotinib plus bevacizumab therapy.

Case Description

A 61-years-old Chinese woman complained cough and fever for 2 weeks. She was admitted into hospital. CT scan showed a 10.1 cm X 6.1 cm mass in the left lung (Figure. 1A-1), with multiple metastatic nodulars of bilateral lungs, mediastinal lymph nodes enlargement, left pleural effusion, and small patchy lesions in the right lung. Pulmonary adenocarcinoma was confirmed by Core needle biopsy for the mass of left lung (Figure. 1A-2). EGFR test of tumor tissue was conducted by direct sequencing and EGFR 19 del was found. Diagnosis of primary lung adenocarcinoma with metastasis harboring EGFR activating mutation positive was established.

The patient was treated with Icotinib (Betta Pharmaceuticals, Hangzhou, China) orally at a dose of 125 mg three times a day for 2.5 months and partial response was reached (Fig. 1B-1). However, after 6 months remission, follow up CT scan found that the primary tumor enlarged and new lesion appeared on the inferior lobe of left lung. CT-guide needle biopsy was performed for the new lesion and intrapulmonary metastasis of lung adenocarcinoma was confirmed by pathologists (Fig 1C1-3). We performed EGFR gene panel test for biopsied specimen by Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS-PCR), and T790M mutation was found.

Subsequently, Osimertinib (Tagrisso, AZD9291, AstraZeneca) at a dose of 80 mg orally once daily was administered. On the follow up CT examination, we found the primary tumor of the left lung shrunk. Two months later, the patient experienced short of breath and pain of the right chest. CT scan showed right pleural effusion, and the metastatic lesion of the inferior lobe of left lung enlarged to 1.6 cm X 1.8 cm (Fig. 1D1-2). We performed thoracentesis and cytopathology found cancer cells in right pleural effusion.

Re-biopsy was performed for the enlarged left lung superior lobe lesion, and ARMS-PCR of the biopsy specimen still revealed EGFR 19 del positive, but EGFR T790M mutation was lost. Treatment of this patient was back to Icotinib at a dose of 125 mg three times each day orally. However, after 2 months, her disease progressed (Fig. 1E1-2). Bevacizumab (Avastin, Roche, Switzerland) was added intravenously at a dose of 7.5 mg/kg on day 0, every 21 days a cycle. After 2 cycles of Icotinib and bevacizumab treatment, the patient got remarkable response, and maintained remission till the last follow-up in 4 months (Fig. 1F1-2). Adverse effects in this patient included Grade 1 nausea after one month treatment and Grade 1 hypertension and rash after 4 months of treatment. No grade 3-4 adverse event was observed.

DISCUSSION

EGFR mutation accounts for 50% NSCLC patients in the East Asia.^{18,19} The exon 19 deletion and the exon 21 L858R mutation of the epidermal growth factor are activating mutations, which enhance the sensitivity of the NSCLC cells to the first-, second- or third-generation EGFR-TKIs, such as gefitinib, afatinib or osimertinib. For the first-line therapy with first-generation EGFR-TKIs in patients with EGFR mutations, the objective response rates (ORR) are 50-80% and progression-free survivals (PFS) are 9-12 month.^{6,7} EGFR T790M mutation of exon 20 is the most common acquired resistance mechanism, which accounts for about 50-60% in patients resistant to the first- generation EGFR-TKIs.²⁰

Osimertinib has high activity in EGFR T790M mutation advanced NSCLC, but resistance happened eventually, with a median PFS 9.6 months.⁸ The resistant mechanism was consider very complicated, while several resistant mechanisms to Osimertinib had been identified. The C797S/G mutation appears to be a leading resistant mechanism to the third-generation EGFR TKIs.¹² The structure of EGFR T790M mutation and C797S/G mutation happened more in cis than in trans.^{12,21-23} MET amplification, EGFR T790M loss, HER-2 or alternative kinase activation, SCLC or squamous cell transformation, and EML4-ALK rearrangement were also reported after resistance to Osimertinib.²⁴

Currently most studies focus on overcoming EGFR C797S/G mutation and alternative kinase activation by using combination therapy. EGFR 19 del /T790M/C797S would resist to all three-generation EGFR-TKIs, but EGFR L858R/T790M/C797S might be sensitive to EGFR monoclonal antibody; and EGFR T790M mutation with C797S in trans might be sensitive to the third-generation EGFR-TKIs.²⁵ All above studies were *in vitro* or *in vivo*, the clinical outcomes were unclear.

Figure1. CT and pathological images showing the therapeutic responses in a 61-year-old woman with left pulmonary adenocarcinoma. (A1) CT scan showed a 10.1 X 6.1cm mass in superior lobe of left lung, and with multiple metastatic nodulars of bilateral lungs. (A2) Nests of adenocarcinoma cells were observed in the fibrous connective tissue, arranged in an alveolar pattern (HE, X10). (B1) After 2.5 months Icotinib treatment, CT scan showed tumor size decreased to 3.2 cm X 2.2cm, partial response was reached. (C1-3) The primary tumor enlarged (3.1cm X 3.0cm) after 6 months remission, with new soft-tissue mass found in the inferior lobe of left lung, indicating disease progressed. The new lesion was biopsied and pathology found solid, poorly differentiated tumor cells consisted predominantly of glandular or adenoid structure, according with metastasis (HE, X40). (D 1-2) The primary tumor and the metastatic lesion enlarged after 2 months of Osimertinib treatment, indicating disease progressed. (E 1-2) The metastatic lesion in the inferior lobe of left lung enlarged continuously after 2 months treatment of Icotinib re-challenged, and right plural effusion appeared. (F 1-2) The primary tumor and intrapulmonary metastatic lesion shrank after 2-cycle chemotherapy, indicating partial response.

At present, there is no standard care for patients who maintained EGFR activating mutation but loss EGFR T790M mutation after Osimertinib treatment. The exact mechanism in Osimertinib resistance of the loss of EGFR T790M is not fully understood. In our previous study, only one of three patients maintained stable disease for three months after first-generation EGFR-TKI re-challenged. For this patient, disease progressed with 2 months of Icotinib treatment, but achieved partial response after combined with bevacizumab therapy. Further studies are needed for the combination of Icotinib and Bevacizumab in the treatment for patients with Osimertinib resistance who loss EGFR T790M mutations in future.

In conclusion, the mechanism of loss EGFR T790M mutation and maintain EGFR activating mutation has not been fully understand; re-challenge with first generation EGFR-TKIs combined with bevacizumab may overcome its resistance but need further study in future.

Conflict of interest statement

All authors disclosed no conflicting interests.

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