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Case Report
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Combination of Amineptine and Gefitinib Overcome Acquired Resistance in T790M/trans-C797S-EGFR-Mutated Non-Small Cell Lung Cancer: A Case Report

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Abstract

Osimertinib, a third-generation Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs), is the second-line treatment of choice for lung cancer patients who develop T790M mutation resistance after treatment with EGFR-TKIs, but resistance still inevitably occurs after use, and the mechanism of resistance and the choice of treatment regimen after resistance remain unclear. We report a case of right lung adenocarcinoma with intrapulmonary Metastasis (pT2N0M1b, stage IV) that developed T790M/trans-C797S-EGFR-mutate after and to provide clinical evidence of EGFR-TKIs in the treatment of lung cancer and to provide reference for future studies on the treatment of similar cases and the mechanism of resistance to Osimertinib.

Introduction

In China, about 50.2% of the Non-Small Cell Lung Cancer (NSCLC) patients have Epidermal Growth Factor Receptor (EGFR) gene mutations, which are more common in women and smoking patients [1]. The results of numerous clinical trials have shown [2,3] that Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs) can significantly improve the prognosis of patients compared with conventional chemotherapy, can be used as a first-line treatment for patients with advanced NSCLC. Nevertheless, EGFR-TKIs inevitably develop drug resistance after a period of use. The mechanisms of resistance are heterogeneous for different types of EGFR-TKIs, and Osimertinib, as a third-generation EGFR-TKIs, is used as the preferred second-line therapeutic agent when resistance occurs after the use of first-generation EGFR-TKIs such as gefitinib and erlotinib [4]. EGFR C797S mutation is a common mechanism of resistance after the use of Osimertinib, and related studies have shown that T790M/trans-C797S-EGFR-mutate occurs after Osimertinib resistance, good results can be achieved with the combined of first- and third-generation TKIs [5]. We now report a case of an advanced lung adenocarcinoma patient who developed resistance after chemotherapy, second-line treatment with first-generation EGFR-TKIs, and third-line treatment with Osimertinib, finally the T790M/trans-C797S EGFR mutation was detected by genetic testing of blood samples, was subsequently treated with first-generation combined with third-generation EGFR-TKIs, which was consistently effective at press time and achieved Progression-Free Survival (PFS).

Case Presentation

A 65-year-old woman with no history of smoking came into the clinic with "physical examination found pulmonary nodules with chest tightness and pain for 1 month" on July 18th, 2014. The patient was found lobulated nodules (about 2.2 cm × 1.3 cm) at the right upper lung, with multiple burrs around, and multiple small nodules in the other two lungs by Computed Tomography (CT) screening in Peking University People's Hospital on June 11th, 2014. Considering the possibility of intrapulmonary metastasis. The diagnosis was infiltrated adenocarcinoma (right upper lung) by pathological results aspiration biopsy. There was no EGFR mutation by Amplification Refractory Mutation System PCR (ARMS PCR). The TNM stage was cT2N0M1b, a. The patient received 4 cycles of pemetrexed + cisplatin chemotherapy (pemetrexed 800 mg, d1; cisplatin 40 mg, d1-3; q21d). The curative effect was evaluated as PR according to the therapeutic effect evaluation criteria for solid tumors (RECIST1.1). After chemotherapy, the patient had skin adverse reactions (grade III): Systemic rash, and the symptoms were relieved after anti allergic and symptomatic treatment.

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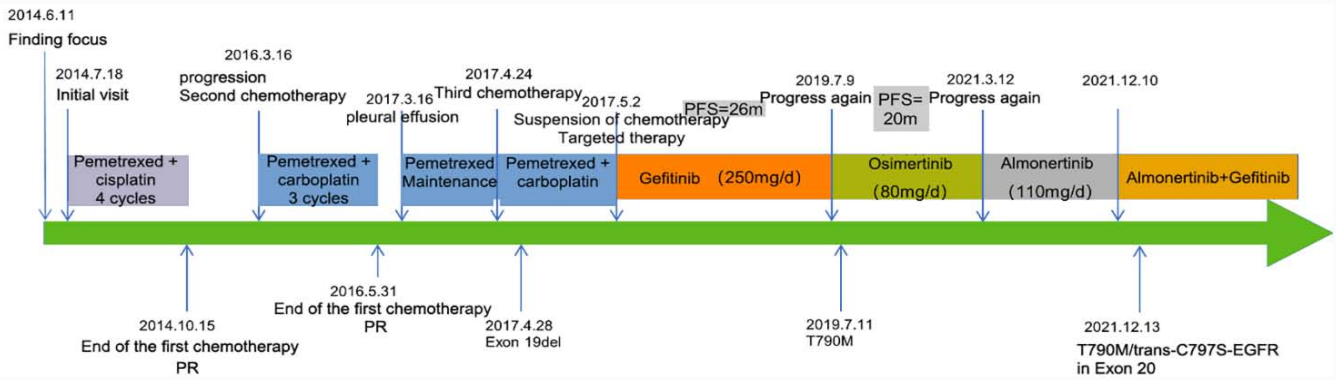

Figure 1: Treatment timeline. The whole treatment process and the detection time of different mutant genes.

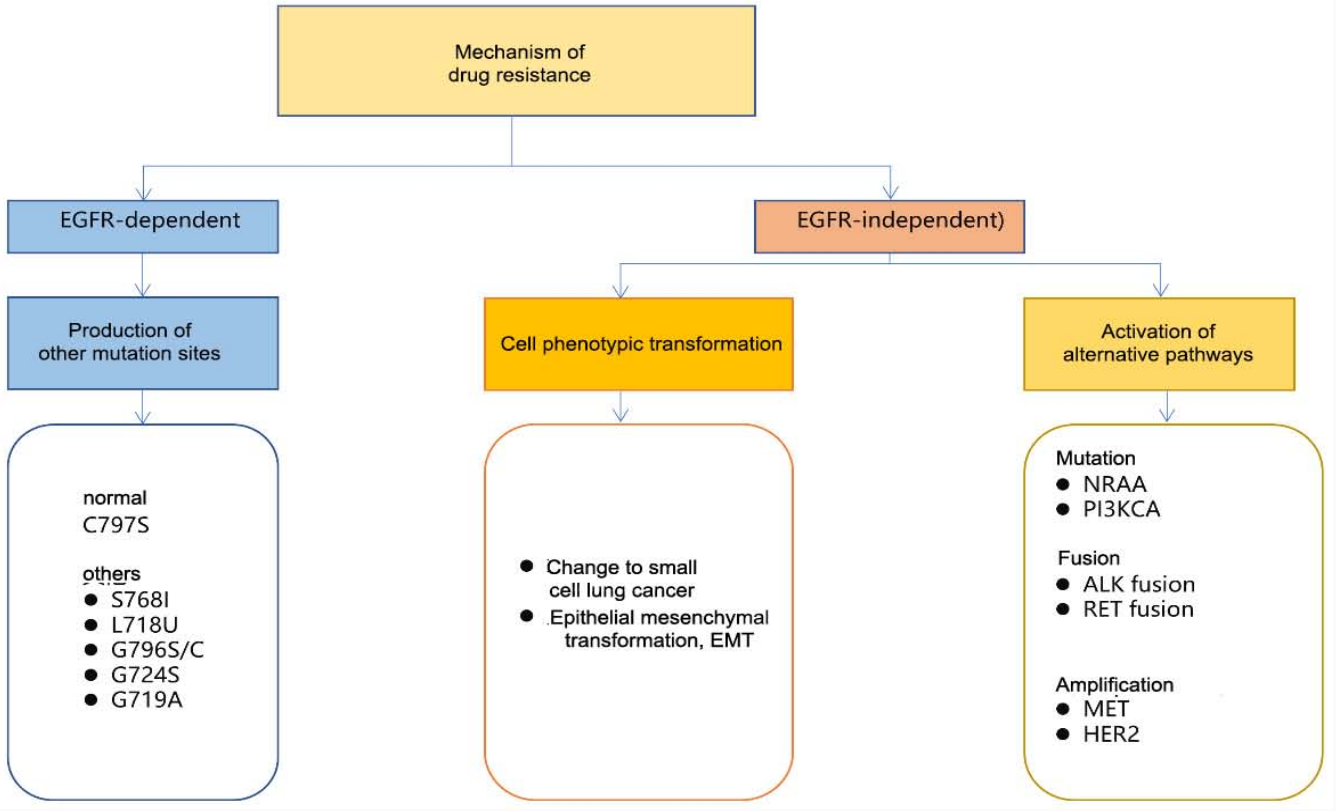

Figure 2: CT images of different periods after EGFR TKIs. A: Before using Gefitinib; B: Use Gefitinib for 2 months; C: Disease progression after 26 months of Gefitinib was used; D: Use Osimertinib for 2 months; E: Tumor progression after maintenance therapy with Almonertinib; F: After 2 months of replacement with Almonertinib + Gefitinib, the lesions were significantly reduced.

On February 25th, 2016, the primary lesion in the upper right lobe of the patient was increased, considering the Progressive Disease (PD). On March 16th, 2016, pemetrexed + carboplatin chemotherapy was performed for 3 cycles (pemetrexed 800 mg, d1; carboplatin 375 mg, d2; q21d). After 3 cycles, the curative effect was evaluated as PR without obvious adverse reactions. CT re-examination on March 16th, 2017 showed that the space occupying lesion at the tip of the upper lobe of the right lung was larger than that in the previous film, and there were multiple nodules and miliary foci in both lungs. The right side was obvious. It was considered as a metastatic tumor, and some of them were larger than that in the previous film. Irregular thickening of the right pleura with right pleural effusion (Figure 2A). As the patient's condition progressed, he was given hydrothorax treatment and the hydrothorax sample was sent for pathological examination. Highly heterogeneous cell clusters were found in the pleural effusion. The diagnosis was: Right lung adenocarcinoma with intrapulmonary metastasis (pT2N0M1b, a, cancerous pleural effusion). Pemetrexed was given for single drug maintenance (pemetrexed 800 mg, D1; q21d), and pemetrexed + carboplatin chemotherapy was given for 1 cycle on April 24th, 2017. On April 26th, 2017, the results of pleural effusion samples detected by ARSM method showed EGFR Exon 19-del. The first-generation EGFR TKIs Gefitinib (250 mg/d) was taken orally on May 2nd, 2017. After two months of treatment, the efficacy was evaluated as PR (Figure 2B). On July 9th, 2019, CT showed new lesions (Figure 2C), the disease progressed again, and Gefitinib was resistant. On July 11th, 2019, the detection of peripheral

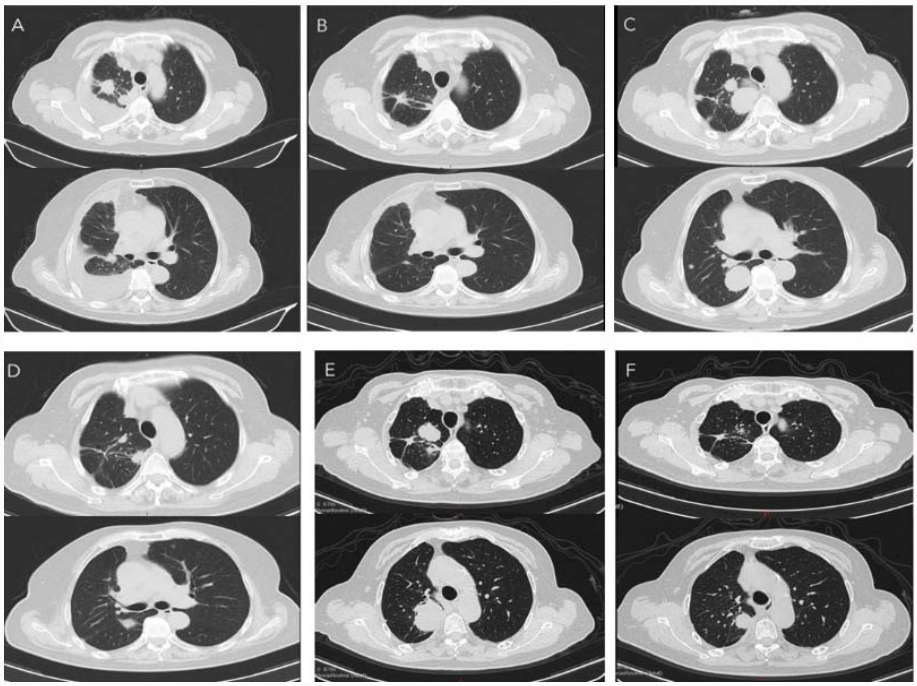

Figure 3: Resistance mechanism of Osimertinib.

blood samples (ARSM method) found that EGFR Exon 20 T790M was resistant to mutation. Subsequently, three generations of EGFR TKIs Osimertinib were given (80 mg/d), and the efficacy reached PR (Figure 2D). On March 12th, 2021, CT examination results showed that the nodules in the upper lobe of the right lung were larger than before, so it was inferred that Osimertinib was resistant. The target drug of the same generation, Almonertinib (110 mg/d), was replaced for maintenance treatment for 9 months to achieve Stable Disease (SD). On December 10th, 2021, CT results showed that the right lung lesion was significantly larger than before (Figure 2E). On December 13th, 2021, the results of ctDNA in plasma by Next Generation Sequencing (NGS) showed an Exon 19 deletion and a T790M/trans-C797S-EGFR in Exon 20. Almonertinib was used in combination with first generation EGFR TKIs Gefitinib. On February 10th, 2022, CT results showed that the right pulmonary nodule was reduced by about 60% compared with that before treatment (Figure 2F), and the curative effect was evaluated as PR. At present, the patient is generally in good condition and continues to receive treatment (Figure 1).

Discussion

The mutation of EGFR gene in non-small cell lung cancer was first reported in 2004 [6]. About 50.2% of lung adenocarcinoma patients in China have EGFR mutations, which are common in women and non-smoking patients. The most common mutations are EGFR Exon 19 deletion (EGFR Exon 19 Del) and Exon 21 L858R mutation (EGFR Exon 21-L858R), accounting for 94.4% of the total EGFR mutations [1]. At present, EGFR TKIs has become the first-line treatment for non-small cell lung cancer patients with positive driver gene mutations. Many phases III clinical trials show that [2,3], compared with chemotherapy regimen, EGFR TKIs has better Response Rate (RR), longer Progression Free Survival (PFS) and less side effects. Gefitinib, Erlotinib and other first-generation EGFR TKIs compete with ATP for the ATP binding region of EGFR in the way of reversible covalent bond binding, resulting in the inhibition of EGFR activity. However, about one year after the first generation of EGFR TKIs was used, many patients developed drug resistance, and the most common drug resistance mutation was EGFR T790M [7]. The EGFR driver gene was not detected in this patient at the initial diagnosis. Therefore, the dual drug combined chemotherapy based on platinum drugs was selected as the first-line treatment. There was progress in the follow-up treatment, and the final chemotherapy failed. Subsequently, EGFR T790M mutation was detected in pleural effusion samples, providing a basis for subsequent targeted therapy. There are two possibilities that the driver gene mutation was not detected initially. First, the patient obtained samples through Percutaneous Transthoracic Needle Biopsy (PTNB) technology for molecular pathological detection. The sample size of tumor tissue was small, and there may be EGFR gene heterogeneity in the tumor tissue, which may lead to false negative test results. The heterogeneity of EGFR gene in lung adenocarcinoma tissue is related to its pathological classification, among which the papillary type, adherent growth type and microemulsion head type are more prone to EGFR mutation [8]. Second, EGFR gene mutation status may change after chemotherapy. In a study involving 203 patients with advanced NSCLS, 36 patients were found to have EGFR mutation from negative to positive after chemotherapy, which suggests that chemotherapy may affect EGFR mutation status in patients with advanced NSCLC [9]. The EGFR driver gene mutation was subsequently detected in this patient. After targeted treatment with Gefitinib, the tumor shrank significantly, the pleural effusion disappeared, and the therapeutic effect reached pr. As of July 9th, 2019, CT showed the progress of the disease, and PFS reached 26 months. The third generation EGF TKIs Osimertinib binds to the cysteine residue at site 797 of EGFR in the form of irreversible covalent bond to exert targeted inhibition. At the same time, it has high selectivity and less binding with wild-type EGFR, which can significantly reduce the occurrence of adverse reactions and give full play to the inhibition of EGFR T790M mutation [10]. The study of AURA3 showed that in the follow-up treatment of

patients with T790M drug-resistant mutation after receiving the first- and second-generation EGFR TKIs, the Response Rate (RR) of Osimertinib was 71% and the median PFS was 11.0 months [4]. After the patient had T790M drug-resistant mutation, the patient was treated with Osimertinib, the focus was reduced, and the therapeutic effect reached PR. After 20 months of using Osimertinib, the drug resistance reappeared. After 9 months of maintenance treatment, the disease was stable (SD). As the first third-generation EGFR TKIs developed by China, Almonertinib has added cyclopropyl to its chemical structure compared with Osimertinib, so as to obtain higher selectivity and inhibitory effect. The introduction of cyclopropyl also enhances the fat solubility of the drug, making it easier to pass through the blood-brain barrier, and has a better effect on patients with brain metastasis. At the same time, in vitro studies showed that Almonertinib had less inhibitory effect on wild-type EGFR, greatly reduced the incidence of side effects such as rash and diarrhea, and had higher safety and tolerance. The results of relevant phase I/II clinical trials showed that the overall response rate of Almonertinib was 69.9%, the disease control rate was 93.4%, the median progression free survival was 12.4 months, and the incidence of grade III and above adverse drug events was 16.4% [11,12]. Studies have shown that drug resistance mutations still occur after 11 months of second-line treatment or 19 months of first-line treatment with third-generation TKIs [13]. At present, the drug resistance mechanisms of the third generation TKIs can be divided into two categories: EGFR dependent and EGFR independent (Figure 3). The EGFR dependent mechanism can be summarized as that the conformation changes of Osimertinib binding site caused by the production of new EGFR mutations leads to the failure of drug inhibition. The most common mechanism is the conformational change of binding site caused by serine substitution of cysteine at Exon 797 of EGFR 20 (EGFR Exon 20 C797S). The EGFR independent mechanism is realized through the activation of alternative pathway, such as the amplification of MET and HER2 or the transfer of dependence on EGFR signal through phenotypic transformation. AURA study showed that about 21% of patients had acquired EGFR gene mutations, of which C797S was the most common, accounting for about 14%. The study indicated that another 19% of patients had met amplification [14]. The other proved that the probability of MET amplification and C797S mutation in patients with first-line resistance to Osimertinib was 15% and 7% [15]. T790M was also not detected in this patient. Therefore, for the patients who used Osimertinib in the first line, the treatment with first generation of EGFR TKIs after drug resistance could still produce good results [4]. Most patients with drug-resistant mutations in the second-line use of Osimertinib have EGFR C797S and T790M at the same time. The two mutations are called trans mutations when they are located in different alleles. They are sensitive to the combined use of the first and third generation EGFR TKIs [15]. The clinical efficacy of this treatment scheme has been verified in the case report [16,17]. An ongoing I/II clinical trial (NCT03122717) is exploring the feasibility of Gefitinib combined with Osimertinib as a first-line drug for the treatment of advanced non-small cell lung cancer with EGFR mutation [17]. The results showed that the patients with T790M/cis-C797S were completely resistant to EGFR TKIs, and chemotherapy was the recommended regimen for the occurrence of such mutations. A recent clinical study found that Cetuximab (EGFR monoclonal antibody) combined with Brigatinib (dual inhibitor of EGFR and ALK) has a good effect on T790M/cis-C797S mutation [18]. In a study involving 17 patients with Osimertinib resistance with T790M/cis-C797S, 5 received Cetuximab + Brigatinib treatment, and the disease control rate reached 100% [19]. However, there is still a lack of unified and effective treatment for patients with T790M/cis-C797S mutation resistance. In 2017, a study reported that EAI045, as the fourth generation EGFR TKIs, showed a good inhibitory effect on EGFR L858R/T790M/C797S mutant, however it only works when combined with Cetuximab, which limits its clinical application [20]. Other fourth generation EGFR TKIs, such as JBJ-04-125-02 [21] and BLU945 [22], which are still in the experimental stage, have shown good inhibitory effects on EGFR T790M/C797S mutant tumor cells at the cellular level. The patient developed T790M/trans-C797S-EGFR-mutation after 29 months of using the third generation EGFR TKIs. The patient was treated with third generation of TKIs Almonertinib combined with first generation of TKIs Gefitinib. The tumor shrank significantly and the therapeutic effect reached PR. Compared with the first- and second-generation EGFR TKIs, the drug resistance mechanism of the third generation TKIs was more complex, and there is a lack of standard treatment after drug resistance.

Conclusion

This case report suggested that the combination of three generations of EGFR TKIs and the first generation of EGFR TKIs was one of the effective schemes for the treatment of patients with T790M/trans-C797S-EGFR-mutation resistance, and provided a reference for the treatment of patients with related drug resistance mutations in clinic.

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