Case Report

Effective targeted therapy based on dynamic monitoring of gene mutations in non-small cell lung cancer

Tan Deng, Jiao Tang, Lijun Zhou, Huaxin Duan

Oncology Department, Hunan Provincial People's Hospital, Changsha 410005, China

Correspondence to: Prof. Huaxin Duan. Oncology Department, Hunan Provincial People's Hospital, Changsha 410005, China.
Email: huaxinduan_123@sina.com.

Abstract: With the rapid development of precision medicine, next generation sequencing (NGS) has provided the ability to decode tumors at the DNA level. In treatment of patients with non-small cell lung cancer (NSCLC), it is of great importance to identify epidermal growth factor receptor (*EGFR*) mutations and drug resistance mechanisms in the late stages. A Chinese Han male patient (64 years old) who was initially diagnosed with EGFR-19-deletion-positive advanced NSCLC had a satisfactory clinical response after treatment with erlotinib. Subsequently, the disease progressed and NGS in plasma-derived circulating tumor DNA (ctDNA) revealed T790M mutation. The patient was then treated with osimertinib. In addition, NGS in ctDNA was performed again after the disease progressed, suggesting that *MET* was amplified, and then the patient was alternatively treated with combination therapy of crizotinib and erlotinib. The disease progressed for the third time, and treatment with osimertinib was undertaken again according to the T790M testing results. Dynamic monitoring of ctDNA was found to be helpful in selecting the appropriate treatment methods and prolonging the survival time of the patient.

Keywords: Non-small cell lung cancer (NSCLC); molecular targeted therapy; next generation sequencing (NGS)

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Introduction

Lung cancer is still the malignant tumor type with the highest morbidity and mortality in the world (1). In recent years, with the development of oncomolecularbiology and the emergence of the concept of precision medicine, several scholars have attempted to provide individualized treatment for breast cancer patients. Molecular targeted therapy, as a new method of tumor treatment different from the conventional treatment methods of malignant tumor, such as surgery, chemotherapy, and radiotherapy, has become an intensely researched area of tumor treatment with its advantages of high efficacy, low toxic side effects, and high specificity for patients with epidermal growth factor receptor (*EGFR*)-mutant lung cancer. *EGFR* has tyrosine kinase activity and is associated with the proliferation, angiogenesis, invasion, and metastasis of tumor cells (2). *EGFR*-tyrosine kinase inhibitors (EGFR-TKIs) can reversibly compete with adenosine triphosphate-binding sites of *EGFR*, and block *EGFR* signal transduction, thereby inhibiting the growth and proliferation of tumor cells (3). Several clinical studies (4-6) have confirmed that EGFR-TKI was superior to chemotherapy alone in the treatment of advanced non-small cell lung cancer (NSCLC) with *EGFR* mutation. In addition, overall response rate (ORR) was estimated to be within 70%, and was shown to significantly prolong progression-free survival (PFS) and overall survival (OS) of patients (7). EGFR-TKIs have been recommended by the National Comprehensive Cancer Network (NCCN) as a potential first-line treatment for advanced NSCLC patients positive for *EGFR* mutations (8).

About 90% of *EGFR* mutations are 19 deletions or L858R point mutations. In the majority of cases, *EGFR* mutation does not simultaneously occur with other carcinogenic gene mutations (such as *KRAS* mutation or *ALK* fusion). In the actual treatment, the majority of patients who are sensitive

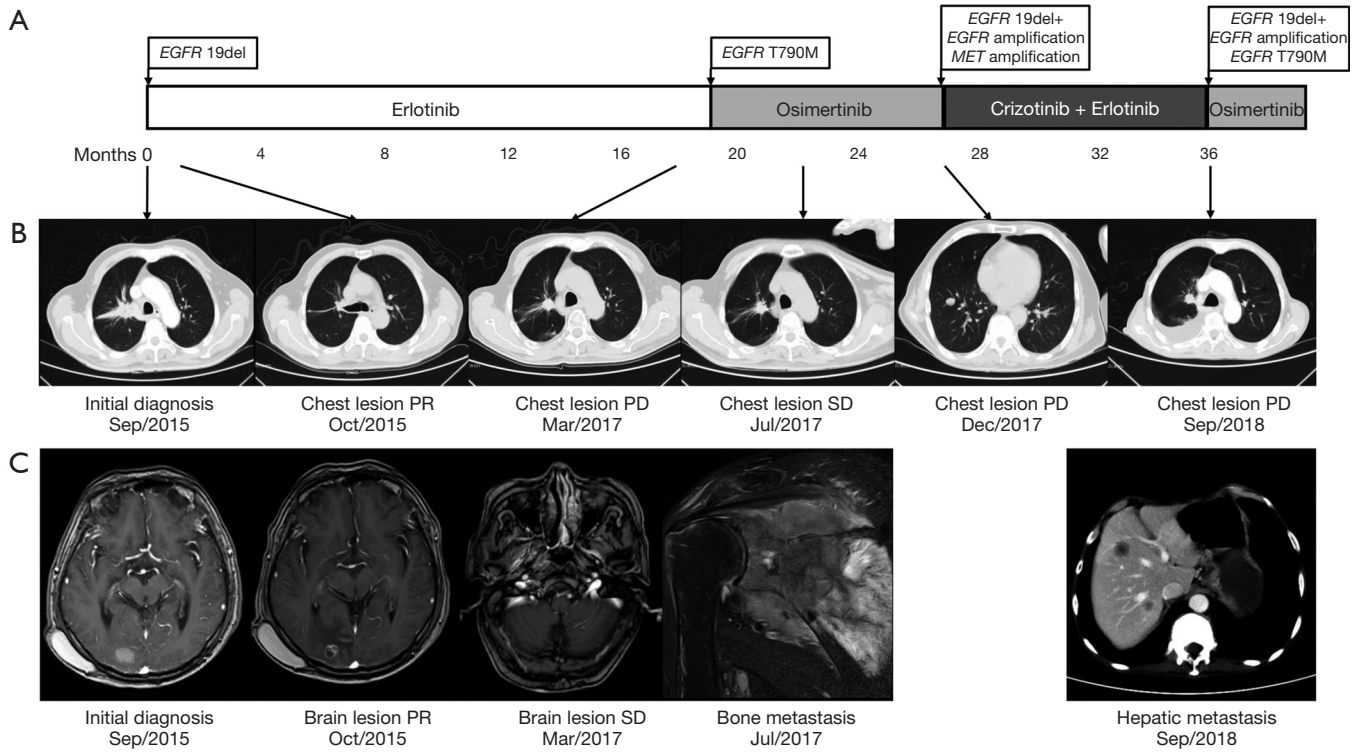

Figure 1 Timeline of patient's therapy and effect of therapy. (A) Genomic testing and targeted treatments; (B) chest CT scanning of primary lung tumor; (C) MRI of brain and bone metastasis; abdominal CT scanning of hepatic metastasis. EGFR, epidermal growth factor receptor; PR, partial remission; PD, progressive disease; SD, stable disease; CT, computed tomography; MRI, magnetic resonance imaging.

to EGFR-TKI therapy develop drug resistance in about 12 months. The most common mechanism of acquired resistance is the *EGFR* T790M gatekeeper mutation which is detectable in approximately 50–60% of patients; the other drug resistance mechanisms include *C-Met*, *HER-2* amplification (15–20%), and others (9).

Osimertinib treatment is effective in patients with T790M mutation, and drug resistance mainly occurs after a period of time. A cohort study used next generation sequencing (NGS) on 143 patients and revealed that 41 patients developed drug resistance. Additionally, T790M mutation was detected in 13 patients, and *EGFR* C797S mutation was detected in 9 patients. Among 28 individuals with loss of T790M, a range of competing resistance mechanisms was detected, including *RET*, *FGFR3*, *BRAF* fusion, and *KRAS* mutations (10). With the broad application of osimertinib in clinical practice, acquired drug resistance has become the main reason for the failure of treatment with EGFR-TKIs (11-17). Investigations of the causes of this drug resistance from molecular and clinical perspectives are of great importance in overcoming this problem. Genomic analysis of cell-free DNA in plasma has been used to explain two new drug resistance mechanisms of osimertinib: acquired *EGFR* C797S mutation and T790M mutation deletion (18). In this study, we report a case of lung adenocarcinoma with T790M mutation deletion and subsequent *MET* amplification as the mechanism of EGFR-TKI resistance.

Case presentation

A 64-year-old Chinese Han male was admitted to our hospital on September 1st, 2015 for vertigo and fatigue lasting more than half a month, along with cough and expectoration for 2 days. He was diagnosed with adenocarcinoma of the right lung by transbronchial biopsy, accompanied by bone metastasis and intracranial metastasis. Tissue detection of *EGFR* gene indicated deletion of exon 19 (*Figure 1A*) by real-time PCR. Erlotinib was taken orally at 150 mg capsule per day and zoledronic acid intravenous drip was used for bone treatment beginning September 7th, 2015. On October 14th, the results of thoracic and abdominal computed

tomography (CT) scanning showed the primary lesion was smaller than before (*Figure 1B*). Magnetic resonance imaging (MRI) of the brain revealed that the metastasis was significantly smaller than before, and the surrounding edema was reduced (*Figure 1C*). The curative effect was evaluated as partial remission (PR). After that, the patient complained of dizziness that was aggravated, and was subsequently treated with whole brain radiotherapy PTV 30 Gy/10 F. In September 2016, the MRI reexamination of the brain showed that the brain lesion was smaller and the surrounding edema had disappeared. However, the thoracic lesions progressed, and the plasma-derived circulating tumor DNA (ctDNA) detection of T790M in *EGFR* gene indicated T790M mutation by targeted NGS, the frequency of which was 1.7%. Since osimertinib has not yet been listed in China, chest radiotherapy PTV 60 Gy/30 F was then successfully performed, and treatment with erlotinib continued. On the March 16th, 2017, chest-abdomen-pelvis CT showed progression of the disease (*Figure 1B*), and MRI of the brain showed stable disease (SD) of the lesion (*Figure 1C*). Osimertinib was taken orally from April 25th, 2017 (*Figure 1A*). On the July 24th, 2017, chest-abdomen-pelvis CT showed the lesion as SD (*Figure 1B*), but the pain in the left shoulder had worsened. The MRI examination of the left shoulder showed metastatic tumor at the left scapula (*Figure 1C*). From August 1st, 2017 to September 8th, 2017, intensity-modulated radiation therapy (IMRT) was carried out by 6-MX X-ray on the left shoulder joints, and the pain was relieved. On December 5th, 2017, chest-abdomen-pelvis CT showed that the main lesion of the right lung was stable, and new lesions appeared in the right lung and the lower lobe of the left lung, indicating progressive disease (PD) (*Figure 1B*). *EGFR* exon 19 p.L747_P753 delinsS (26.99%), *MET* amplification (4), and *EGFR* amplification (4) were found by targeted NGS of ctDNA (*Figure 2*). Targeted therapy with crizotinib plus erlotinib was started. In August 2018, chest CT scanning showed pleural effusion (*Figure 1B*), abdominal CT scanning showed hepatic metastasis (*Figure 1C*), suggesting PD. Panel detection of cancer driver gene revealed *EGFR* exon 19 p.L747_P753 delinsS (85.78%), exon 20 p.T790M (11.75%), *EGFR* amplification (4), *KRAS* exon 2 G12R (0.73%), and KRAS exon V14I (0.14%) by targeted NGS of ctDNA (*Figure 3*). At present, the patient is under treatment with osimertinib.

Discussion

Selection of molecular targeted drugs according to different molecular characteristics can significantly prolong the median survival time of patients. Kris *et al.* (19) conducted a retrospective analysis on 733 patients with advanced NSCLC, and found that the maximum median survival time for patients who had a gene mutation that could be targeted by drugs and receive the corresponding targeted therapy was 3.49 years, which was significantly higher than that of the other two groups. Moreover, targeted therapy, similar to chemotherapy, also faces the drug resistance problems and therapeutic approaches should be further studied to find out new targets. The use of various targeted drugs, the continuous monitoring of drug resistance in treatment process, and advancing targeted therapies all depend on the wide application of NGS in clinical practice.

In this study, a typical case of *EGFR*-mutation-positive pulmonary adenocarcinoma combined with brain metastasis was reviewed. The drug resistance was dynamically monitored in peripheral blood during the treatment, the targeted therapy was carried out, and sustained remission was eventually achieved. Initially, *EGFR* gene detection indicated a typical exon 19 deletion, and the disease was controlled after treatment with erlotinib (PFS was 12 months). Afterwards, the disease progressed, reflecting resistance to erlotinib, the genetic testing results showed T790M mutation, and erlotinib continued to be taken orally for 5 months after local treatment. Subsequently, the patient was treated with osimertinib for continuous targeted therapy (PFS was 8 months). After 28 months of treatment, the disease progressed again. The NGS results showed that in addition to *EGFR* 19del+, *EGFR* gene copy number and *MET* gene copy number were both amplified. Then, crizotinib plus gefitinib therapy was undertaken. After 36 months of treatment, the NGS results showed a T790M mutation; thus, the patient was alternatively treated with osimertinib.

Compared with the traditional detection methods, the sensitivity of NGS is a remarkable advancement, with a reported detection sensitivity of 0.1–1.0%. Increased sensitivity has made it possible to detect ctDNA in blood samples and has enabled the analysis of fusion genes and copy number variations. Additionally, the detection method of ctDNA is relatively non-invasive, and patients do not need to tolerate a greater risk, causing patients to have a better willingness and compliance for ctDNA detection (20).

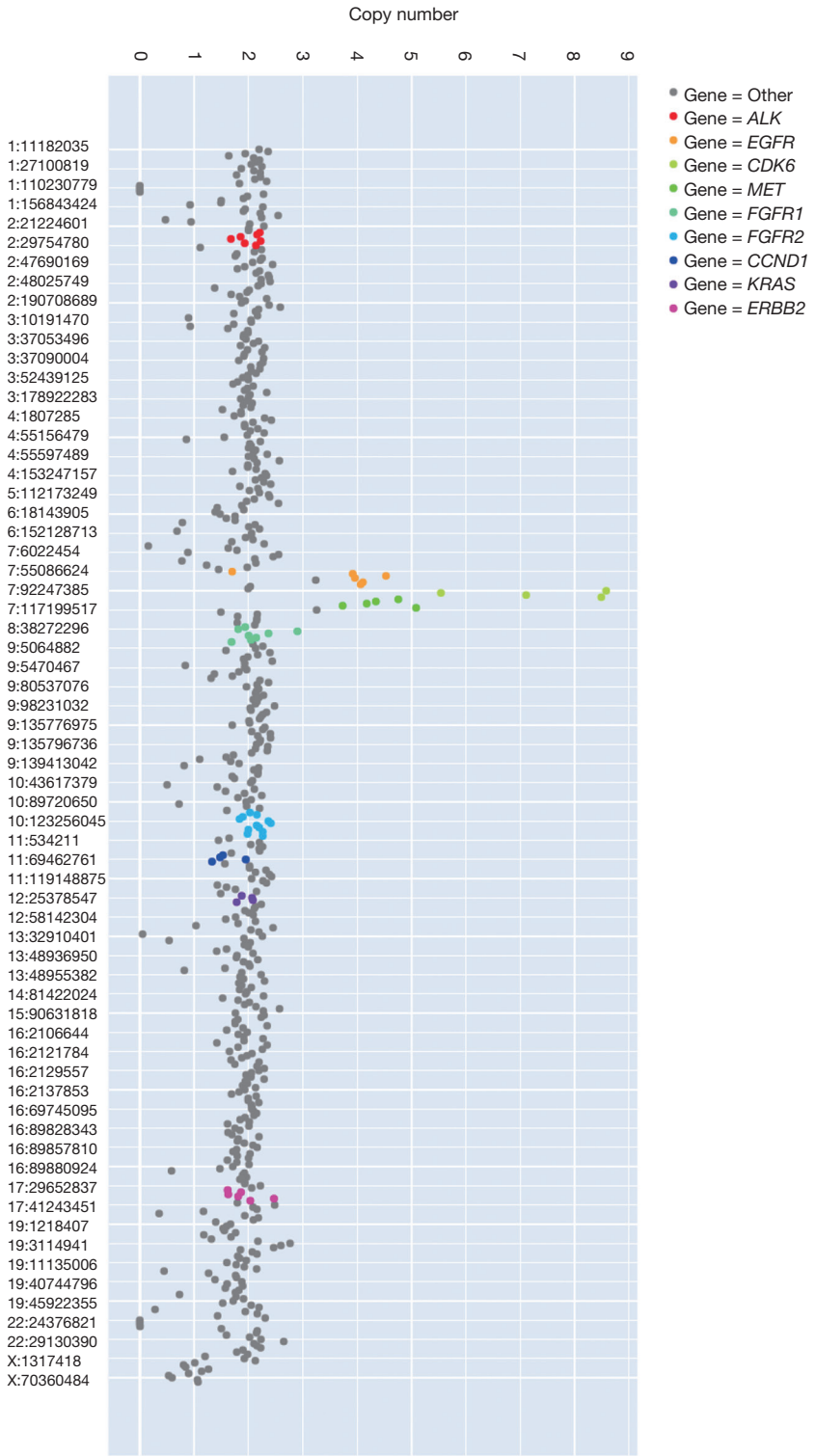

Figure 2 Results of gene copy number amplification. EGFR, epidermal growth factor receptor.

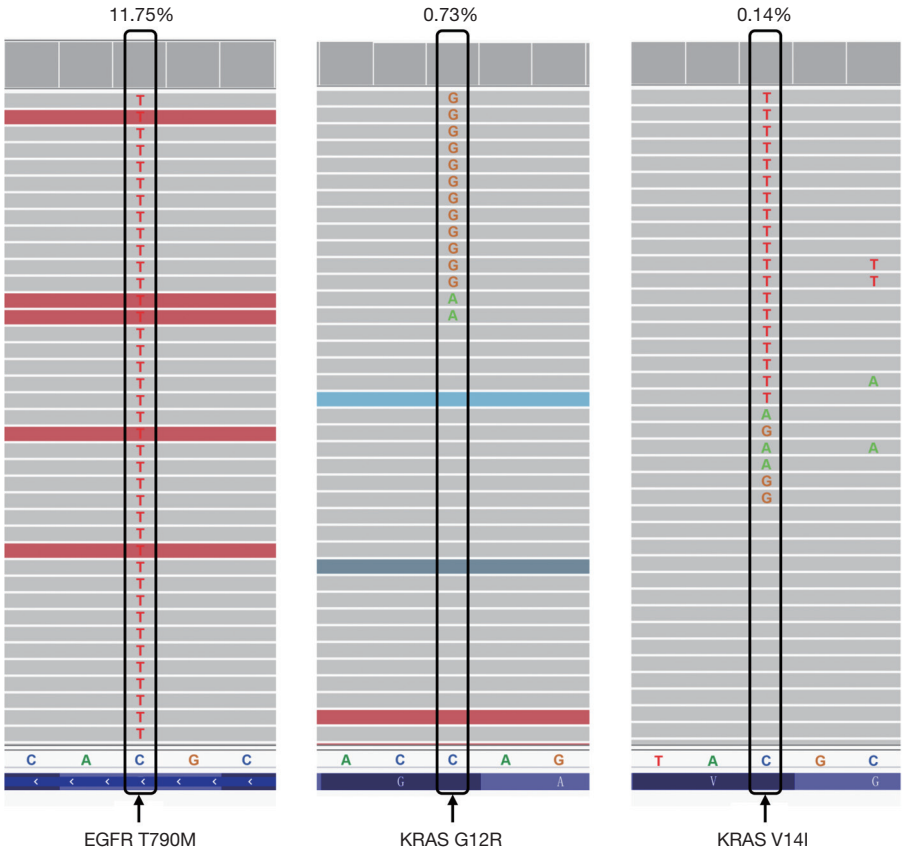

Figure 3 IGV screen shot of *EGFR* T790M, *KRAS* G12R, and *KRAS* V14I. IGV, interactive genome viewer. EGFR, epidermal growth factor receptor.

Therefore, ctDNA is highly preferable for genetic testing in patients with acquired drug resistance over puncture biopsy. Hence, the NGS detection of ctDNA was found to be more convenient to dynamically monitor the real-time gene information of patients' tumors, so as to achieve a more precise treatment (21).

Another advantage of NGS is that it can simultaneously detect multiple genes. In addition to point mutation and insertion/deletion, it can also detect copy number variation and chromosome rearrangement (22). Moreover, it is able to effectively use limited tissue samples to find out classical T790M and other non-T790M drug resistance mechanisms, which are particularly important for patients with advanced NSCLC. In this study, the mechanism of acquired resistance to first-line osimertinib, including *MET* gene amplification, was detected, which provided a therapeutic insight for patients with advanced NSCLC.

Radiotherapy is one of the main means of local treatment (23). With the increasing popularity of stereotactic radiotherapy, the accuracy of radiotherapy in treatment of lesions can be effectively improved, and the incidence of radiation damage can be reduced. According to the presented case, radiotherapy plays a significant role in the treatment of patients with locally advanced resectable NSCLC. After 7 months of treatment with Erlotinib, bone and brain metastasis occurred in September 2016. After whole brain radiotherapy, the patient's tumor size decreased, while the chest lesions enlarged; chest radiotherapy was thus performed, in which the lung mass was reduced. These two occasions of radiotherapy use kept the disease under control to a certain extent and prolonged the duration of the application of erlotinib. Additionally, 3 months after the first use of osimertinib, the patient developed right cervical lymph node metastasis and left scapular metastasis. The effective duration for the use of osimertinib was prolonged for 4 months by radiotherapy of the neck and left shoulder joints and treatment with zoledronic acid. Therefore, it can be concluded that adjuvant radiotherapy plays an important role in disease control and can relieve the enlargement and metastasis of local tumors while also prolonging the action

time of targeted drugs.

In conclusion, dynamic monitoring of tumor genomic profiles can detect the driving genes and drug resistance mechanisms and thus guide cancer treatment. In this study, the total survival time of NSCLC patients in stage IVA after radiotherapy and targeted therapy was found to be more than 3 years, indicating the significance of dynamic monitoring of gene mutations for cancer treatment.

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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 case report and any accompanying images.

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