Lung Cancer 129 (2019) 72–74

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Mutation tracking of a patient with EGFR-mutant lung cancer harboring de novo MET amplification: Successful treatment with gefitinib and crizotinib

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ARTICLE INFO

Keywords:
De novo MET amplification
EGFR mutant
Dynamic monitoring
Non-small cell lung cancer

ABSTRACT

Objective: De novo mesenchymal-epithelial transition (MET) amplification is believed to promote primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in the non-squamous non-small cell lung cancer (NSCLC). We sought to seek the treatment of a patient with EGFR-mutant NSCLC harboring de novo MET amplification.

Materials and methods: After clinical diagnosis, tissue and plasma samples were obtained from the patient and subjected to next-generation sequencing to identify and dynamic monitor the mutations.

Results: The patient was treated with gefitinib monotherapy in the beginning and experienced primary resistance to gefitinib but achieved a good response to the combination therapy of gefitinib and crizotinib. He achieved a 16.8-month progress free survival with the combination therapy. NGS of plasma circulating cell-free tumor DNA shown that L858R mutation was no longer detectable and the copy number of MET dropped when the patient got remission.

Conclusions: The combination of EGFR- and MET- tyrosine kinase inhibitors may be an effective treatment for the rare mutations.

1. Introduction

De novo mesenchymal-epithelial transition (MET) amplification is believed to promote primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in the non-squamous non-small cell lung cancer (NSCLC) [1,2], which has been observed in approximately 3% of patients with EGFR mutations [3]. When both the EGFR and MET signaling pathways are activated, two inhibitors are used to block each signaling regularly [4–6]. For patents who had EGFR mutations and acquired MET amplification, clinical examples have demonstrated that combination of EGFR and MET inhibitors or crizotinib monotherapy is effective [5,6]. However, treatment of patients who had EGFR mutant and de novo MET amplification is unknown. Thus, it is necessary to explore the treatment of this rare mutations.

2. Case report

A 63-year-old Chinese male never-smoker was diagnosed with stage IV lung adenocarcinoma based on computed tomography (CT) and CT-guided transthoracic needle biopsy of lung in September 2015. A chest and abdomen computed CT scan was performed, revealing a right lung mass, an ipsilateral leaf lobe nodule, right pleural thickenings with pleural effusion, and bilateral adrenal metastases. Next-generation sequencing (NGS) was conducted with the biopsy specimen from the lung, the result was showed as a concurrent EGFR p. L858R mutation and MET amplification. MET amplification was confirmed by fluorescent in situ hybridization (MET/CEP7 [centromeric enumeration probe for chromosome 7] ratio > 15). Of note, he did not harbor anaplastic lymphoma kinase (ALK)/c-ros oncogene 1 (ROS1) rearrangements, and MET mutations. Initially, He underwent 4 cycles of carboplatin/pemetrexed/bevacizumab, followed by 8 cycles of maintenance pemetrexed/bevacizumab until progressive disease (Fig. 2A). The progress free survival of the first-line chemotherapy was 7.17 months. Clinical course is shown in Fig. 1. Subsequently, the patient was treated with gefitinib (250 mg once daily) as second-line therapy. After 4 weeks therapy, the CT scan displayed an enlarged right lung mass (Fig. 2B), bilateral lung lesions and right adrenal gland, which were ta rget lesions. We did NGS in plasma-derived circulating tumour DNA (ctDNA) to detect additional mutations using an ultra-deep (20 000 ×) 168-gene panel named LungPlasma (Burning Rock Biotech, Guangzhou, China), which

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https://doi.org/10.1016/j.lungcan.2019.01.009
Received 3 November 2018; Received in revised form 2 January 2019; Accepted 21 January 2019
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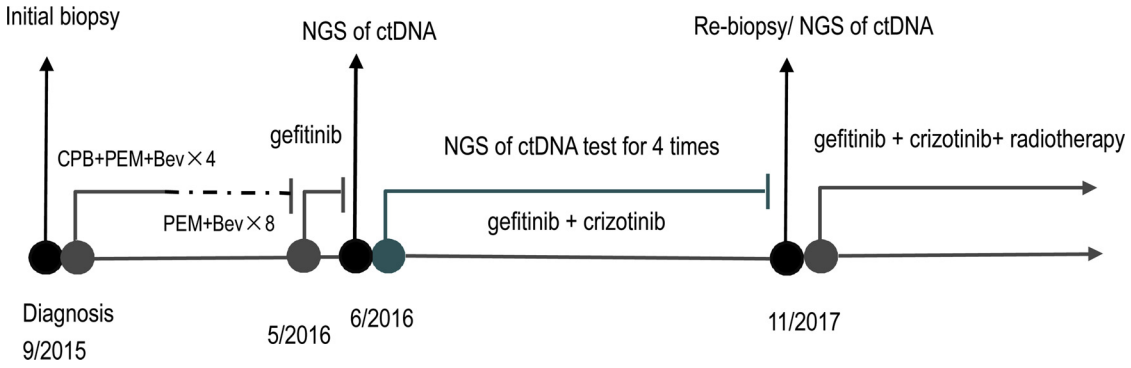

Fig. 1. Clinical course. CPB: carboplatin, PEM: pemetrexed, Bev: bevacizumab, NGS : next-generation sequencing.

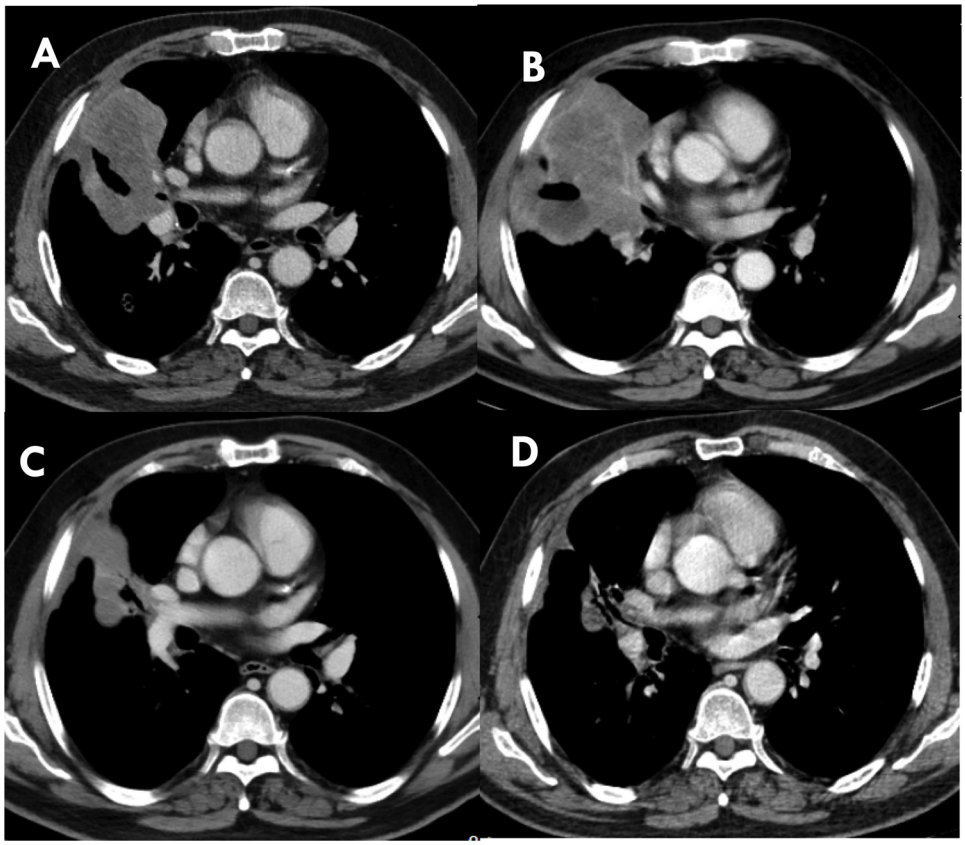

Fig. 2. Axial computed tomography images of a patient with advanced non–small cell lung cancer harboring a concurrent epidermal growth factor receptor gene (EGFR) L858R mutation and MET amplification, (A) after chemotherapy, the CT scan displayed an enlarged right lung mass, (B) interval progression of disease after 4 weeks of single-agent gefitinib, (C) dramatic interval improvement in right lung mass thickening after 4 weeks of combination gefitinib and crizotinib, and (D) right lung lesion almost disappeared after 8 weeks of combination gefitinib and crizotinib.

revealed L858R mutation and MET amplification, but no T790 M. MET amplification was defined as the average copy number (CN) was greater than or equal to 2.25 and 60% of capture region CN was significantly higher than the baseline (CN = 2) ($P \leq 0.005$). The patient was considered as primarily resistant to gefitinib.

When both the EGFR and MET signaling pathways were activated, EGFR and MET inhibitors were used to block each signaling regularly [4–6]. Then, the patient was treated with gefitinib (250 mg once daily) and crizotinib (200 mg twice daily). After 4 weeks, he achieved about 73% lesions reduction of his right lung (Fig. 2C) and right adrenal gland. After 8 weeks, these lesions almost disappeared (Fig. 2D). The patient kept response for 16.8 months with no adverse events. Unfortunately, his right adrenal metastases increased; while the lesions in lung were still good enough. Then NGS of ctDNA in plasma shown L858R and MET amplification, but NGS of a biopsy specimen from the right adrenal did not revealed gene mutation. He received a combined regimen, radiotherapy of adrenal metastases was added to the pretreatments, and got a stable of the disease.

During the patient was treated with gefitinib and crizotinib, we conducted 5 times NGS of ctDNA to track mutations. Dynamic changes of L858R and MET amplification are demonstrated in Fig. 3. NGS of ctDNA shown that L858R mutation was no longer detectable and the copy number of MET dropped to normal when the patient got response. In the 15th month, L858R appeared again and the copy number of MET kept stable, but disease kept response in the imaging. However, the disease progressed after 2 months. The reappearing of L858R was associated with disease aggressiveness.

3. Discussion

In our case, we think that MET amplification is a “driver mutation” rather than “passenger mutation” [7]. First, MET amplification was found before TKIs treatment. Although the dynamic changes of MET amplification CN correspond with the levels of L858R, it does not imply that these aberrations are in the same cells as a result of resistance mechanism. Levels of them correspond with the systemic tumor burden.

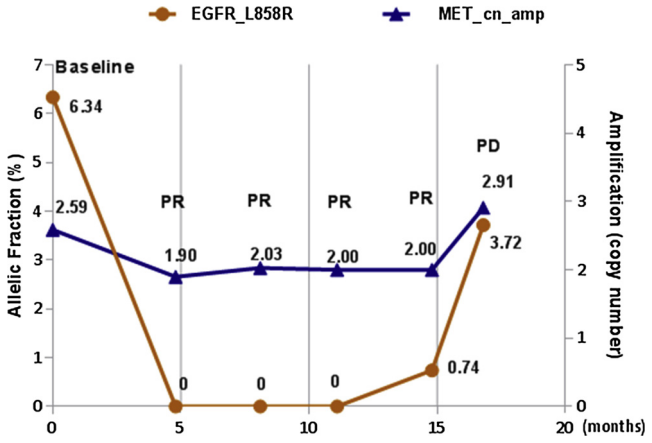

Fig. 3. Dynamic monitoring of response during the patient was treated with gefitinib and crizotinib. Dynamic changes of L8FI58R and MET amplification tested by next generation sequencing of plasma circulating cell-free tumor DNA (ctDNA) are displayed. The y axis represents allelic fraction or amplification copy number, and the x axis represents the time of response. PR, partial response; PD, progressive disease.

What's more, he was treated with gefitinib monotherapy in the beginning and experienced primary resistance to gefitinib but achieved a good response to the combination therapy of gefitinib and crizotinib. Thus, we thought that the MET amplification might have influence on tumor cells growth in this patient. Based on these evidences, we thought that MET amplification might be a driver gene.

Seldom reports showed the treatment benefited in NSCLC patients who had EGFR mutant and de novo MET amplification. In the only example, Gainor et al. described a patient with the rare mutations. This patient was treated with erlotinib monotherapy in the beginning and experienced primary resistance to erlotinib but achieved a good response to the combination therapy of erlotinib and crizotinib [4]. This case provided significant proof for combination strategies in EGFR-mutant and concurrent MET amplification. But Gainor et al. did not report the long-term survival of the case. In our case, the patient achieved a 16.8-month PFS, which had not previously been reported. The resistance mechanism of EGFR mutant and de novo MET amplification needs further investigation.

The level of cfDNA correlates with prognosis [8]. In our case, ctDNA levels declined sharply after successful targeted therapy (gefitinib and crizotinib) while increased rapidly when the disease progressed, which suggested that ctDNA was a surrogate for tumor burden. The reason is as follows. Studies have demonstrated that ctDNA is shed into the bloodstream by cells undergoing apoptosis or necrosis [9]. For this patient, tumor growth was inhibited when the patient was treated with gefitinib and crizotinib. Owing to lack of proliferation and apoptosis, there was no release of ctDNA. Thus, EGFR mutation disappeared and the copy number of MET dropped to normal in plasma DNA when the patient got response. As the right adrenal metastases increased in volume, so did the cellular turnover and hence the number of apoptotic and necrotic cells. The ctDNA level increased rapidly when disease progressed. Levels of ctDNA reflect the systemic tumor burden and it also correspond with clinical efficacy. Therefore, dynamic changes of specific mutations in ctDNA may be used in monitoring disease state and predicting progression in advance of imaging.

Driver mutations of the lung and right adrenal are different, that's may be because intra-tumor genetic heterogeneity and bias of a single-site tissue biopsy [10]. ctDNA is theoretically more likely to reflect systemic tumor burden, which may be helpful in find micro-metastatic lesions. This is a new approach that could help overcoming the challenge caused by tumor heterogeneity.

4. Conclusion

As far as we know, this was the first time that the progress free survival of the patient harboring EGFR p. L858R mutation and de novo MET amplification was reported. He was also the first Asian NSCLC patient with the rare mutations. Our limited experience suggested that combination of EGFR and MET tyrosine kinase inhibitors might be an effective treatment for the rare mutations. Levels of ctDNA could be utilized in monitoring disease state and predicting progression in advance of imaging.

Funding

There is no financial support.

Ethics

This case was approved by the institutional ethic review boards of Henan Cancer Hospital.

Conflict of interest statement – all authors

Authors declared no conflict of interest.

Acknowledgements

The authors would like to thank department of molecular pathology Center in Henan Oncology Hospital for technical assistance. We also thanks to the patient and his family.

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