Case Report

Tumor heterogeneity with novel MET fusion showed different response to cabozantinib in non-small cell lung cancer

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Abstract: Mesenchymal-epithelial transition (MET) amplification is one of the mechanisms of EGFR-TKI resistance, MET inhibitors combined with EGFR-TKI can overcome this resistance, but same tumor lesions could be divided into clones with different drug-sensitivities due to tumor heterogeneity. We report a patient with EGFR-sensitive mutations and MET-amplified lung adenocarcinoma finding MET D1228N, novel CAPZA2-MET fusion mutation after developing crizotinib resistance. He treated sequentially with cabozantinib+icotinib and achieved SD for 4 months. Re-examination of peripheral blood ctDNA showed that MET fusion disappeared. In this study, we revealed firstly that heterogeneity cause distinguished responses to cabozantinib in non-small cell lung cancer.

Keywords: EGFR-mutated NSCLC, MET amplification, crizotinib resistance, cabozantinib

Introduction

MET amplification is one of the mechanisms of EGFR-TKI resistance, accounting for approximately 5% of EGFR-TKI resistance-related cases [1]. MET inhibitors combined with EGFR-TKI can overcome this resistance [2], but secondary mutations of MET can still cause secondary resistance [3-5]. However, little data on specific molecular factors affecting drug sensitivity and resistance exists. We report a patient with EGFR-sensitive mutations and MET-amplified lung adenocarcinoma treated sequentially with cabozantinib+icotinib after developing crizotinib resistance.

Case report

A 72-year-old man with no history of smoking or family history of cancer was diagnosed with cT2N3M0 stage IIIB lung adenocarcinoma in January 2013. He underwent 6 courses of pemetrexed plus carboplatin chemotherapy and achieved PR. In March 2014, the lung lesion were found to progress; PCR of the tumor tissue revealed deletion of EGFR exon 19 del, and targeted therapy with oral icotinib 125 mg t.i.d. was started. The best outcome achieved was CR that was maintained for 3 years.

In March 2017, he experienced progressive disease (PD) with adrenal gland and retroperitoneal lymph node metastasis. The patient enrolled in a Chinese phase II clinical trial of the EGFR-TKI mefatinib, but withdrew 50 days later due to inability to tolerate side effects. Re-biopsy and NGS panel analysis revealed EGFR L747_P753delinsS, MET amplification, and CAPZA2-MET fusion. Next, oral crizotinib 250 mg b.i.d was started, and the patient achieved PR for 5 months. In March 2018, intracranial and hepatic metastasis was detected (Figure 1A, 1D). Liquid biopsy analysis revealed EGFR L747_P753delinsS, MET D1228N, MET amplification and CAPZA2-MET fusion (Figure 2). MET D1228N is responsible for resistance to the type I MET inhibitor crizotinib. However, there are also reports that MET D1228V/H confers sensitivity to the type II MET inhibitor cabozantinib, but MET D1228N may confer resistance [4, 5]. The patient consented to experimental treatment with 125 mg icotinib t.i.d.+80 mg cabozantinib q.d. in April 2018. There was some relief of the patient’s lower back pain, but due
Cabozantinib for crizotinib-resistant MET mutations

![Figure 1. Changes in imaging before and after treatment with cabozantinib (Cab) plus icotinib (Ico). A-C: Changes in intracranial lesions before and after combination therapy; D-F: Changes in liver lesions before and after combination therapy.](image)

to significant side effects including nausea, vomiting, discomfort, and a hand and foot rash, the icotinib dose was reduced to 125 mg b.i.d in June 2018. The number of intracranial lesions was reduced, the liver lesions were stable after 3 months of combination therapy (Figure 1B, 1E), and the concentrations of tumor markers were significantly lower than those before the treatment (Figure 2).

In July 2018, the patient was unable to further tolerate the side effects of the combination therapy, and icotinib was discontinued. Levels of the tumor markers increased compared to those before discontinuation (Figure 2). Re-examination of peripheral blood ctDNA showed that EGFR L747_P753delinsS, MET amplification, but CAPZ2A-MET fusion disappeared (Figure 2). We speculated that MET fusion may be the responsible sites to cabozantinib that was ablated primarily with their clone. Later, head MRI and abdominal CT re-examination revealed definite progression of the lesions (Figure 1C, 1F). However, the patient was cachexic with an ECOG score of 4 and could not tolerate further treatment. He died of heart failure at the end of August.

**Discussion**

We reported a case of inoperable stage IIIB lung adenocarcinoma. The patient underwent chemotherapy and multiple genetic tests to optimize targeted treatment regimens and achieved a total survival of 5.5 years, reflecting the great value of precision treatment of lung cancer.

We described a genetic alteration profiles in a patient with lung adenocarcinoma before and after treatment. Before treatment with icotinib plus cabozantinib, EGFR L747_P753delinsS, MET D1228N, MET amplification and CAPZ2A-MET fusion were identified in this patient. However, at disease progression, CAPZ2A-MET fusion disappeared, but EGFR L747_P753delinsS, MET D1228N and MET amplification were still existed.

Our case highlights several key aspects in the management of EGFR-mutated lung cancer with MET amplification as an acquired resistance mechanism. First, it demonstrates the efficacy of crizotinib in MET-amplified lung adenocarcinoma. A few clinical case studies have also reported the successful administration of
Cabozantinib for crizotinib-resistant MET mutations

dual EGFR and MET therapy, with the duration of response ranging from 4 to 9 months [2]. Secondly, we demonstrated the value of ctDNA dynamic monitoring in the targeted therapy of lung adenocarcinoma and provided valuable information on the effect of MET secondary mutations on the sensitivity to MET inhibitors. The ctDNA NGS after development of crizotinib resistance revealed MET D1228N mutation, a variant that confers resistance to type I MET inhibitors. MET D1228N is clearly responsible for resistance to type I MET inhibitors [5-7], but the effect of D1228N on the sensitivity to type II MET inhibitors is still unclear. In vitro studies have found that D1228N confers sensitivity to type II MET inhibitors [7], but no confirmatory clinical data are available. Our patient was treated with a combination of cabozantinib and icotinib. SD was evaluated on imaging, with significantly decreased levels of tumor markers and disappearance of the CAPZA2-MET fusion on re-examination. Our prediction that cabozantinib may be clinically effective against lung carcinoma harboring MET D1228N is novel. However, the patient showed an increase in the levels of tumor markers and progression of intracranial lesions after 4 months of combina-

tion treatment. Liquid biopsy and re-biopsy may be considered to be complementary methods of mutation analysis. Besides, a novel fusion, CAPZA2-MET, was identified in our case with lung adenocarcinoma. The novel rearrangement led to the fusion between exon 1 of CAPZA2 and exon 2-21 of MET.

In conclusion, we have reported the genetic alteration profiles in a patient with lung adenocarcinoma before and after treatment. This study suggests that liquid biopsy and re-biopsy may be complementary methods of mutation analysis.

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Disclosure of conflict of interest

None.

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Cabozantinib for crizotinib-resistant MET mutations

