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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. Rebiopsy and NGS panel analysis revealed *EGFR* L747_P7533delinsS, *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

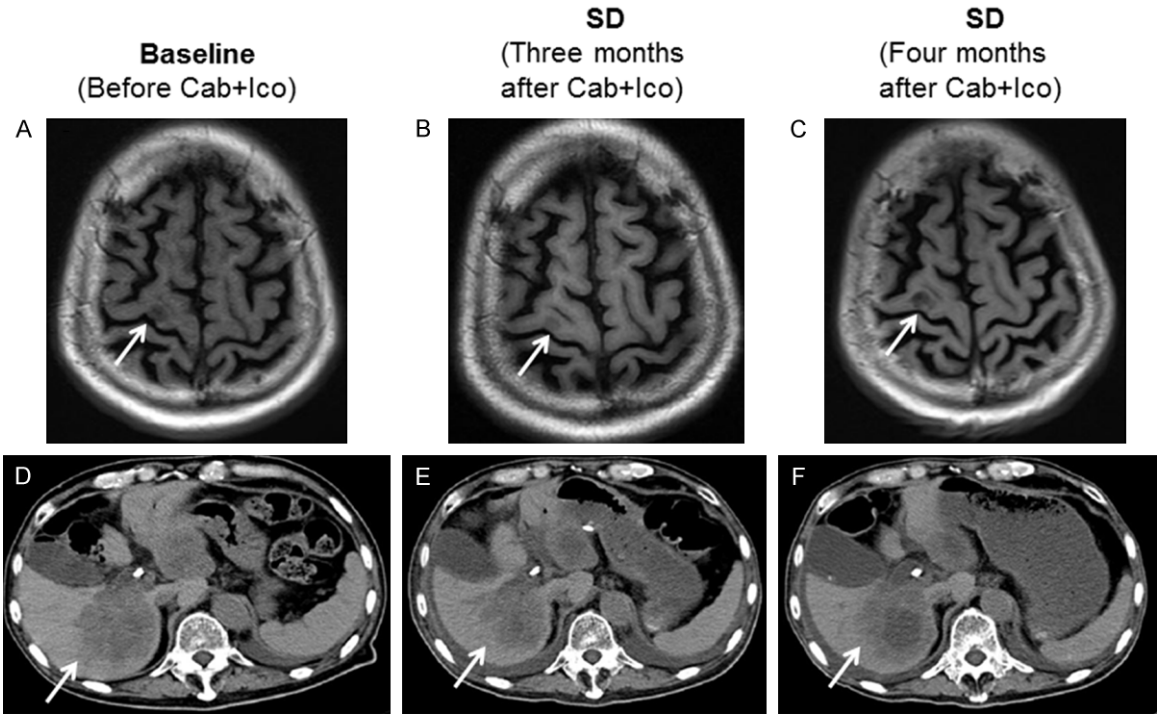

Figure 1. Changes in imaging before and after treatment with cabozantinib (Cab) plus icotinib (Ico). A-C: Changes in intracranial lesions before and after combination therapy; D-F: Changes in liver lesions before and after combination therapy.

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 *CAPZA2-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 *CAPZA2-MET* fusion were identified in this patient. However, at disease progression, *CAPZA2-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

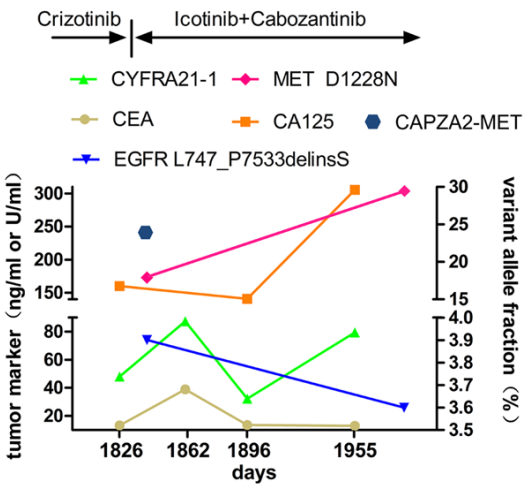

Figure 2. Changes in tumor markers and variant allele fraction (VAF) during treatment with cabozantinib and icotinib. The x-axis indicates treatment time, and the y-axes indicate tumor marker concentration and VAF. Tumor marker concentration markedly decreased after cabozantinib and icotinib treatment and then increased subsequently. ctDNA suggested that drug-sensitive *CAPZA2-MET* fusion disappeared and drug-resistant *MET* D1228N increased as advantage.

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 combination 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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