Crizotinib plus erlotinib overcomes osimertinib resistance in a seriously-ill non-small cell lung cancer patient with acquired MET amplification

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To the Editor: A 59-year-old Chinese man who presented with a severe cough and short of breath was admitted into hospital in October, 2018. Computed tomography scan showed a 4.0 cm × 2.0 cm tumor located on the lower lobe of right lung [Figure 1A] and multi-bone lesions, core needle biopsy was performed and adenocarcinoma was confirmed by pathologists. Diagnosis of metastatic lung adenocarcinoma with T4N3M1c in stage IVB was made by oncologists and pathologists. Next generation sequencing (NGS) with the biopsied tumor was done, and epidermal growth factor receptor (EGFR) exon 21 L858R mutation with mutant allele fractions (MAF) of 24.8% was found. Icotinib (Betta Pharmaceuticals Co., Ltd, Hangzhou, China), a first-generation EGFR tyrosine kinase inhibitor (TKI), at a dose of 125 mg orally, three times a day was administered. The patient got a partial response (PR) after 5 months according to the Response Evaluation Criteria in Solid Tumors 1.1 [Figure 1F]. The patient also displayed poor median overall survival compared with MET amplification negative group (15.6 vs. 30.7 months).

Osimertinib is used globally to treat EGFR-mutant non-small cell lung cancer with TKI resistance mediated by the EGFR T790M mutation. Acquired resistance to osimertinib is a growing clinical challenge that is poorly understood.

In this case, we reported the clinical efficacy of combinatorial therapy of first-generation EGFR-TKI with metronomic chemotherapy or fluorescence in situ hybridization. A combinatorial treatment, consisting of crizotinib (250 mg twice daily) with first-generation EGFR-TKI erlotinib (150 mg once daily), was administrated. The patient’s ECOG score improved to 2; and the primary lung tumor decreased by 51% in length [Figure 1F]. The patient also obtained significant improvement in symptoms such as cough, dyspnea, and appetite. His disease was under control for 2 months at the last follow-up visit. The side effect was mild acne and anorexia. No diarrhea, pneumonitis, or transaminitis happened.

Patients with MET amplification combined with T790M mutations appear to have an earlier resistance to third-generation of EGFR-TKI. Wang et al[2] reported that patients with MET amplification after osimertinib resistance commonly had inferior median progression-free survival than patients without MET amplification (3.5 vs. 9.9 months). Patients in MET amplification group also displayed poor median overall survival compared with MET amplification negative group (15.6 vs. 30.7 months).

MET is a tyrosine kinase receptor located at 7q21-32. Amplified c-MET promotes downstream signal transduction through bypass activation to avoid cell death induced by EGFR-TKIs. This promotes the proliferation of cancer cells, which ultimately leads to the resistance of patients to EGFR-TKIs. Therefore, it is necessary to simultaneously inhibit EGFR and MET to overcome the EGFR-TKI resistance caused by MET amplification.[3,4]
**MET inhibitor crizotinib after MET amplification** was diagnosed by NGS. The patient achieved PR after 1 month of treatment, although he had poor PS (PS = 4) before MET inhibitor therapy. Therefore, poor PS was not a contraindication for concurrently combined use of crizotinib and erlotinib. This combination treatment was poorly investigated for the seriously ill patient. The results suggest that repeated NGS-based detection after the acquisition of resistance to the drug is helpful to guide further treatment strategies. The strategies to overcome drug resistance should be individualized based on the mechanisms of drug resistance as well as the ways of progression.

In conclusion, patients with MET amplification after osimertinib resistance may benefit from crizotinib plus erlotinib treatment, and poor PS is not a restraint for combined targeted therapy. Further studies with a larger sample size are warranted.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

**Conflicts of interest**

None.

**References**

1. Chabon JJ, Simmons AD, Lovejoy AF, Esfahani MS, Newman AM, Haringsma HJ, et al. Circulating tumour DNA profiling reveals heterogeneity of EGFR inhibitor resistance mechanisms in lung cancer patients. Nat Commun 2016;7:11815. doi: 10.1038/ncomms11815.
2. Wang Y, Li L, Han R, Jiao L, Zheng J, He Y. Clinical analysis by next-generation sequencing for NSCLC patients with MET amplification resistant to osimertinib. Lung Cancer 2018;118:105–110. doi: 10.1016/j.lungcan.2018.02.007.
3. Trovato M, Torre ML, Ragonese M, Simone A, Scarfi R, Barresi V, et al. HGF/c-met system targeting PI3K/AKT and STAT3/phosphorylated-STAT3 pathways in pituitary adenomas: an immunohistochemical characterization in view of targeted therapies. Endocrine 2013;44:735–743. doi: 10.1007/s12020-013-9950-x.
4. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039–1043. doi: 10.1126/science.1141478.

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