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 1B]. He was found multi-brain metastasis on magnetic resonance imaging and the right lung tumor was enlarged [Figure 1C] after 9 months of icotinib treatment. NGS was done with the new biopsied progressed lung tissue, which indicated that T790M mutation was negative and the MAF of *EGFR* exon 21 L858R decreased from 24.8% to 1.83%. Taking into account of the patient's refusal of recommended chemotherapy, osimertinib (80 mg once daily) was administrated to the patient. The lung tumor progressed after 1 month [Figure 1D]. Systemic therapy with carboplatin and pemetrexed was performed and a stable disease was reached after 2 months of the treatment. However, disease progressed after 4 months [Figure 1E], and the patient's Eastern Cooperative Oncology Group (ECOG) performance status (PS) decreased to grade 4. NGS with serum was done and the MAF of *EGFR* exon 21 L858R mutation increased to 5.5%; *MET* amplification with a copy number of 3.1 was also found. Considering the patient's critical ill condition, re-biopsy was unavailable and *MET* amplification was not re-confirmed by immunohistochemistry 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.

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.

Patients with *MET* amplification combined with T790M mutations appear to have an earlier resistance to third-generation of EGFR-TKI.[1] 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-q31. 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]

In this case, we reported the clinical efficacy of combinatorial therapy of first-generation EGFR-TKI with

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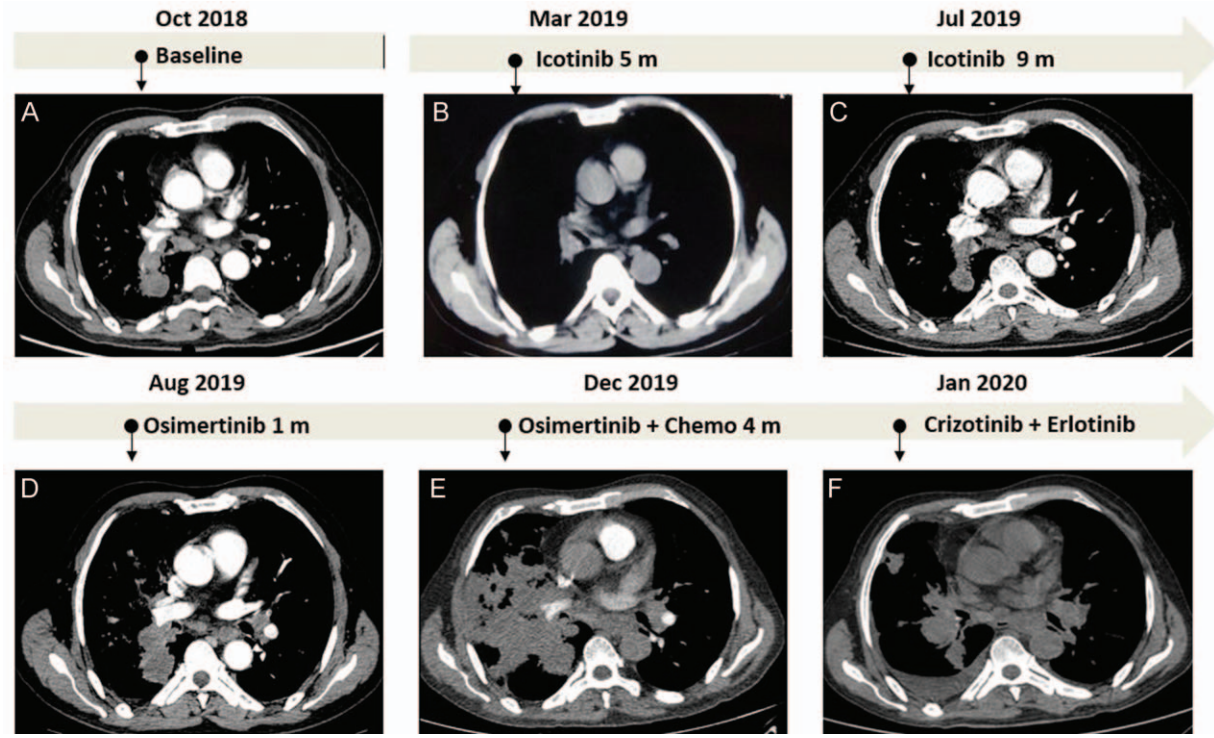

Figure 1: Primary tumor changes on CT scan. (A) Primary tumor located on the lower lobe of right lung. (B) Partial response achieved after 5 months of icotinib treatment. (C) Progressed disease after 9 months of icotinib treatment. (D) Tumor progressed after 1 month of osimertinib treatment. (E) Progressed disease after 4 months of chemotherapy. (F) CT scan after 1 month of crizotinib and erlotinib treatment. CT: Computed tomography.

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, Scarfì 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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