De novo MET amplification promotes intrinsic resistance to first-generation EGFR tyrosine kinase inhibitors

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ABSTRACT
First-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) could induce dramatic tumor responses in non-small-cell lung cancer patients with EGFR-activating mutations. However, a small proportion of patients have no tumor response on initial EGFR TKI treatment with an activating EGFR mutation and the primary resistance mechanism is not well understood. Here, we report the patient with primary dual MET/EGFR mutation treated with icotinib shows a disease progression, but the chest computed tomography shows the mass has significantly shrunk after 3 weeks of single-agent crizotinib. These suggest that de novo MET amplification could be a potential mechanism of intrinsic resistance to first-generation EGFR TKI.

Introduction
Lung cancer is the most common cause of cancer-related death in the world, and approximately 85% of lung cancers are non-small-cell lung cancers (NSCLCs).1,2 First-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), icotinib, could induce dramatic tumor response in NSCLC patients with EGFR-activating mutations, such as the exon 19 deletion and L858R point mutation.3,4 However, 20–30% NSCLC patients have no objective tumor regression on initial EGFR TKI treatment with an activating EGFR mutation, and the intrinsic resistance mechanism is not well understood.5

Besides T790M mutation, MET amplification is an important mechanism of acquired resistance to EGFR TKI.6 However, de novo MET amplification is a rare phenomenon in lung cancer patients with a frequency of 3%, and few cases have been reported about intrinsic resistance to first-generation EGFR TKI associated with MET amplification.7 Crizotinib is a first-generation, oral, small-molecule TKI of ALK, ROS1, and c-MET kinases.8 It has been already reported that patients with de novo MET amplification could benefit from crizotinib.9

Herein, we describe a patient with EGFR 19 deletion, and de novo MET amplification shows a disease progression after treatment of icotinib but achieves tumor response on single-agent crizotinib. This is a rare phenomenon which suggests that de novo MET amplification could be a potential mechanism of intrinsic resistance to first-generation EGFR TKI.

Case presentation
A 68-y-old smoker presented with dry cough and low-grade fever in the afternoon. Positron Emission Tomography-Computed Tomography (PET-CT) demonstrated right lung upper lobe soft tissue mass, retroperitoneal lymphadenopathy, adrenal and bone metastasis (Figure 1A). The tumor markers, CA125, elevated with values of 143.19 U/ml. Subsequently, the pathological analysis of pulmonary biopsy specimen revealed squamous cell carcinoma (CK (+), P40 (+), TTF-1 (−), NapsinA (−), and CD56 (−)) consistent with primary lung cancer. Molecular analysis of the tumor tissue by next-generation sequencing (NGS) showed an EGFR exon 19 deletion (c.2253_2276del, p.Ser752_Ile759del) and c-MET gene amplification before treatment (Figure 2). NGS test showed negative for ALK/ROS1 rearrangements and MET mutations. Based on these results, the patient was clinically diagnosed with T2bN1M1, stage IV squamous cell carcinoma with sensitive EGFR mutation.

Then, the patient was treated with chemotherapy with gemcitabine (1000 mg/m2, d 1 and 8) and received icotinib hydrochloride (125 mg, thrice a day) at the same time. After 3 weeks of therapy, the patient felt worse and had a persistent fever. The tumor markers, as mentioned above, remained abnormal with values of 77.06 U/ml. The CT scan of the chest showed that the soft tissue mass in the right lung upper lobe increased and metastatic nodules were found in both lungs (Figure 1B). Although the lesion increased on CT imaging, the tumor marker CA125 decreased. Therefore, at the request of the patient’s family, the patient continued to receive the treatment of icotinib. However, after 2 months of icotinib, the CT image of the patient showed no improvement in the lesion and more lung metastases than before (Figure 1C). Obviously, the disease has progressed and icotinib failed to achieve the desired effect. After 2 months of ineffective treatment with icotinib, the patient was taken off icotinib and started on crizotinib (250 mg, twice a day). Then, the patient felt better with no
fever and cough. Three weeks later, repeat chest CT showed the lung mass had significantly shrunk (Figure 1D). The value of CA125 was 74.48 U/ml, and the value of Cyfra211 was 5.03 ng/ml.

Figure 1. The computed tomography images exhibit a patient with co-existence of EGFR exon 19 deletion and de novo MET amplification shows intrinsic resistance to first-generation EGFR TKI. (A) Baseline assessment before EGFR TKI. (B) The tumor increased and metastasized to both lungs after 3 weeks of icotinib. (C) No improvement in the lesion and lung metastases more than before. (D) The tumor shrunk significantly after 3 weeks of single-agent crizotinib.

Figure 2. Gene sequencing results of the tumor tissue before treatment.
Discussion

As first-line treatment, first-generation EGFR-TKI showed longer median progression-free survival in patients with TKI-sensitizing EGFR mutations compared with patients treated with chemotherapy (10.8 months, vs. 5.4 months), as well as a higher response rate (73% vs. 30.7%, \( P < .001 \)). Although vast majority of the patients with great responses to first-generation EGFR-TKI ultimately underwent tumor progression and inevitably became resistant to them within 6–12 months, few cases of primary resistance to icotinib have been reported. In this case, the patient we presented here with EGFR 19 deletion and de novo MET amplification showed disease progression after 3 weeks of icotinib. De novo MET amplification could be a possible mechanism of intrinsic resistance to icotinib.

The common mechanisms of EGFR-TKI resistance in NSCLC include insurgence of secondary mutations in the EGFR gene (T790M mutation), phenotypic transformation (histological transformation from adenocarcinoma to small cell lung cancer), and activation of alternative pathways (amplification of the MET oncogene). The presence of the MET gene amplification was observed in approximately 22% of the cases by repeated tumor biopsy. Although MET amplification was the most common mechanism of resistance second to T790M, it seems to be a rare event in patients never exposed to EGFR TKI.

MET receptor is a transmembrane tyrosine kinase encoded by proto-oncogene MET that could activate downstream signaling pathways such as RAS/ERK/MAPK, PI3K-AKT when bound to the HGF ligand. Those signaling pathways were important for cell proliferation, survival, migration, motility, and invasion. Dysregulation of the MET pathway in lung cancer via MET gene amplification could promote resistance to EGFR TKI. It has been observed that MET was amplified in 3% patients without treatment. This may suggest that MET amplification could be found in lungs cancers never treated with EGFR TKIs. Recently, it also has been found an coexistence of MET amplification and the T790M mutation in drug-sensitive EGFR mutation lung cancer cells which were only sensitive to a multikinase inhibitor against MET suggested that MET amplification could occur independently.

Intrinsic resistance is usually defined as an immediate inefficacy of EGFR-TKIs. The patient with EGFR 19 deletion (c.2253_2276del, p.Ser752_Ile759del) and de novo MET amplification, we discussed here, experienced progression of disease and metastasis of both lungs after 3 weeks of icotinib. Obviously, it was a failure for the EGFR-TKI-naïve patient to achieve the desired effect with the therapy of icotinib. This case promoted us to pay more attention to the role of MET amplification in intrinsic resistance to EGFR-TKI. De novo MET amplification was an unusual oncogenic event in lung cancer, especially in dual mutation patients, and patients with de novo MET amplification benefiting from crizotinib had been reported recently. These suggested that de novo MET amplification may be associated with intrinsic resistance to EGFR TKIs and patients with dual MET/EGFR mutation could benefit from MET inhibitors.

Conclusion

This is the first case discussing about the patient with EGFR exon 19 deletion, and de novo MET amplification has disease progressed after treatment of EGFR TKI but achieved significantly radiographic response to single-agent crizotinib. It highlights the role of de novo MET amplification in intrinsic resistance to first-generation EGFR TKI and suggests that icotinib may not be appropriate for patients with dual MET/EGFR mutation as first-line treatment. However, this is a rare phenomenon and the mechanism of primary resistance needs further investigation.

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Ethical approval

All procedures performed in the human participant were in accordance with the Declaration of Helsinki and with the ethical standards of the institutional and/or national research committee.

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