Successful crizotinib monotherapy in EGFR-mutant lung adenocarcinoma with acquired MET amplification after erlotinib therapy

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Abstract

MET is a driver oncogene in non-small-cell lung cancer (NSCLC), and its amplification is associated with acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors. A 56-year-old Japanese male with lung adenocarcinoma harboring an EGFR exon 21 L858R mutation received erlotinib to which he responded for 12 months. After disease progression, re-biopsy analyses revealed newly developed MET amplification. Neither EGFR exon 20 T790M mutation nor MET exon 14 mutations were detected. The MET inhibitor, crizotinib, showed a dramatic response. This is the first report of successful crizotinib single-agent therapy in EGFR-mutant NSCLC that acquired MET amplification during erlotinib therapy.

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1. Introduction

MET is a driver oncogene in non-small-cell lung cancer (NSCLC) [1]. Crizotinib was initially invented as a MET inhibitor. Subsequently, its comparable inhibitory activity against anaplastic lymphoma kinase (ALK) and ROS1 was identified [2], and crizotinib is currently used as the first generation ALK inhibitor to treat patients with ALK-rearranged NSCLC. The efficacy and safety of crizotinib in NSCLC with aberrant MET signaling (including MET gene amplification and MET mutations) has yet to be fully elucidated, although some reports have suggested the treatment benefit of crizotinib [3–5]. MET gene amplification is a major cause of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-induced resistance in tumors with EGFR mutations [6–8]. When both the MET and EGFR signaling pathways were activated, two inhibitors were used to block each signaling [9,10]. In this report, we describe a dramatic response to crizotinib monotherapy in a lung adenocarcinoma patient who had EGFR-sensitive mutation and acquired MET amplification during erlotinib therapy.

2. Case report

A 56-year-old Japanese male former smoker was histologically diagnosed with stage IV lung adenocarcinoma based on bone metastasis biopsy specimen in March 2013. Mutational analysis with PCR-based assay (cobas® EGFR Mutation Test v2) revealed the EGFR exon 21 L858R mutation. He initially underwent four cycles of carboplatin/pemetrexed/bevacizumab, followed by 17 cycles of maintenance pemetrexed. However, his disease progressed by June 2014. An EGFR-TKI, erlotinib, was initiated and he continued to respond for 12 months. In November 2015, new lesions in the brain, parotid gland, skin, lung, abdominal lymph nodes, and bone were detected (clinical course is shown in Fig. 1A). A re-biopsy of parotid...
gland metastasis showed a persistent L858R mutation but not a T790M. Fluorescence in situ hybridization (FISH) analysis showed MET amplification that had not been observed in initial biopsy specimens (Fig. 2A). ALK and ROS1 were negative by immunohistochemical staining, and no mutations were detected in MET exon 14 by Sanger sequencing. He sequentially received two cycles of docetaxel and one course of nivolumab, but his disease progressed and he was hospitalized for his worsening general condition (Eastern Cooperative Oncology Group [ECOG] performance status of 4).

After he gave informed consent, crizotinib was initiated at 250 mg twice daily. Within a week, palpable lesions (skin and parotid gland metastases) rapidly shrank; computed tomography showed a dramatic response, with multiple lung metastases almost completely diminished (Fig. 1B). His performance status was improved to grade 1 and he was discharged. Crizotinib has been continued for more than 4 months.

3. Discussion

Although treatment with EGFR-TKIs is effective in patients with NSCLC with activating EGFR mutations, almost all patients acquire resistance to EGFR-TKIs. T790M, a secondary EGFR kinase domain mutation, is the most common mechanism of acquired resistance. MET amplification is another mechanism of acquired resistance to EGFR-TKIs, and is detected in 5–21% of cases [6–8,11]. We previously used FISH analysis to show MET gene amplification in 13.7% of resected NSCLC patients [11].

Although crizotinib is theoretically effective for patients with MET amplification [2], few reports demonstrate the treatment benefit in those who acquired MET amplification during EGFR-TKI therapy. We have summarized cases who had EGFR-mutant NSCLC with MET amplification and were treated with MET inhibitors in Table 1 [9,10,12]. Case 1 had double primary lesions [9]: one tumor in the left lower lobe harbored an EGFR exon19 deletion, and the other primary tumor in the right upper lobe harbored MET amplification. Combination therapy with crizotinib and erlotinib was started and controlled the disease well. Case 2 was diagnosed as having both MET amplification and an EGFR mutation in molecular analyses of a biopsy specimen taken at initial diagnosis [10]. Although erlotinib monotherapy failed to control the disease, addition of crizotinib to erlotinib yielded a good response. These two cases already had MET amplification before EGFR-TKI treatment. In contrast, our patient had an EGFR mutation and then newly developed MET amplification after erlotinib therapy, suggesting that MET amplification occurred as a mechanism of acquired resistance. Recently, Ou et al. also reported a patient who developed MET amplification after the third-generation EGFR-TKI, osimertinib therapy (Case 3) [12].

We consider our case is worth discussing in two points. First, our...
case harboring two aberrant oncogenes, EGFR-sensitive mutation and developed MET amplification, was treated with crizotinib monotherapy. Ideally, combination therapy with crizotinib and EGFR-TKI was initiated. Case 1 and case 2, who had MET amplification before EGFR-TKI treatment, were successfully treated with erlotinib and crizotinib. Case 3 was initially treated with crizotinib, and subsequently, osimertinib was added. In our case, the poor condition did not allow to initiate combination therapy. Involuntarily crizotinib monotherapy was administered, which induced dramatic tumor regression. We still detected an EGFR L858R mutation by the re-biopsy analysis. Furthermore, phosphorylated EGFR was still positive at initial diagnosis, which were still present at the time of progression. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

![Figure 2](image-url)

**Table 1**

| Case | Age | Sex | Histology | Smoking status | EGFR mutation | MET amplification | Technique | Interpretation for positive | Timing of detecting MET amplification | MET Exon 14 mutation | Therapy | Response |
|------|-----|-----|-----------|----------------|----------------|-------------------|-----------|--------------------------|--------------------------------------|---------------------|----------|----------|
| 1    | 75  | F   | ADC       | Former         | Exon 19 deletion | Positive        | FISH      | MET/CEP7 ratio 6.5         | initial diagnosis                  | WT                  | crizotinib + erlotinib | PR       |
| 2    | 73  | F   | ADC       | Never          | Exon 21 L858R   | Positive        | FISH, NGS | MET/CEP7 ratio > 15.0     | initial diagnosis                  | WT                  | crizotinib + erlotinib | PR       |
| 3    | 73  | F   | ADC       | Never          | Exon 19 deletion | Positive        | NGS       | copy number 30 after osimertinib resistance | WT                       | crizotinib          | SD       |
| 4    | 56  | M   | ADC       | Former         | Exon 21 L858R   | Positive        | FISH      | MET/CEP7 ratio 2.1         | after erlotinib resistance          | WT                  | crizotinib          | PR       |

*EGFR: epidermal growth factor receptor, ADC: adenocarcinoma, WT: wild type, NGS: next generation sequencing, FISH: fluorescence in situ hybridization, CEP7: centromere probe of chromosome 7, PR: partial response, SD: stable disease.*
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Conflicts of interest

The authors declare no competing interests.

Author contributions

All authors contributed toward the conception and design, data analysis, drafting, and critically revising the paper, and agree to be accountable for all aspects of the work.

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