Successful Treatment of a Patient With NSCLC Harboring an EGFR Mutation and a Concomitant Met Exon 14 Skipping Mutation Combining Afatinib and Crizotinib

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Clinical Practice Points

- The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, afatinib, and the MET inhibitor, crizotinib, can safely be combined in standard dosage.
- MET Exon 14 skipping mutation seems to be a strong bypass pathway and may inhibit the effectiveness of afatinib in patients with sensitizing EGFR mutation.
- In the rare cases of sensitizing EGFR and concomitant MET Exon 14 skipping mutations, the combination of an EGFR tyrosine kinase inhibitor and MET inhibitor could be an effective treatment option.

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Introduction

A 53-year old white, female former-smoker (15 pack-years) was diagnosed with non−small-cell lung cancer (NSCLC) of the middle lobe in April 2016. Histopathologic evaluation revealed an adenocarcinoma with a common sensitizing (Exon 19 deletion) epidermal growth factor receptor (EGFR) mutation (c.2235_2249delGGAATTAAGAGAAGC, p.Glu746_Ala750del). The initial tumor stage was cT2 cN3 cM0. The patient presented herself in good general condition (performance status [PS], 0) and with a history of Hashimoto thyroiditis and no further comorbidity.

Treatment was initiated with 3 cycles of cisplatin and pemetrexed, and the follow-up positron emission tomography (PET)-computed tomography (CT) scan showed partial remission. Therefore, an ablative radio-chemotherapy up to 50.4 Gy at the primary tumor site with simultaneous boost on PET positive tumor and lymphnode metastases up to 61.6 Gy was performed.

Following a 12-month period of progression-free survival, the patient developed new contralateral mediastinal lymph node metastases as well as a malignant pericardial effusion. Mediastinoscopy with biopsy of the PET-positive lymph nodes and pericardial window surgery was performed. Next-generation sequencing (NGS) of these biopsies detected the known EGFR mutation, but also a concomitant Met Exon 14 skipping mutation (MET-Gen Fusion between Exon 13 and Exon 15) (Figure 1). The allele frequency of the EGFR mutation was 46.55% in a tumor sample containing 90% tumor cells, indicating that 1 of 2 alleles is mutated and that the majority of tumor cells carry the EGFR mutation. Other EGFR mutations, in particular T790M, were not detected. Owing to the next-generation sequencing platform used (IonTorrent PGM, Oncomine Focus Panel [Thermo Fisher Scientific], RNA-based analysis of the MET skipping alteration), it is not possible to calculate the allele frequency. Comparative estimation from the original data indicate that only a minor fraction of the tumor cells harbor the MET Exon 14 skipping mutation. Management of postoperative complications (severe pneumonia, Dressler syndrome) led to a delay of systemic treatment for 5 months. Repeated imaging

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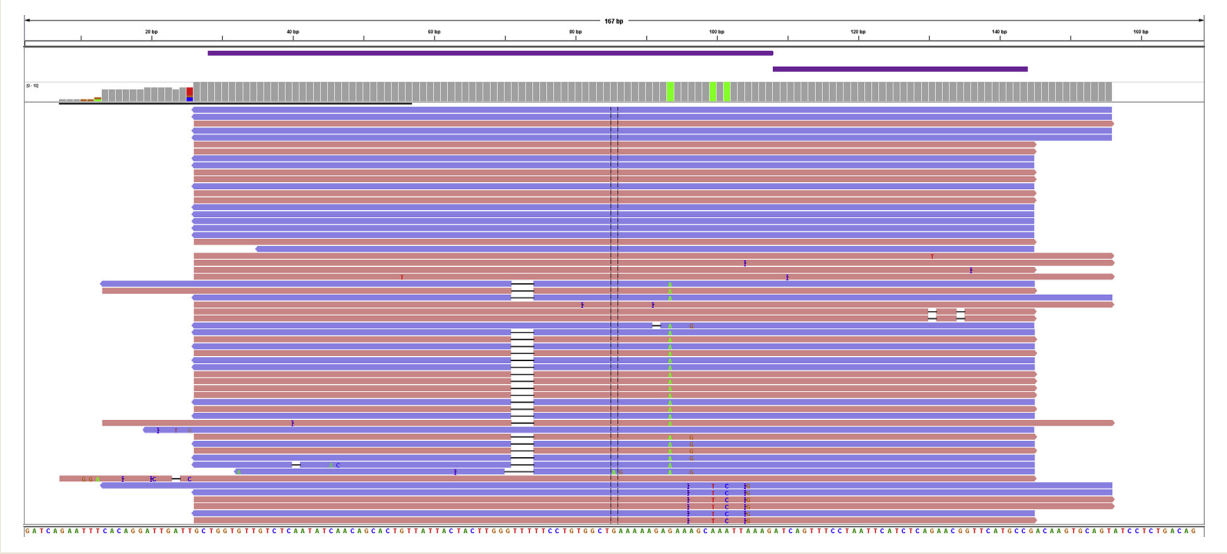
Figure 1 Detection of the MET-Exon 14 Skipping Alteration in the Integrative Genomics Viewer.[1] The Integrative Genomics Viewer Image Shows the Detection of the MET Exon 14 Skipping Alteration (chr7:116411708 - chr7:116414934) by RNA-Sequencing of MET Exon 13 to 15 Performed on an Ion Torrent Personal Genome Machine Using the Oncomine Focus Assay. Sequencing Reads Were Sorted by Mapping Quality (Highest at the top) From the Original Data. All Together, 1301 Total Reads of the MET Exon 13-15 mRNA Could Be Detected (749 Forward Reads [Red Bars] and 552 Reverse Reads [Blue Bars]).



revealed further tumor progression with new liver metastases, progressive pulmonary tumor manifestations, and a single occipital brain metastasis (Figure 2). Stereotactic radiation of the brain metastasis was performed and systemic treatment with afatinib (40 mg daily) was initiated. Repeat imaging after 6 weeks of afatinib showed a clinically relevant pulmonary embolism as well as progression of the known liver metastases. The thoracic tumor manifestations were stable according to Response Evaluation Criteria In Solid Tumors criteria (Figure 2).

The patient's general condition had also deteriorated to PS 2. We discussed the case in our interdisciplinary tumor board and recommended an individual approach with concomitant blockage of the Met Exon 14 skipping mutation using crizotinib at a dosage of 250 mg twice daily. Afatinib was reduced to 30 mg daily to prevent possible side effects. Until now, in Germany crizotinib has not been approved for the treatment of Met Exon 14 mutated NSCLC either as monotherapy or as combination treatment. Therefore, we requested reimbursement from the patient's insurance. Off-label use was preliminarily permitted for 3 months. The treatment was started after the patient gave her written informed consent. The concomitant treatment with afatinib and crizotinib was well-tolerated. After the initial weeks, the patient reported grade 2 to 3 nausea and grade 2 diarrhea, which both attenuated to grade 1 after several weeks of supportive treatment and use of loperamide.

Combined treatment with afatinib and crizotinib led to a tremendous response with complete remission of the liver metastases and a partial remission of the pulmonary tumor manifestations after 6 weeks (Figure 2) and a significant improvement of her general condition (PS 1). Follow-up PET-CT scan after a further 6 weeks continued remission with only minimal uptake of fluorodeoxyglucose.

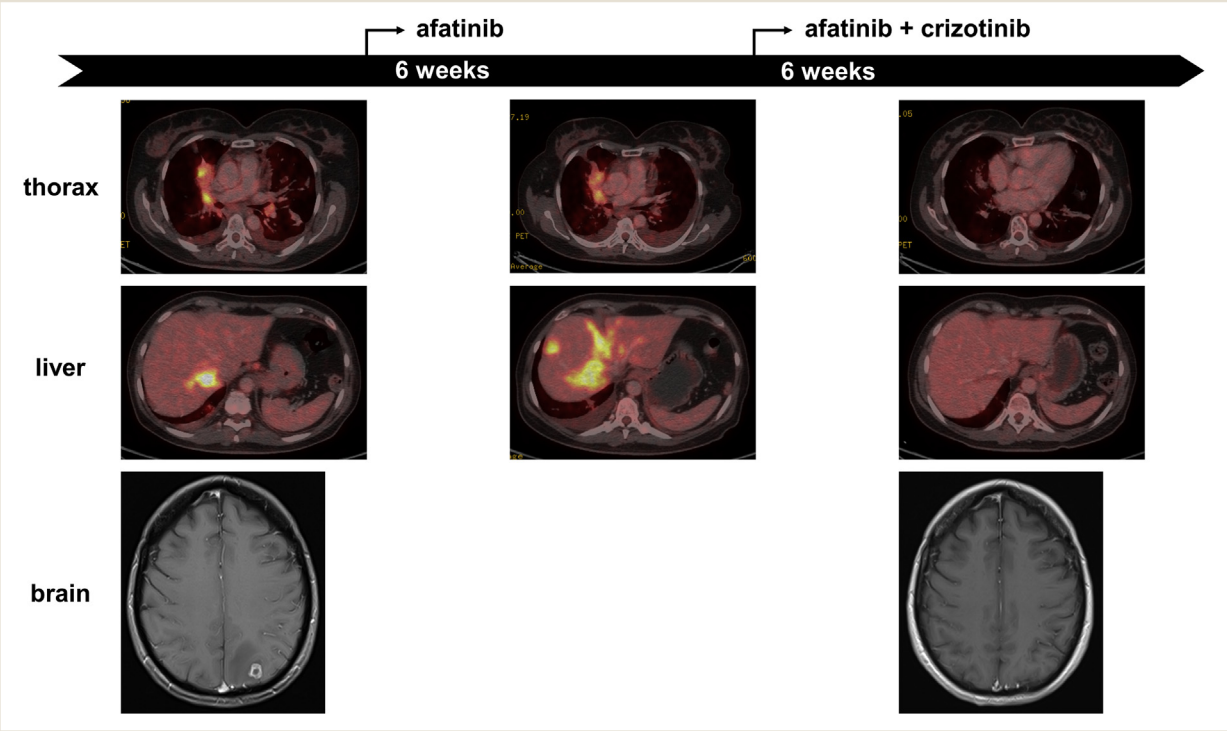
Discussion

The MET pathway is well known to be responsible for some cases of acquired resistance to tyrosine kinase inhibitor (TKI) treatment of EGFR mutations in NSCLC.[2,3] This resistance mechanism is mediated by MET amplification rather than MET mutation in about 5% to 20% of patients progressing under TKI treatment.[2-4] To the best of our knowledge, this is the first report of a concomitant common EGFR mutation and a MET Exon 14 skipping mutation in NSCLC. The MET Exon 14 skipping mutation itself is known to be a rare driver mutation in patients with NSCLC.[4,5] Some studies have shown that crizotinib and other MET inhibitors are effective in patients with MET amplification and MET Exon 14 skipping mutations.[6,7]

Although our patient harbored a known sensitizing EGFR mutation (Exon 19 deletion), afatinib treatment failed, indicating that the MET Exon 14 skipping mutation provides a strong bypass pathway and inhibits the effectiveness of afatinib. The combination of afatinib (30 mg/daily) and crizotinib (250 mg twice daily) was highly effective, administration was safe, and side effects were manageable.

There are few data regarding the combination of EGFR and MET TKIs. All of the available studies only combined first-generation EGFR TKIs, either gefitinib or erlotinib, and were used in patients with sensitizing EGFR mutation and MET amplification.[8-10] These data also indicate a moderate toxicity profile without grade 4 or 5 toxicities.[8-10]

Figure 2 Timeline of Response to Tyrosine Kinase Inhibitor Treatment. This Figure Shows the Timeline of Progression at 3 Different Tumor Sites (Thorax, Liver, and Brain) After 6 Weeks Under the Treatment With Only afatinib and the Very Good Response to the Combination Treatment With Afatinib and Crizotinib. The Single Brain Metastasis Was Treated With Stereotactic Irradiation.



Both common EGFR mutations and the Met Exon 14 skipping mutation are prominent driver mutations in NSCLC; therefore, we decided to combine both drugs rather than to switch from afatinib to crizotinib after treatment failure. It is not known if the Met Exon 14 skipping mutation is the dominant mutation in this setting and if crizotinib alone would be a sufficient treatment option.

As this case, on the one hand, seems to be a really rare condition, on the other hand, recent research and the broader use of panel sequencing have shown that co-mutations are more frequent than supposed in the past. Besides, co-mutations may have an important impact on treatment response and patient's outcome. A recent study showed that 71% of patients with NSCLC with EGFR mutation who were treated with TKIs had at least 1 additional co-mutation involving in 67% of cases TP53, in 13% CTNNB1, and in 7% KRAS, MET, SMAD4, PIK3CA, FGFR1, FGFR3, NRAS, DDR2, and ERBB4.[11] In addition, concomitant anaplastic lymphoma kinase (ALK) rearrangements were described in 1% to 1.5 % of all patients with EGFR mutations.[12] Jiao and colleagues showed that concomitant TP53 is a negative prognostic marker in patients with EGFR mutations.[13] However, until now, there has been much uncertainty in many cases of concomitant mutations as to if they have an impact on treatment response and whether these patients should be treated in a different way. This should motivate larger interventional studies to answer these questions.

Conclusion

To our knowledge, this is the first report of a patient with NSCLC with a common EGFR mutation and a concomitant Met Exon 14 skipping mutation. The Met mutation could represent an important bypass pathway and may inhibit the effectiveness of afatinib. This case demonstrates that the combination of the Erb-family inhibitor afatinib with the Met inhibitor crizotinib was a highly effective and also tolerable treatment for our patient.

Disclosure

The authors have stated that they have no conflicts of interest.

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