Acquired Exon 14 MET Mutation Associated With Resistance to Alectinib in a Patient With ALK-Rearranged NSCLC

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Background

ALK gene rearrangement in NSCLC is observed in 5% of adenocarcinoma tumors, with patients usually manifesting response to ALK tyrosine kinase inhibitors (TKIs); but unfortunately, acquired resistance ineluctably occurs. Currently, ALK-independent resistance mechanisms remain poorly characterized. Here, we report the identification of an acquired exon 14 MET mutation associated with resistance to alectinib in a patient with multimetastatic NSCLC.

Case Report

A 68-year-old nonsmoker woman was diagnosed in September 2018 with multisite metastatic adenocarcinoma of the lung. Bone biopsy led to the diagnosis of nonsquamous NSCLC with the expression of CK7+ TTF1+ at immunohistochemistry (IHC). ALK rearrangement was detected by IHC (clone 5A4). The DNA next-generation sequencing (NGS) gene panel revealed no additional gene alterations.

The patient started the second-generation ALK TKI alectinib 600 mg twice daily in October 2018. After 6 weeks of treatment, a thoracoabdominal and brain computed tomography scan revealed partial response (~70%). After 12 months, the patient presented with progression of a single liver metastasis. Liver biopsy confirmed the metastatic nature of the lesion. The ALK rearrangement was found by both IHC and fluorescence in situ hybridization (FISH). ALK rearrangement was detected by IHC (clone 5A4). The DNA next-generation sequencing (NGS) gene panel revealed no additional gene alterations.

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Discussion

Crizotinib, a first-generation TKI of ALK, ROS1, and MET has been supplanted in first-line therapy by more potent and selective second-generation ALK TKIs. On the basis of the results of the clinical trials and the approval of the Food and Drug Administration and the European Medicines Agency, alectinib is currently the preferred therapy for untreated patients with ALK-positive metastatic NSCLC.1,2

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Despite initial sensitivity to ALK TKIs, ALK-positive tumors develop resistance, encompassing the following two broad categories: on-target mechanisms (such as ALK kinase domain mutations and gene amplification) and off-target mechanisms (predominantly bypass signaling pathways). In almost 56% of the patients who progressed on the second-generation ALK inhibitor developed ALK resistance mutations.3

Currently, ALK–independent resistance mechanisms remain poorly characterized. Dagogo-Jack et al.4 performed a fluorescence in situ hybridization and NGS gene panel to detect MET alterations on 207 posttreatment tissue (n = 101) or plasma (n = 106) specimens from patients with ALK–positive lung cancer. MET amplification was detected in 15% of the tumor biopsy specimens. One plasma specimen from a patient who had a relapse after sequential alectinib and brigatinib harbored MET exon 14 skipping without MET amplification. MET mutations, however, were not detected in any of the tissue specimens.4 Furthermore, secondary mutations in the MET kinase domain have been described as a resistance mechanism to MET TKIs in NSCLC with MET exon 14 skipping.5 In addition, our activating MET mutation in exon 19 (Asp1246His) was reported after progression during the combined therapy with gefitinib and crizotinib in a patient with advanced NSCLC with primary EGFR mutation and secondary acquired MET amplification.6

To the best of our knowledge, this clinical case is the first to report an acquired exon 14 MET mutation–mediated resistance to alectinib in a patient with ALK rearrangement NSCLC.

We had chosen to treat our patient at the time of progression under alectinib with crizotinib with a short time efficacy of 3\(\frac{1}{2}\) months.

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