A Case of Lung Adenocarcinoma Harboring a Rare LOC285000-ALK-NCK2 Gene Fusion Identified by Next-Generation Sequencing With Long-Term Response to Crizotinib

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ABSTRACT

Most patients with NSCLC, initially sensitive, will develop resistance after a period of time after the application of ALK inhibitors. We present here a rare LOC285000-ALK-NCK2 gene fusion with response to crizotinib treatment; the patient achieved a progression-free survival of 23 months.

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Keywords: Lung cancer; ALK gene; Crizotinib

Introduction

About 5% of patients with NSCLC have the ALK fusion gene,1 which has at least 90 distinct fusion partners.2 Identifying ALK gene rearrangements in NSCLC is important as the presence of the alterations have an impact on the treatment response and management. Here, we reported that a lung adenocarcinoma case that harbored a rare ALK fusion obtained long-term good clinical results from crizotinib regimen.

Case Presentation

In December 2015, a 78-year-old male patient with a history of smoking presented to the hospital with lung nodules and mediastinal lymphadenopathy. On the basis of computed tomography guided thoracic puncture biopsy combined with imaging, he was diagnosed as having stage IV lung adenocarcinoma.

Although pathologic diagnosis revealed EGFR negative, the patient took erlotinib by himself from December 2015 to March 2016 owing to the relief of back pain (Fig. 1). In April 2016, the patient experienced sudden inoperability of both lower limbs, and magnetic resonance imaging (MRI) revealed metastases in thoracic and lumbar spine with a slight compression of the spinal cord. Radiotherapy was recommended to the patient, but he refused. In April 2016, single-agent pemetrexed chemotherapy was performed for one cycle, followed by next-generation sequencing using a 416 tumor-related gene panel. Next-generation sequencing identified the break and rearrangement of the ALK gene (breaking site at intron 19) and LOC285000-NCK2 spacer region in plasma (Fig. 2) with an allele frequency of 1%. At the same time, there were BIM, TET2, ARID2, CYP2D6, CYP3A5, and GSTM1 genes and other concomitant

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Figure 1. The timeline for the clinical course of the patient from diagnosis until last follow-up date with radiographic images is revealed. CT, computed tomography; MRI, magnetic resonance imaging; PD, progressive disease; SD, stable disease.

Figure 2. The Integrative Genomics Viewer screenshot (A) of LOC285000-ALK-NCK2 gene fusion are displayed by next-generation sequencing. The schematic diagram (B) represents the LOC285000-ALK-NCK2 fusion protein domain structure.
mutations and the tumor mutation burden was 2.2 mutations per Mb. Therefore, oral crizotinib was administered. No ALK fusion was detected after crizotinib treatment.

In March 2018, brain MRI revealed abnormal enhancement of left frontal lobe (5 mm) and brain metastasis was considered owing to the medical history. After four cycles of pemetrexed and bevacizumab, the patient achieved stable disease. In April 2019, the patient developed dizziness and occasionally delirium symptoms. Meanwhile, the right frontal lobe lesions were slightly enlarged in MRI. Then crizotinib was changed to alectinib in June 2019. After 2 months, the patient achieved stable disease, and has been treated with alectinib so far.

Informed consent was obtained from the patient.

Discussion

In this case, we found a rare ALK gene fusion with response to crizotinib treatment, and the patient achieved a progression-free survival of 23 months. LOC285000 is an RNA gene with only one exon, and is affiliated with the long noncoding RNA class. NCK2, which is a nonenzymatic adaptor protein composed of three N-terminal SH3 domains and one C-terminal SH2 domain, plays a crucial role in connecting the signaling pathways of tyrosine kinase receptors. This LOC285000-ALK-NCK2 gene fusion retains the complete kinase domain of ALK that may have some impact on the activation of ALK kinase and associated downstream pathways. Not all the intragenic rearrangement is transcribed to the same fusion variant by DNA sequencing. So RNA or protein assays should be used for further verification. However, RNA sequencing and ALK immunohistochemistry were not performed owing to limited tumor specimen. Thus far, this is the first case reporting this rare ALK fusion, and further validation and clinical considerable warrant further study.

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