CASE REPORT

HIP1-ALK–Rearranged Lung Cancer in a Young Adult With BRAF V600E Mutation Detected After ALK Tyrosine Kinase Inhibitor Therapy: A Case Report

Aiko Ogimoto, MD, Naoko Katsurada, MD, PhD,* Atsuhiko Yatani, MD, Chihiro Mimura, MD, Masatsugu Yamamoto, MD, PhD, Motoko Tachihara, MD, PhD

Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

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ABSTRACT

HIP1-ALK is a relatively rare fusion pattern in ALK-rearranged NSCLC. Existing studies on the efficacy of ALK tyrosine kinase inhibitor (TKI) resistance mechanisms and treatment strategies in HIP1-ALK–rearranged lung cancer are limited. Here, we report the case of an 18-year-old man with HIP1-ALK–rearranged adenocarcinoma who developed BRAF V600E and V1180L mutations after ALK TKI therapy, in whom the administration of BRAF and MEK inhibitors was ineffective. Brigatinib was effective after chemotherapy with cytotoxic drugs. Development of effective treatments is desirable for rare variants of ALK-rearranged lung cancer after acquiring resistance to ALK TKIs.

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Keywords: HIP1-ALK; BRAF V600E; Lung adenocarcinoma; Resistance mechanism; Case report

Introduction

ALK rearrangement fusions are found in 3% to 8% of NSCLC, and more than 90 rare ALK fusion partners have been reported.[1] Although the EML4-ALK fusion accounts for the majority, the HIP1-ALK fusion has a relatively higher incidence than those of non–EML4-ALK fusion partners.[1] Nevertheless, data on the efficacy of ALK tyrosine kinase inhibitors (TKIs) and resistance mechanisms to ALK TKIs in HIP1-ALK–rearranged lung cancer are limited.[2] We report the case of a 16-year-old man with HIP1-ALK–rearranged lung cancer in which the BRAF V600E mutation and V1180L mutation for ALK were detected after treatment with ALK TKIs.

Case Presentation

A 16-year-old man with no pertinent medical history who visited our hospital with the chief complaint of dyspnea was diagnosed with having advanced lung adenocarcinoma (cT3N0M1a stage IVA) with a mass in the right middle lobe of the lung, right pleural effusion, and pericardial effusion. Owing to the urgency of the condition, carboplatin plus nab-paclitaxel was initiated as first-line treatment before the results of oncogenic driver

*Corresponding author.

Dr. Ogimoto and Dr. Katsurada contributed equally to this work as co-first authors.

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Address for correspondence: Naoko Katsurada, MD, PhD, Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: nk1208@med.kobe-u.ac.jp

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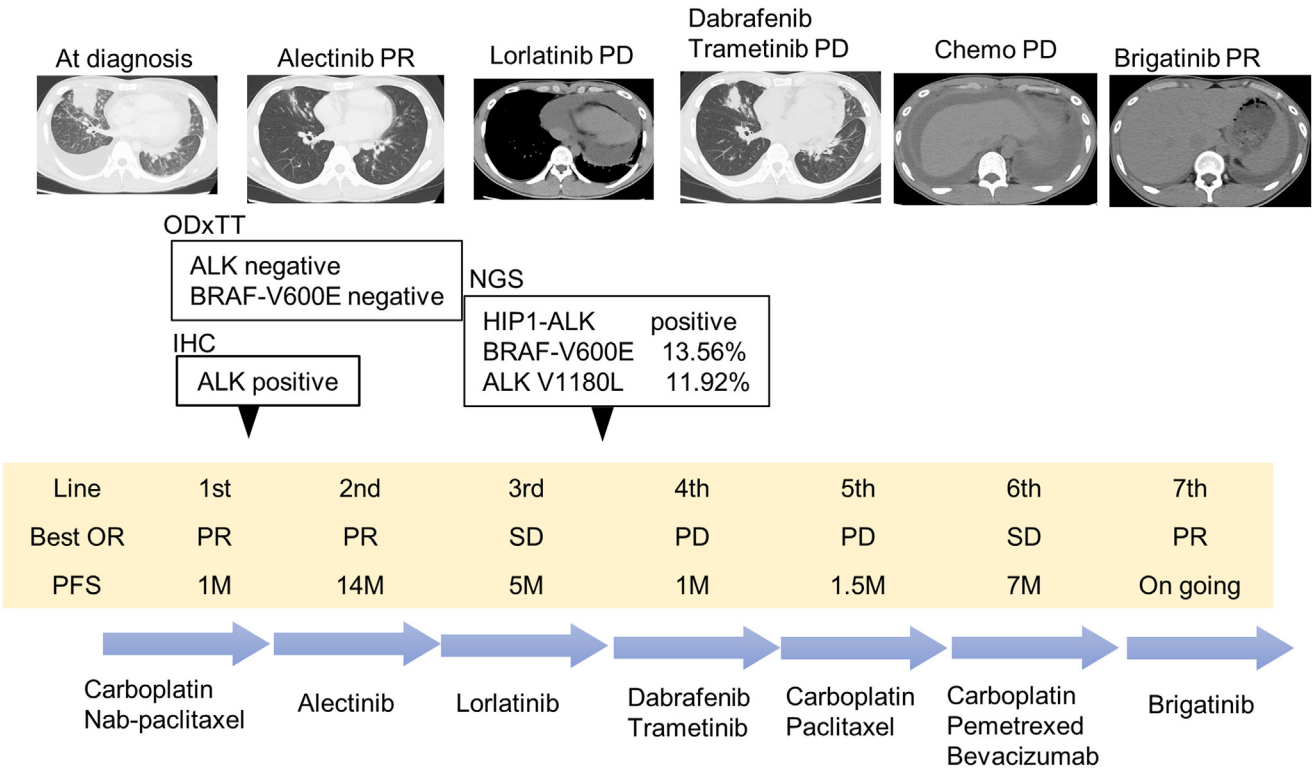

Figure 1. Timeline of events summarizing treatment history and results of genetic testing. IHC, immunohistochemistry; M, month; NGS, next-generation sequencing; ODxTT, Oncomine Dx Target Test; PD, progressive disease; PR, partial response; SD, stable disease.

alterations were obtained. After one course of chemotherapy, the patient was identified as ALK positive by immunohistochemistry of formalin-fixed, paraffin-embedded tumor sections, and second-line treatment with alectinib was initiated. The best treatment response with alectinib was a partial response (according to the Response Evaluation Criteria in Solid Tumors guidelines version 1.1). After the increase in pericardial effusion after 14 months, third-line treatment with lorlatinib was initiated. The best treatment response to lorlatinib was stable disease. A further increase in pericardial effusion was observed after 5 months, necessitating pericardial drainage. Next-generation sequencing (NGS) using Oncomine Precision Assay on Ion Torrent Genexus System (Thermo Fisher Scientific, San Francisco, CA) of the pericardial effusion revealed HIP1-ALK fusion (H30; A20), BRAF V600E (variant allele fraction: 13.56%), and V1180L mutation for ALK (variant allele fraction: 11.92%). The initial diagnostic specimen analyzed using the Oncomine Dx Target Test (Thermo Fisher Scientific, San Francisco, CA) multi-CDx System revealed no ALK fusion gene, ALK mutation, or BRAF V600E. One month after the initiation of dabrafenib and trametinib as the fourth-line treatment, reaccumulation of pericardial effusion worsened, and enlargement of the mass in the right middle lobe was observed. Subsequently, carboplatin plus paclitaxel was started as the fifth-line treatment. With an increase in pericardial effusion after 6 weeks, carboplatin plus pemetrexed plus bevacizumab was started as the sixth-line treatment. The best treatment response was a stable disease. Abdominal distention and increased ascites were reported after 7 months. Cytologic examination of ascitic fluid revealed the presence of malignant cells. Brigatinib was started as the seventh-line treatment, resulting in improved abdominal distention within a week and a reduction in ascitic fluid, as observed on computed tomography after 2 months. Figure 1 illustrates the clinical course of the patient.

Discussion

As observed in this case, HIP1-ALK is found in young adults and nonsmokers.[2] Despite several studies highlighting the effectiveness of crizotinib, studies on the effectiveness of alectinib for HIP1-ALK–rearranged lung cancer are limited.[1,2] Five variants of HIP1-ALK have been reported, with H30:A20 being one of the variants.[1] The effectiveness of ALK TKIs varies among different HIP1-ALK variants. Alectinib was effective for HIP1-ALK (H30:A20), with a progression-free survival exceeding 19 months, whereas crizotinib had a poorer response.[1] In this case, alectinib had effectiveness with a progression-free survival of 14 months.

Several studies have identified ALK point mutations and AKAP9-BRAF fusions as resistance mechanisms to

crizotinib in HIP1-ALK.[2] Nevertheless, to our knowledge, studies on BRAF V600E or ALK V1180L mutations as resistance mechanisms to ALK TKIs in HIP1-ALK are unavailable, although acquired resistance has been reported in EML4-ALK–rearranged lung cancer.[3] In our case, BRAF V600E and V1180L mutations were negative at the time of diagnosis and detected after administration of alectinib and lorlatinib. This suggests that the BRAF V600E and ALK V1180L mutations develop as mechanisms of resistance to ALK TKIs. The failure to detect HIP1-ALK fusion in the specimens at the initial diagnosis is due to the inability of Oncomine Dx Target Test to detect the HIP1-ALK variant (H30; A20). Although the immunohistochemistry assay of pretreatment tissue sample was positive for ALK, the fact that HIP1-ALK was not detected by the pretreatment NGS assay is considered a limitation because the NGS assay methods for the pretreatment and post-treatment samples are different. We used the pericardial effusion for the NGS assay to identify molecular status. The molecular diagnostic yield of NGS using cell-free DNA from pleural fluid samples has been reported to be comparable to that of biopsy samples and higher than plasma cell-free DNA.[4] The molecular testing of body cavity fluids accumulating in malignant tumors could provide useful therapeutic information. Although it might be difficult to perform in routine clinical practice, multiple NGS analyses during the treatment course are desirable for identification of resistant mechanisms and the best treatment sequence.

Combination therapy with BRAF and MEK inhibitors was ineffective. Shi et al.[5] reported that in a patient-derived xenograft mouse model, a combination of ALK TKIs, BRAF inhibitors, and MEK inhibitors was effective against the BRAF V600E mutation as a resistance after ALK TKI treatment. ALK TKI alone and combination therapies of BRAF and MEK inhibitors without ALK TKI were not effective. Another study reported that the administration of ensartinib and dabrafenib for the BRAF V600E mutation detected post-alectinib in EML4-ALK–rearranged lung cancer; however, the treatment was discontinued owing to severe adverse events.[6] Further research is needed to address BRAF V600E as a resistance mechanism to ALK TKI. In addition, most studies focused on EML4-ALK, and whether they can be applied to rare variants of ALK-rearranged lung cancers, including HIP1-ALK, needs to be verified. Brigatinib was effective after the development of resistance to alectinib and lorlatinib. Brigatinib may be efficient in acquiring the ALK point mutation V1180L in HIP1-ALK–rearranged lung cancer, although the genomic alteration was not evaluated immediately before the administration of brigatinib. Only one study has reported the efficacy of brigatinib for acquired ALK mutations after crizotinib in HIP1-ALK–rearranged lung cancer.[2] This study revealed an increased binding affinity of brigatinib to the acquired ALK mutation (Q1146K/L1152V) in molecular dynamics simulation.

Conclusions

BRAF V600E and V1180L mutations were identified as resistance mechanisms for ALK TKIs in HIP1-ALK–rearranged NSCLC. Combination therapy with BRAF and MEK inhibitors was ineffective. Accumulating data on resistance patterns and treatment sequences are desirable to gain a better understanding of the resistance mechanism and develop treatment strategies for rare variants of ALK-rearranged NSCLC.

CRediT Authorship Contribution Statement

Aiko Ogimoto: Writing—original draft, Investigation, Data curation.

Naoko Katsurada: Writing—original draft, Review and editing, Investigation, Conceptualization.

Atsuhiko Yatani: Writing—review and editing, Investigation.

Chihiro Mimura: Writing—review and editing, Investigation.

Masatsugu Yamamoto: Writing—review and editing, Investigation.

Motoko Tachihara: Writing—review and editing, Investigation, Supervision.

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