Case Report

Durable clinical response to ALK tyrosine kinase inhibitors in *ALK*-rearranged non-small cell lung cancer: a case report

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Background: Anaplastic lymphoma kinase (*ALK*) rearrangement is a key oncogenic driver promoting the expression of ALK protein in non-small cell lung cancer (NSCLC). ALK tyrosine kinase inhibitors (TKIs) have significantly improved survival benefits. However, the emergence of drug resistance limits their clinical benefits.

Case Description: We herein report a patient benefited from the sequential use of ALK TKIs (crizotinib, brigatinib, and lorlatinib) based on liquid biopsy testing. A female patient with stage IIIB NSCLC had a progression after chemotherapy and sequential radiotherapy. DNA-based next-generation sequencing (NGS) assay was performed in bronchoscopic biopsy tissue sample, demonstrating *EML4-ALK* (E13:A20) rearrangement. Crizotinib was administered, and partial response (PR) was achieved with a progression-free survival (PFS) of 8 months. Brigatinib was used when NGS simultaneously identified the six mutations *ALK* E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A, with the retention of *EML4-ALK*. The best overall response of brigatinib was a stable disease, and the PFS was 10 months. Lorlatinib was prescribed at brigatinib progression with five out of the six *ALK* mutations undetected. The patient took alectinib after lorlatinib resistance with *ALK* L1196M. The overall survival was four years.

Conclusions: *EML4-ALK* rearrangement was detected after chemotherapy treatment in an NSCLC patient with a remarkable therapeutic response with ALK TKIs based on liquid biopsy testing. We also revealed crizotinib acquired resistance mediated by multiple mutations *ALK* E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A, while five mutations were undetected after brigatinib treatment. ALK F1174C may be the resistant mutation of brigatinib.

Keywords: Non-small cell lung cancer; crizotinib resistance; tyrosine kinase inhibitors (TKI); *EML4-ALK*; case report

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Introduction

Anaplastic lymphoma kinase (*ALK*) rearrangement is found in 5–6% of all non-small cell lung cancers (NSCLCs) (1). It is a key oncogenic driver resulting in AKI protein overexpression and activation of its kinase domain. The first-generation ALK-tyrosine kinase inhibitor (TKI) crizotinib is the standard treatment for ALK rearrangement NSCLC (2). However, almost all patients treated with crizotinib develop resistance, mediated mainly by acquired secondary *ALK* resistance mutations (3).

The second-generation TKIs, such as brigatinib, are effective in crizotinib-resistant patients with secondary mutation (4). Lorlatinib is a reversible third-generation ALK inhibitor for the treatment of *ALK*-positive NSCLC; and it can overcome multiple ALK TKIs resistance

mutations and shows promising activity against brain metastasis (5).

Investigating how specific acquired mutations predict sensitivity to ALK kinase inhibitors is urgent. Here, we discuss *ALK* E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A mutations simultaneously emerging during treatment with crizotinib for an NSCLC patient harboring an *EML4-ALK* rearrangement, who then responded to brigatinib therapy. Five *ALK* mutations were not detected at brigatinib progression, and L1196M was detected at lorlatinib progression. The patient achieved a durable clinical response to ALK TKIs (crizotinib, brigatinib, and lorlatinib). We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2838/rc).

Case presentation

A 61-year-old Chinese woman without a smoking history was diagnosed with stage IIIB lung adenocarcinoma (*Figure 1A* and *1B*) in a local hospital in July 2017. The patient underwent a fine-needle biopsy of the left lower lobe. No rearrangement or amplification of *ALK*, *ROS*, and *MET* was found by fluorescence in situ hybridization (FISH) and no *EGFR* and *KRAS* mutation was found in exon 18–21 using the droplet digital PCR (ddPCR) system. The patient was initially treated with two cycles of chemotherapy regimens of pemetrexed and cis-platinum, then changed to four cycles of pemetrexed and carboplatin because of adverse effects. Stable disease (SD) was achieved after three months; therefore, the patient underwent stereotactic body radiation therapy (SBRT) in the lung lesion of the left lower lobe in January 2018. The prescription dose of SBRT was 95% PGTV 50Gy/50F. Her computed tomography (CT) revealed thoracic spinal metastasis in May 2018, and palliative radiotherapy against T3-T6 and T8-T10 was used to relieve pain in the lower back and the right hip. The therapeutic course (*Figure 1C*), and radiological examinations (*Figure 1D-1G*) are summarized in *Figure 1*.

The patient was referred to our hospital for further treatment in November 2018. Her chest CT scanning showed an enlarged primary tumor mass lesion (50 mm × 44 mm) in the left lower lobe, multiple lymph nodes and pleural effusions (*Figure 1D*), and liver metastasis (19.4 mm × 13.6 mm), indicating tumor progression. Bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed to obtain the biopsies of tissue from the left lower lobe and lymph nodes. To explore cancer-related genetic alterations, DNA-based next-generation sequencing (NGS) was performed using a targeted panel consisting of 168 cancer-related genes (Lung Plasma, Burning Rock, Guangzhou, China) with lung biopsy specimens and whole blood cells. *EML4-ALK* (E13:A20, indicating the fusion variant 1 between *EML4* exon 13 and *ALK* exon 20) rearrangement was identified in both tissue and plasma circulating tumor DNA (ctDNA). The allelic fraction (AF) was 11.09%. No other *ALK* mutation was detected (*Figure 2A*). Subsequently, the patient initiated crizotinib (250 mg, bid) treatment in December 2018. The patient achieved a partial response (PR) two months later with shrunken primary (39.3 mm × 34.8 mm) and metastatic tumors (*Figure 1E*), and a significant reduction in the blood tumor markers, particularly carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) (*Figure 2B*). The progression-free survival (PFS) was 8 months. Follow-up CT imaging showed three low-density masses in the left lung in August 2019 (*Figure 1F*). Magnetic resonance imaging (MRI) showed multiple small contrast-enhancing lesions, suggesting brain metastasis. Crizotinib was discontinued.

To identify the mechanism underlying resistance to crizotinib, ctDNA was analyzed using NGS (Lung Plasma, Burning Rock, Guangzhou, China). In addition to *EML4-ALK* rearrangement, six *ALK* point mutations were detected, including E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A (*Figure 2A*). Except for E1129V, other mutations are reported as a resistance mechanism of ALK inhibitor crizotinib but are sensitive to the second-generation ALK inhibitor brigatinib (6). Therefore, brigatinib was administered in September 2019. She experienced an overall improvement in her clinical symptoms. The levels of CA19-9 and CEA were also observed to be decreased after brigatinib treatment, especially the CA19-9 level was close to the normal range during brigatinib treatment (*Figure 2B*). The patient obtained SD with 10 months of PFS. A follow-up CT scan showed the primary lung tumors were stable (*Figure 1G*).

However, the patient tended to have worse ability to perform activities and higher levels of chest pain and cough, and plasma was sent for NGS in July 2020. ctDNA analysis showed the retention of *EML4-ALK* and *ALK* F1174C, but the other five mutations were not detected without the emergence of new mutations (*Figure 2A*). The abundance of *EML4-ALK* and *ALK* F1174C (AF 51.81% and 65.67%) was significantly higher than before brigatinib treatment, indicating disease progression. So brigatinib

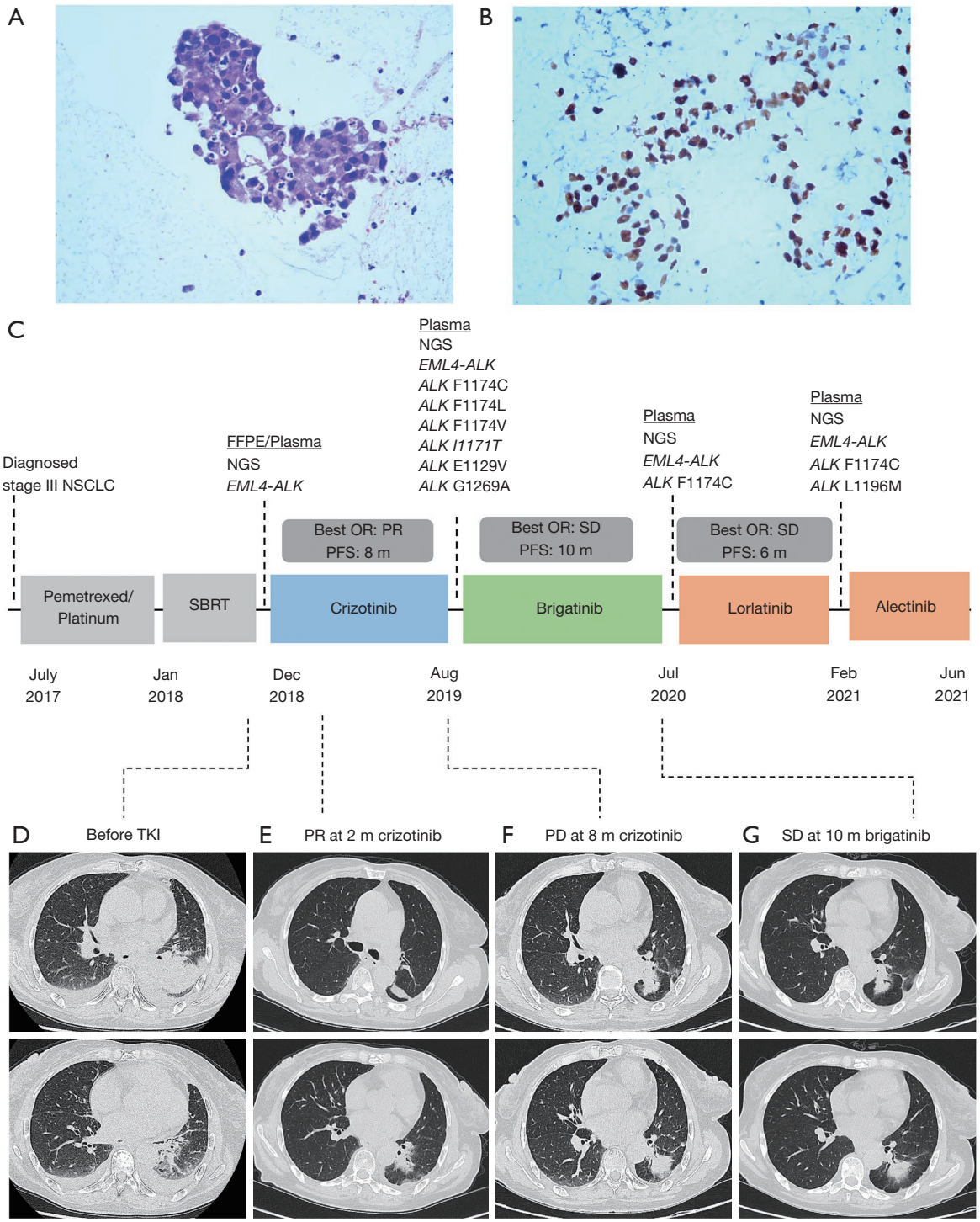

Figure 1 Clinical summary of pathology results, therapeutic course, and radiological examinations. (A) Hematoxylin-eosin staining of tumor biopsy (magnification 100×). (B) IHC staining of TTF1 (magnification 100×). (C) The therapeutic course of the treatment. (D) CT imaging before crizotinib therapy. (E) CT imaging of PR after 2 months of crizotinib therapy. (F) CT imaging of PD after 8 months of crizotinib therapy. (G) CT imaging of SD after 10 months of brigatinib treatment. FFPE, formalin-fixed, paraffin-embedded; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OR, overall response; PFS, progression-free survival; PR, partial response; PD, progression disease; SD, stable disease; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitors.

A

ALK mutation	Dec 2018	Aug 2019	Jul 2020	Feb 2021
EML4-ALK (E13:A20)	11.09%	15.32%	51.81%	57.14%
E1129V	ND	2.91%	ND	ND
F1174C	ND	4.07%	65.67%	70.72%
F1174L	ND	0.24%	ND	ND
F1174V	ND	0.81%	ND	ND
I1171T	ND	4.60%	ND	ND
G1269A	ND	0.52%	ND	ND
L1196M	ND	ND	ND	2.72%

B

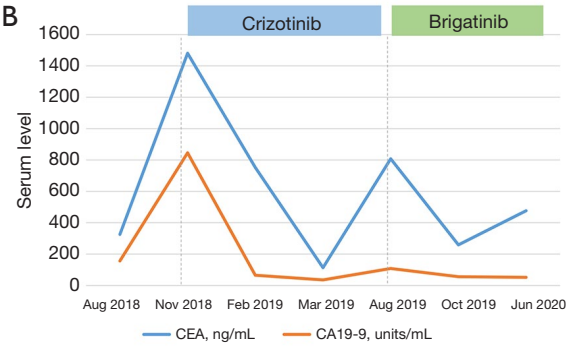

Figure 2 The change of allelic fractions and blood tumor markers during the course of treatment. (A) *ALK* mutations and their corresponding allelic fractions during TKI treatment. (B) Serum level of CA19-9 and CEA during crizotinib and brigatinib treatment. The normal range of CA19-9 is 0–37 units/mL. The normal range of CEA is 0–5 ng/mL. ND, not detectable; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

was discontinued. Subsequently, the patient was switched to lorlatinib and her general condition improved during that time with a PFS of 6 months. In February 2021, the patient experienced dyspnea, anorexia, nausea, worsening chest pain, and appeared cachectic. Her performance score was 3. ctDNA analysis by NGS detected the emergence of *ALK* L1196M (AF 2.72%) and retention of *EML4-ALK* (AF 57.14%) and *ALK* F1174C (AF 70.72%) (*Figure 2A*). Alectinib was initiated with the patient's consent but she experienced vomiting and severe nausea, which may lead to the oral medication not being effective. The patient's general condition worsened, and she passed away in a local hospital with the an overall survival (OS) of about four years.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We herein report a patient who achieved a durable clinical response to the sequential use of ALK TKIs, crizotinib, brigatinib, and lorlatinib and underwent multiple repeat liquid biopsies throughout the course of the disease. A female patient was presented with stage IIIB disease and no common driver mutations were detected with FISH and ddPCR. So she was initially treated with chemotherapy and radiation therapy with no good response. She then developed stage IV disease with lymph node and liver metastasis. With DNA-based NGS, *EML4-ALK* variant 1 was detected both in tissue and plasma. The patient achieved a rapid and excellent clinical response to crizotinib with relief of all symptoms. *ALK* E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A mutations emerged at progression with brain metastasis then responded to brigatinib therapy. With sequential ctDNA analysis by NGS, lorlatinib was used based on gene mutations. The OS was 4 years.

Five FDA-approved ALK TKIs include crizotinib, brigatinib, lorlatinib, ceritinib, and alectinib. ALK resistance mutations that emerge during treatment significantly limit their effectiveness (7). In our case, the best response to crizotinib treatment was PR, and the PFS was 8 months. Secondary mutations in the tyrosine kinase domain of ALK confer resistance to crizotinib, including *ALK* L1196M, G1269A, C1156Y, G1202R, I1171T/N/S, S1206C/Y, E1210K, L1152P/R, V11180L, I1151T, G1128A, and F1174V (6). The number of *ALK* resistance mutations increases with each successive generation of ALK TKI (8). In our case, we simultaneously detected six mutations from ctDNA after only TKI treatment once, which is rare. Patient with *ALK* E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A responded to brigatinib lasting 10 months and brigatinib was discontinued when her general condition worsened, at which time liquid biopsy detected the accumulation of *EML4-ALK* variant 1 and *ALK* F1174C. *ALK* F1174C is reported to be resistant to crizotinib but sensitive to brigatinib (6,9). However, we

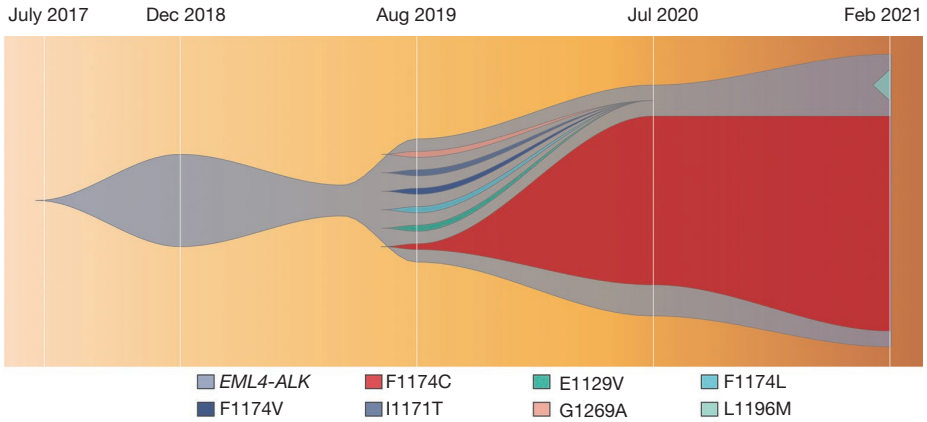

Figure 3 *ALK* gene evolution of reported mutations via ctDNA NGS. NGS, next-generation sequencing.

noticed the *ALK* F1174C might be the resistance mutation of brigatinib. *ALK* F1174C was also reported to be sensitive to lorlatinib and alectinib (6). Patients harboring *ALK* F1174X mutation (including known and unknown F1174 missense mutations, like F1174 C/I/L/M/S/V etc.) show a good response to lorlatinib in a phase II study of advanced *ALK*-positive NSCLC patients (7). On the basis of this finding, the patient was switched to lorlatinib and achieved SD for 6 months. When she relapsed on lorlatinib, *ALK* L1196M was detected with the stepwise accumulation of ALK resistance mutations *EML4-ALK* variant 1 and *ALK* F1174C. *ALK* L1196M was the first reported resistance mutation (10), generating resistance to crizotinib. We detected *ALK* L1196M after resistance to lorlatinib. An *in vitro* study showed that compound *ALK* mutations F1174C and L1196M could cause resistance to lorlatinib (11). The patient's clinical condition was poor upon lorlatinib progression, and treatment of alectinib was not effective due to her vomiting and severe nausea.

With the development of NGS technology, liquid biopsy has now been used to monitor the genetic alterations of ctDNA. It plays a significant role in treatment choice and monitoring response in patients. ctDNA analysis is a promising strategy for analyzing TKI resistance in oncogene-driven NSCLCs (12). Serial ctDNA analysis was necessary for detecting mutations of resistance as well as tumor heterogeneity and clonal evolution (*Figure 3*). We found *ALK* F1174C as the potential mechanism of brigatinib resistance.

Our study has some limitations. Due to the patient's poor clinical condition during late stage treatment (performance score 2–3), no invasive examinations for tissue biopsy were applied. So we can only monitor the genetic alterations based on liquid biopsy only, which may miss some key information on the resistance mechanism from tissues biopsy. It's reported that the median OS time from diagnosis in stage IV *ALK*-rearranged NSCLC patients was 81 months (13). However, the OS of our patient was only 4 years, and the most prolonged PFS of each TKI was 10 months. It indicated underlying ALK TKI resistance, probably mediated by off-target mechanisms such as bypass signaling, lineage changes, or Epithelial-Mesenchymal Transition (7,14).

Conclusions

We reported a patient benefited from the sequential use of ALK TKIs (crizotinib, brigatinib, and lorlatinib). A female patient with stage IIIB NSCLC detected *EML4-ALK* (E13:A20) rearrangement after chemotherapy and sequential radiotherapy and had a PR to crizotinib. *ALK* E1129V, F1174C, F1174L, F1174V, I1171T, and G1269A mutations emerged at crizotinib progression then responded to brigatinib therapy. Lorlatinib was used based on ctDNA analysis by NGS. Our case contributed to understanding the complexity of acquired resistance mechanisms in sequential ALK inhibitor therapy patients achieved durable clinical benefit.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2838/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2838/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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