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Exceptional Survival with Lorlatinib in ALK-Rearranged Lung Cancer: A Case Report

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ABSTRACT

Genetic alterations in the ALK gene occur in approximately 3-5% of cases of non-squamous non-small cell lung cancer (NSCLC). These rearrangements are critical in determining how cancer cells respond to treatment with ALK inhibitors. However, over time, some patients may develop resistance, leading to disease progression. In such cases, performing genetic analysis is crucial to detect new mutations that could be driving resistance, enabling healthcare providers to select the most appropriate next-line therapy. We present the case of a 56-year-old patient with advanced NSCLC who had an exceptional progression-free survival of 71 months. This case highlights the potential benefits of using sequential ALK inhibitors in the treatment of advanced ALK-rearranged lung adenocarcinoma. This case emphasizes the importance of genetic testing and tailored treatment approaches and offers optimism for improved patient outcomes in individuals with ALK-positive lung adenocarcinoma.

Keywords: Cancer, ALK, Lorlatinib, NSCLC, Case report

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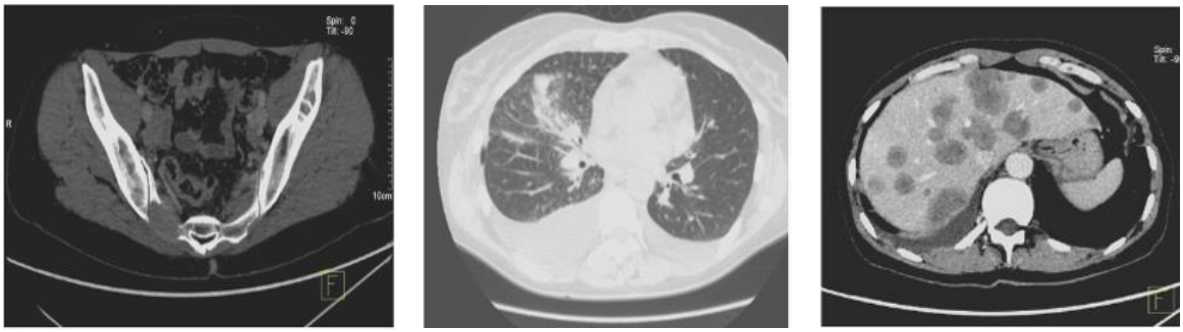
Introduction

Genetic mutations in the ALK (anaplastic lymphoma kinase) gene are detected in approximately 3-5% of cases of non-squamous non-small cell lung cancer (NSCLC) [1-3]. The ALK rearrangement is typically observed in younger, female patients who have never smoked [3, 4]. This rearrangement significantly influences how cancer cells respond to treatment with ALK tyrosine kinase inhibitors (TKIs) [2, 3]. Currently, three generations of ALK inhibitors exist, and the sequence of their administration can affect the survival outcomes of patients with advanced NSCLC [3, 5, 6]. Although initial responses to these inhibitors are often positive, many patients eventually relapse [3, 5]. For this reason, genetic testing of biopsy samples from metastatic sites is commonly performed [5, 7]. As new mutations causing resistance to treatment emerge, genetic profiling plays a vital role in determining the best course of treatment for patients whose conditions have progressed [3, 5, 6]. In this case report, we present the case of a patient with ALK-rearranged lung adenocarcinoma who received a combination of three generations of ALK inhibitors—crizotinib, alectinib, and lorlatinib—and achieved progression-free survival (PFS) of 71 months [8, 9].

Case report

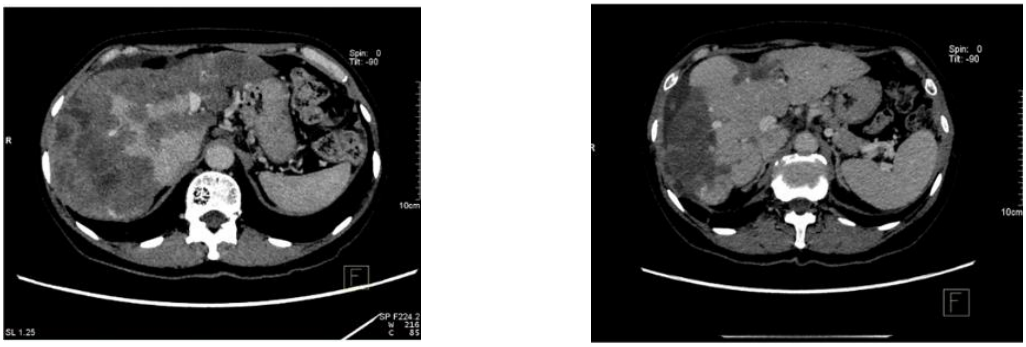
In February 2017, a 56-year-old female patient, with no smoking history, was diagnosed with adenocarcinoma of the right lung. Her primary complaint was a chronic cough that had persisted for about two months. Imaging studies revealed numerous metastatic lesions in the liver and skeletal system, indicating advanced stage IV disease. Brain imaging results showed no evidence of metastasis to the central nervous system (CNS) **(Figure 1)**.



a) b) c)

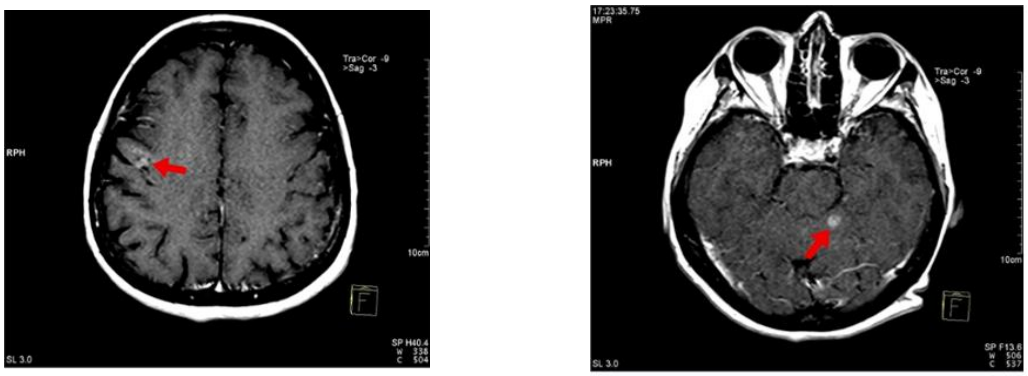
Figure 1. Pre-treatment imaging depicting the progression of the disease; Metastatic lesions: a) sacral area; b) right lung; and c) liver.

Initially, the patient underwent chemotherapy with a regimen of paclitaxel and cisplatin for three cycles, along with one cycle of cisplatin administered directly into the pericardial space. Genetic testing revealed a positive ALK gene rearrangement in 76% of the cell nuclei. Based on these results, the patient started targeted therapy with crizotinib (200 mg twice daily), a first-generation ALK inhibitor, in combination with intravenous bisphosphonates, beginning in April 2017. She continued this treatment until March 2020. After 36 months, imaging revealed worsening liver metastases and physical exams showed signs of neurological involvement, including ptosis, gait, and balance issues **(Figure 2)**. In March 2020, neuroimaging confirmed the presence of four metastatic lesions in the CNS **(Figure 3)**. As a result, the patient received stereotactic radiotherapy for the brain lesions and switched to second-line therapy with Alectinib (600 mg twice daily), a second-generation ALK inhibitor. This combination provided a relatively long progression-free survival of six months. In May 2020, the patient underwent stereotactic radiation targeting the metastatic lesion in the right frontoparietal region, receiving a 24 Gy dose delivered via the VMAT technique.



a) b)

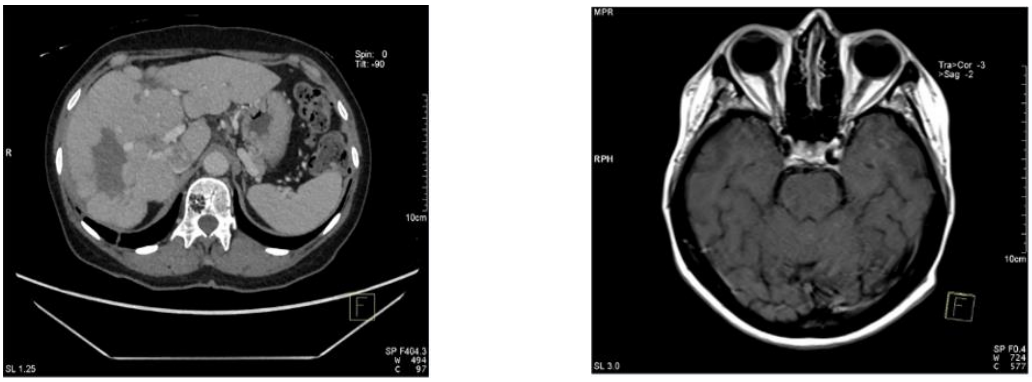
Figure 2. Metastatic lesions in the liver: a) February 2020; and b) May 2020.



a) b)

Figure 3. Central nervous system (CNS) metastases; March 2020.

Following the continued progression of liver metastases, the patient was placed on third-line therapy with lorlatinib (100 mg daily), a third-generation ALK inhibitor, beginning in October 2020. This treatment resulted in a reduction in the size of the primary tumor, with significant improvement in clinical symptoms, and the disease was considered stable. The brain metastases remained visible but showed no signs of further growth **(Figure 4)**. During lorlatinib therapy, the patient experienced an elevation in lipase levels, reaching stage 3 after the eighth cycle of treatment. No toxicities beyond grade 1, as per CTCAE, were reported. However, in November 2021, the patient was diagnosed with osteonecrosis of the jaw.



a) b)

Figure 4. Imaging of metastatic lesions during lorlatinib treatment: a) liver, and b) central nervous system (CNS).

In August 2022, neuroimaging revealed the presence of liver lesions, raising concerns about the potential for metastasis. To confirm the progression, a second biopsy of the liver was performed, which confirmed metastatic changes. Genetic analysis, conducted on biopsy samples from the metastatic sites, identified the presence of KLC-ALK fusion. Consequently, the treatment regimen was adjusted to include both bevacizumab and lorlatinib, resulting in the stabilization of the progressive changes. As of the latest data available at the time of publication, the patient has achieved progression-free survival (PFS) of 71 months **(Figure 5)**.

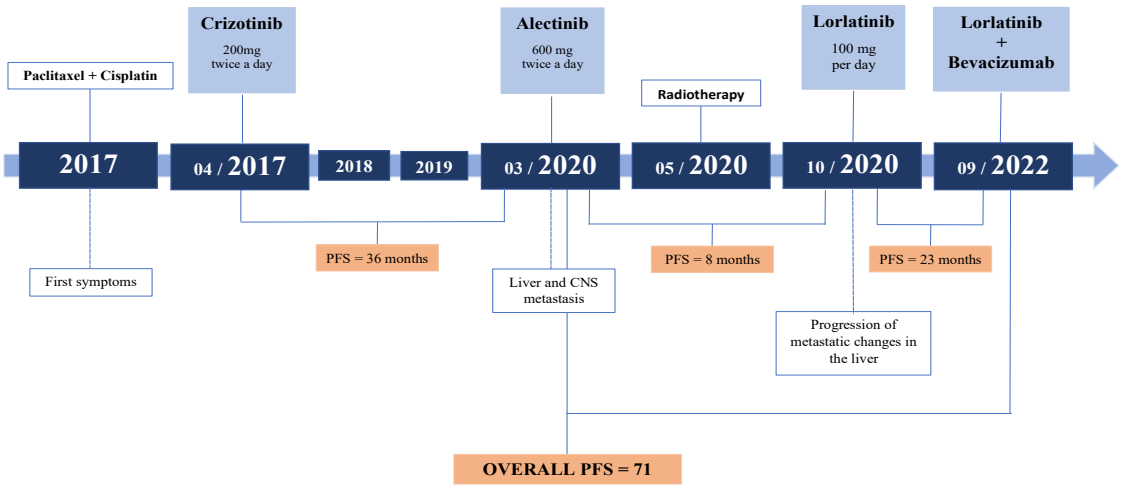


Figure 5. Timeline of events for a case study.

Results and Discussion

This report details an exceptional response to treatment with lorlatinib, leading to an overall progression-free survival (PFS) of 71 months, including a continuous PFS of 36 months, through a sequence of three ALK inhibitors: crizotinib, alectinib, and lorlatinib. Lorlatinib is commonly prescribed for patients who have experienced progression after using first- and second-generation ALK inhibitors, and it has shown greater efficacy

in addressing central nervous system (CNS) metastases compared to other ALK inhibitors [10-12]. In the present case, following progression on lorlatinib, a follow-up liver biopsy was performed, and subsequent gene sequencing using FoundationOne®CDx—an advanced next-generation sequencing (NGS) platform—uncovered mutations in the KLC1-ALK fusion, ALK-SCAMP5 non-canonical fusion, and MDM2 amplification [13, 14]. These genetic findings supported the continued use of lorlatinib in combination with bevacizumab, with the cancer remaining responsive to the therapy.

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) [15], can cross the blood-brain barrier. It has been found effective in treating brain metastases in NSCLC, especially when paired with chemotherapy or targeted therapies [16].

The decision to resume lorlatinib therapy in this patient was informed by existing research on the re-use of lorlatinib in cases where patients had relapsed following initial treatment with the drug [17]. With the fast-paced evolution of treatments for NSCLC, more patients are now benefiting from personalized targeted therapies that focus on specific genetic mutations [3, 5]. Through repeated biopsies, new mutations, gene fusions, and patterns of resistance can be identified, allowing for the selection of more appropriate drugs to address disease progression [3, 5].

Conclusion

In conclusion, treating NSCLC with ALK gene rearrangement remains a significant challenge, particularly after lorlatinib therapy when there is disease progression. This emphasizes the importance of performing repeat biopsies in patients undergoing targeted treatments, as these tests can help detect new, treatment-resistant mutations. Identifying such mutations allows for the selection of more suitable drugs, or even sensitizing previously used therapies. Moreover, these findings underscore the potential advantages of administering higher-generation drugs without prior use of lower-generation alternatives or reintroducing drugs previously used in treatment.

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Ethics Statement: None

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