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Pathological complete response to neoadjuvant lorlatinib in a patient with unresectable ALK-Positive locally advanced non-small cell lung cancer: A case report

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ABSTRACT

Anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs) have demonstrated substantial effectiveness in individuals with advanced ALK-positive non-small cell lung cancer (NSCLC). However, the controversy over using ALK-TKIs for neoadjuvant therapy in ALK-positive NSCLC has not been fully explored. This case study describes the clinical progression of a patient initially diagnosed with unresectable stage III (cT1bN2M0) lung adenocarcinoma, who was later discovered to harbor an ALK mutation through next-generation sequencing. The patient underwent surgery to achieve a radical resection of the right upper lung lesion after neoadjuvant therapy with lorlatinib and a pathological complete response (pCR) was confirmed by pathological analysis. To our knowledge, it has never been reported that neoadjuvant therapy with lorlatinib resulted in pCR for an ALK-positive patient with stage III NSCLC who was initially unresectable. Therefore, our findings indicate that utilizing ALK-TKIs as neoadjuvant therapy could be considered a viable choice for ALK-positive NSCLC patients.

1. Introduction

Treatment for stage III NSCLC patients is tailored to each individual and directed by a multidisciplinary treatment. Neoadjuvant chemotherapy is recommended for stage III patients, with the possibility of surgical resection if deemed appropriate. Clinical trials such as NeoADAURA [1] have shown superior clinical outcomes with neoadjuvant targeted therapy compared to neoadjuvant chemotherapy in patients with EGFR mutations. The effectiveness and safety of neoadjuvant therapy for ALK-positive NSCLC are currently uncertain.

Lorlatinib, a third-generation ALK inhibitor, was specifically engineered to efficiently penetrate the blood-brain barrier and attain elevated concentrations within the central nervous system (CNS) [2]. Previous studies have demonstrated the strong anti-tumor efficacy of lorlatinib in advanced NSCLC following the ineffectiveness of first- or second-generation ALK inhibitors [3,4]. Shaw et al. found that lorlatinib resulted in extended progression-free survival and increased rates of intracranial response compared to crizotinib

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for advanced NSCLC patients [5]. However, further research is needed to determine lorlatinib's safety and efficacy for locally advanced NSCLC. Here, we report a case with locally advanced ALK-positive NSCLC achieved pCR after the treatment of lorlatinib.

2. Case presentation

A 60-year-old Asian male with a 30-year smoking history was found to have a dense nodule in the upper right lung *via* chest computed tomography (CT) as part of his annual medical examination in 2020. The nodule measured 1.3 × 0.9 cm and was found to have enlarged to that size at a follow-up CT scan in 2022, along with the enlargement of multiple mediastinal lymph nodes, with the largest measuring 2.2 × 1.3 cm. The patient received treatment at a tertiary care hospital, and a diagnosis of NSCLC was confirmed by pathological assessment of ultrasound-guided transbronchial needle aspiration. Immunohistochemistry analysis revealed NapsinA (+++), TTF-1 (+++), and P40 (−) expression in primary lesions and TTF-1 (++) and NapsinA (++) in 4R lymph nodes (Fig. 3A and B). It was determined that no significant metastases were present on magnetic resonance imaging of the head, upper abdominal enhanced CT scan, and whole-body bone emission CT scan. According to the 8th edition of the AJCC/UICC staging system, the patient's classification was cT1bN2M0, which corresponds to stage IIIA. Next-generation sequencing (NGS) confirmed an ALK fusion status to guide treatment decisions.

Following the NCCN Guidelines for NSCLC (version 2023) and multidisciplinary team (MDT) discussions, neoadjuvant therapy is a feasible choice for individuals diagnosed with stage IIIA NSCLC and concurrent mediastinal lymph node metastasis. Based on the patient's ALK fusion status, neoadjuvant therapy with lorlatinib was commenced with a dose of 100 mg orally daily on August 12th, 2022, with written informed consent. After one cycle of lorlatinib therapy (28 days), a chest CT scan revealed a 31 % decrease in the size of the primary tumor and a 35 % reduction in the largest mediastinal lymph nodes, though the clinical stage remained IIIA (cT1aN2M0). However, no significant changes in tumor size were observed after the next two cycles of lorlatinib (Fig. 1). The patient

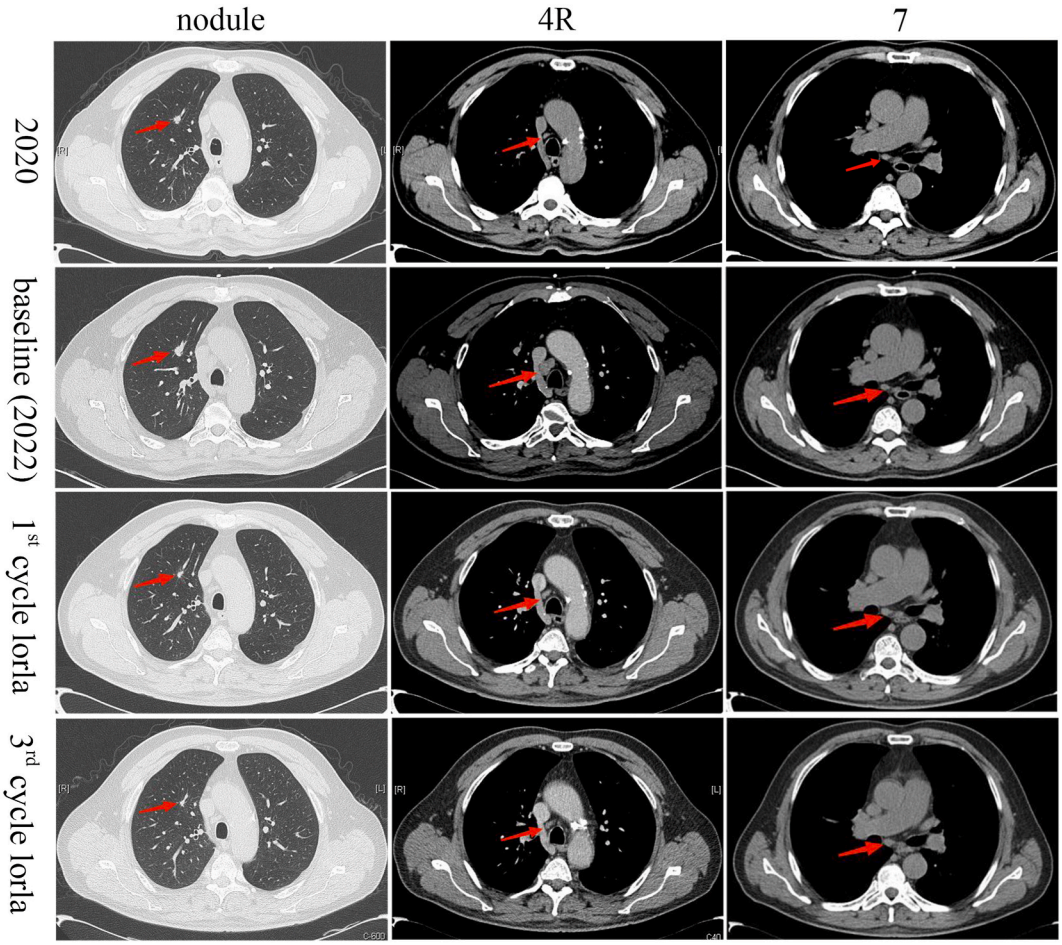

Fig. 1. The CT scans of 2020, baseline (2022), after the first cycle, and after the third cycle of lorlatinib (the red arrows stand for the primary tumor, station #4R, and #7 lymph node respectively). The maximum diameter of primary tumor from 2020 to the third cycle of lorlatinib is 8.0, 13.0, 9.0, and 7.5 mm, respectively. The maximum diameter of station #4R lymph nodes from 2020 to the third cycle of lorlatinib is 8.5, 22.5, 14.7, and 11.5mm. No significant changes were observed in station #7 lymph nodes during the whole treatment cycle. CT, computed tomography.

experienced grade 2 hyperlipidemia as the only adverse effect of the neoadjuvant therapy.

Two days after the last dose of lorlatinib, the patient underwent video-assisted thoracoscopic surgery for right upper lobectomy and systematic lymph node dissection after a discussion by a multidisciplinary team. The surgery resulted in complete surgical resection (R0) with mild adhesion and minor intraoperative bleeding (Fig. 2A–F). Postoperative pathological examination revealed fibrosis nodule and no tumor cells in both the lymph nodes and primary lesions, indicating a pathological complete response (pCR) (Fig. 3C and D). Atrial fibrillation occurred six days after surgery without apparent triggers and was managed with amiodarone. Nine days after surgery, the patient was discharged without any further in-hospital complications. The original lorlatinib regimen was continued four days after discharge, and CT reexamination was advised every three months for recurrence detection. The treatment process is outlined in Fig. 4.

3. Discussion

Given the pronounced heterogeneity characterizing stage III NSCLC, ongoing debates persist surrounding treatment strategies. Chemotherapy is still the main form of treatment for patients who lack specific genetic mutations. The combination of chemotherapy and immunotherapy, as shown in several phase III clinical trials [6], has demonstrated improved outcomes and may potentially emerge as a standard treatment approach for stage III NSCLC in the future. Notably, targeted therapy assumes a pivotal role as a treatment modality in patients exhibiting driver mutations. Neoadjuvant targeted therapy is an emerging field that has shown promising results in recent years. Currently, neoadjuvant targeted therapies are mostly used for EGFR-positive NSCLC, with limited data on ALK-TKI efficacy in ALK-positive NSCLC [7]. Zhang et al. documented two cases of N2 ALK-positive NSCLC achieving pCR after neoadjuvant crizotinib therapy [8]. Bing et al. detailed a case of ceritinib-induced pCR in a patient with stage IIIb ALK-positive NSCLC who had developed resistance to crizotinib [9]. However, there is a lack of cases reporting pCR following neoadjuvant lorlatinib therapy in locally advanced ALK-rearranged NSCLC patients.

Lorlatinib is structurally optimized to effectively block resistant ALK mutations and also cross the blood-brain barrier. In the CROWN trial [10], lorlatinib demonstrated a high intracranial response rate among patients with measurable brain metastases at the outset (71 % complete response). Additionally, lorlatinib significantly reduced the incidence of CNS progression, potentially preventing metastases and prolonging progression-free survival.

The EMERGING (CTONG1103) trial [11] investigated the safety and effectiveness of neoadjuvant therapy in patients with EGFR-positive stage IIIA NSCLC, with a comparison between erlotinib and the traditional platinum-containing dual treatment. Although neoadjuvant erlotinib exhibited a superior overall response rate (ORR) than chemotherapy, there was no obvious difference observed. The optimal duration of neoadjuvant erlotinib therapy (42 days) was also questioned. Further exploration is needed to determine the optimal length of neoadjuvant therapy. Based on the risk of intraoperative adhesion and bleeding with long-term neoadjuvant therapy and the findings of the EMERGING (CTONG1103) study, a three-month ALK TKI therapy was chosen after the consultation with the patient's family. Upon postoperative pathological examination, this patient who underwent three-cycle neoadjuvant therapy with lorlatinib showed fibrous tissue proliferation in the primary lesions and lymph nodes, indicating the feasibility of lorlatinib in achieving pCR in ALK-positive NSCLC. However, chest CT after the third lorlatinib cycle showed no significant changes in the lung and mediastinal metastatic lymph nodes compared to the lesion size after the first cycle, with the development of minor hyperlipidemia during neoadjuvant therapy. Additional research is necessary to determine the optimal dosing cycle of lorlatinib while

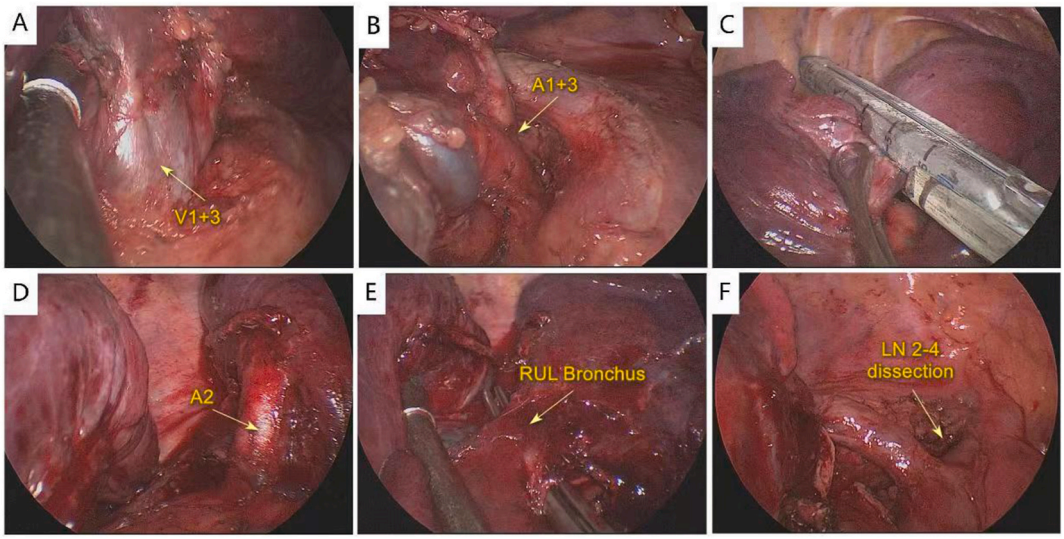

Fig. 2. Intraoperative findings. (A) Separation of the upper lobe veins. (B) Separation of the upper lobe arteries. (C) Open the posterior oblique fissure. (D) Exposure to the posterior ascending rami. (E) Sever the right lung bronchus. (F) Superior mediastinal node trauma.

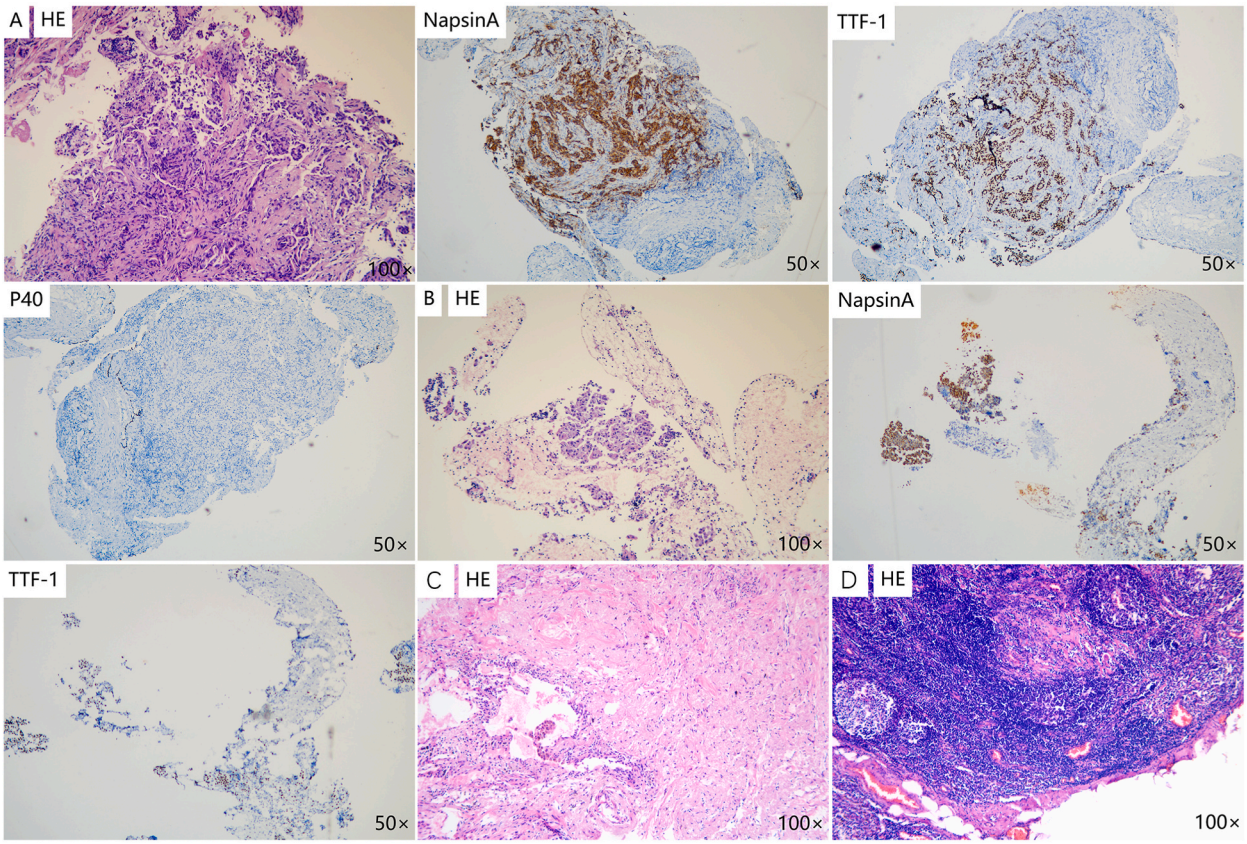

Fig. 3. Hematoxylin-eosin (HE) staining and immunohistochemistry (IHC) images about primary lesions and lymph nodes. (A) The HE staining of lung tissue shows the infiltration of heterotypic cells. IHC examinations reveal positive NapsinA, TTF-1, and negative P40. (B) The HE staining of 4R lymph nodes shows some epithelial cells arranged in nests. IHC examinations reveal positive TTF-1, NapsinA. (C, D) Postoperative pathology showed a fibrosis nodule, with a downstaging to pCR. C: primary lesion, D: 4 group lymph nodes.

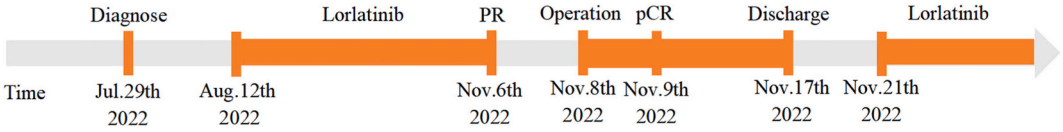

Fig. 4. A depiction of the administration of therapy during an episode of care is presented in the timeline. PR, partial response; pCR, pathological complete response.

balancing efficacy and side effects.

The optimal duration of postoperative lorlatinib therapy remains a matter of debate. In clinical trials, such as ADJUVANT [12], RADIANT [13], EVAN [14], and SELECT [15] studies, patients were treated with either gefitinib or erlotinib for nearly 24 months. In the ADAURA trial, patients were subjected to osimertinib for 3 years [16]. In all the trials mentioned above, patients receiving TKI treatment had significantly lengthier DFS at 24 months. Based on these observations, the current one-year duration of adjuvant TKI therapy may be inadequate, with at least two years required to minimize disease recurrence. Nevertheless, the ideal length of adjuvant TKI therapy is still unclear.

For patients who do not achieve pCR through neoadjuvant therapy, NGS must be frequently assessed post-surgery to identify gene mutations. For this case, since the patient achieved pCR, our postoperative follow-up procedure primarily involves reassessment of blood tumor markers and CT scans. Additionally, we employ ctDNA-based minimal residual disease (MRD) detection to promptly identify occurrences of patient's relapse or metastasis.

4. Conclusions

To our knowledge, this is the first instance in which neoadjuvant lorlatinib was utilized to treat ALK-positive lung adenocarcinoma.

The case substantiates that optimal therapeutic impacts can be attained through neoadjuvant lorlatinib administration in advanced ALK-rearranged lung adenocarcinoma. These results can be useful in guiding the development of effective clinical treatment plans for patients suffering from such conditions.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Ruiqi Chen: Conceptualization, Data curation, Writing – original draft. **Lilan Zhao:** Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Juan Zhang:** Data curation, Validation. **Lingwen Guo:** Data curation, Validation. **Zhizhong Chen:** Data curation, Validation, Writing – review & editing. **Xiaojie Pan:** Conceptualization, Data curation, Project administration, Supervision, Validation, Writing – review & editing. **Wenshu Chen:** Conceptualization, Data curation, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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