CASE REPORT

Lorlatinib After Alectinib-Induced Pneumonitis: A Case Report

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ABSTRACT

ALK gene rearrangements are detected in approximately 3% to 5% of NSCLC. *ALK* tyrosine kinase inhibitors, such as third-generation lorlatinib, have exhibited remarkable efficacy in *ALK*-rearranged NSCLC; however, they have been associated with a low incidence of treatment-limiting and potentially fatal drug-induced interstitial lung disease (ILD). There is concern that this may represent a class effect, a theory that is supported by a number of case reports. Because of clinical trial exclusion criteria, there are limited prospective data to guide decision-making after *ALK* tyrosine kinase inhibitors–induced ILD. A systematic review of the literature was conducted and only identified four reported cases of lorlatinib safety in this context. Here, we report the successful sequencing of lorlatinib in a patient who discontinued alectinib secondary to grade 3 drug-induced ILD.

Keywords: Lorlatinib; Alectinib; Pneumonitis; NSCLC; Case report

Introduction

Rearrangements of the *ALK* gene are detected in approximately 3% to 5% of NSCLC. First (crizotinib) and second-generation (ceritinib, alectinib, brigatinib) tyrosine kinase inhibitors (TKIs) have exhibited remarkable efficacy against this molecularly distinct oncogene-addicted lung cancer. However, they have also been associated with treatment-limiting and potentially fatal drug-induced interstitial lung disease (DI-ILD) in approximately 1% to 4%.[1] This presents as progressive dyspnea, cough, and a spectrum of radiographic changes. It has been hypothesized to be drug-related hypersensitivity pneumonitis and there has been concern that this may represent a class effect of *ALK* TKIs.[2] This has been supported by its generally late onset, resolution after drug discontinuation, and reoccurrence with reintroduction.[2,3] However, acute and severe cases have also been reported with diffuse alveolar damage and high mortality. Risk factors include smoking history, older age, worse performance status, pleural effusions, concomitant ILD, and Japanese ethnicity.[3,4]

Lorlatinib is a third-generation TKI directed against *ALK* and c-ros 1 kinases.[5] The registrational phase 1 and 2 trial (NCT01970865) of lorlatinib reported substantial response rates, and to date, the incidence of DI-ILD has been low, with only a single case of grade 4 toxicity reported in the phase 2 cohort.[5] However, patients with a history of ILD were specifically excluded and there is little data regarding the safety of lorlatinib in patients who discontinued first- or second-generation TKIs because of DI-ILD.[1] This is of great clinical interest, not just because of the clinical efficacy of TKIs for

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Table 1. Previously Reported Cases of Lorlatinib After *ALK* TKI Associated Lung Disease Identified by Systematic Review

Report	Demographics	Initial TKI	Time of Onset of ILD	Bronchoscopy	Timing of Lorlatinib and Concurrent Steroids	Outcome
Myall et al.[3]	80M cT3N2M1c NSCLC Asian, nonsmoker	Alectinib	18 d	Not performed because of respiratory status	Several wk after DI-ILD Prednisone 2 mg once daily	No recurrence of ILD after 10 wk therapy Discontinue because of progression
Myall et al.[3]	66F cT1cN2M1c NSCLC Caucasian, nonsmoker First-line pembrolizumab	Alectinib	26 d	Patient declined bronchoscopy	Not specified Had third-line carboplatin and pemetrexed before starting lorlatinib Concurrent dexamethasone 2mg twice daily	No recurrence of ILD after $>$ 10 mo Disease response
Kashizaki et al.[6]	57M stage IVB NSCLC Japanese First-line cisplatin + pemetrexed	Alectinib	3 mo	BALF revealed increased lymphocyte ratio (34.4%) TBLB revealed organizing pneumonia nonspecific interstitial pneumonia overlapping pattern	4 mo of third-line nab-paclitaxel (PD) before starting lorlatinib No concurrent steroids	No recurrence of ILD after 33 mo Stable disease
Monzonís et al.[7]	53F stage IV NSCLC Ex-smoker First-line cisplatin + pemetrexed Second line crizotinib Third-line alectinib	Brigatinib	1 wk	Not specified	Successfully rechallenged with brigatinib for 5 mo before progression and starting lorlatinib No concurrent steroids	Recurrent ILD on d 1 Bilateral infiltrates on CT High-dose methylprednisolone and successful steroid wean
Present case	83F cT4N2M1 NSCLC Nonsmoker, Caucasian	Alectinib	4 mo		Steroids were weaned over 8 wk and then commenced lorlatinib 50 mg No concurrent steroids	No recurrence after 9 mo Disease response

BALF, bronchoalveolar lavage fluid; CT, computed tomography; DI, drug-induced; F, female sex; ILD, interstitial lung disease; M, male sex. PD, progressive disease; TBLB, transbronchial lung biopsy; TKI, tyrosine kinase inhibitor.

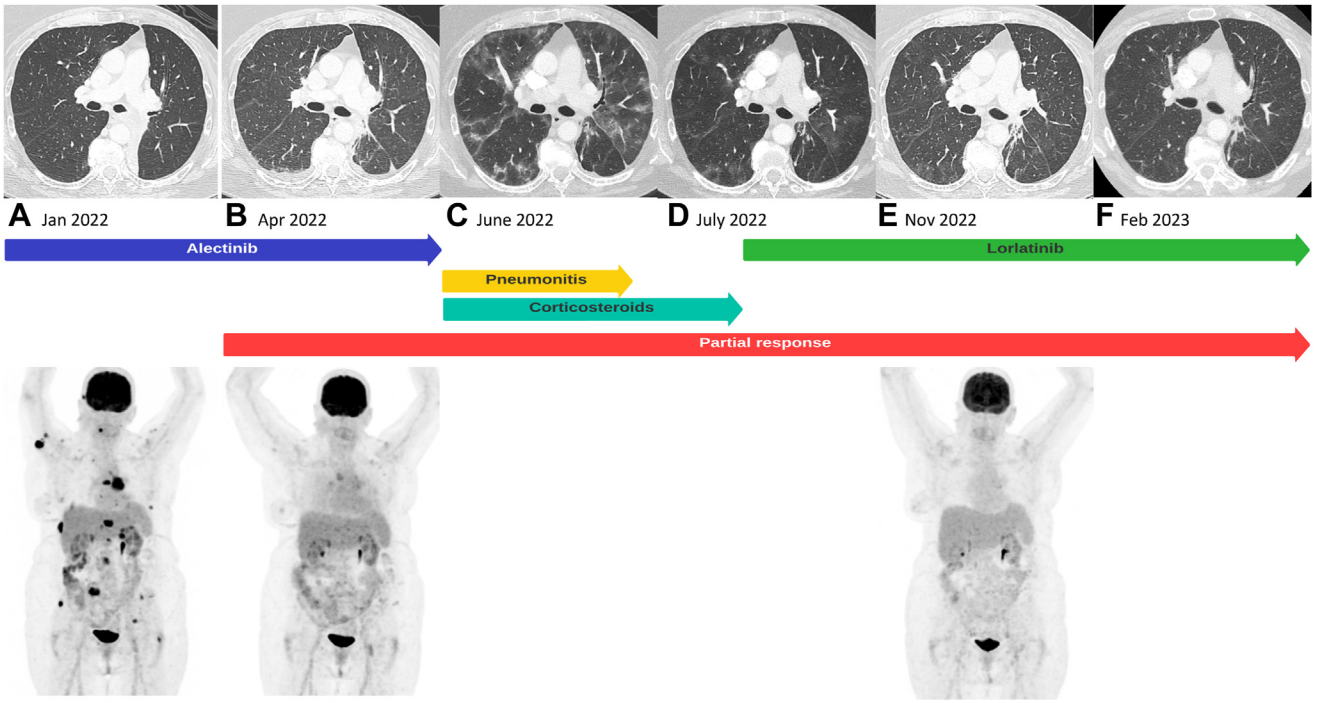

Figure 1. Radiologic presentation with acute lung toxicity secondary to alectinib for ALK-positive lung adenocarcinoma. (*A*) Baseline CT/PET revealing left hilar disease and FDG-avid metastatic disease; (*B*) radiologic and metabolic partial response to alectinib; (*C*) extensive bilateral ground-glass opacities developed 4 months after commencing alectinib; (*D*) Near-complete resolution of opacities after discontinuation of alectinib and 4 weeks of oral corticosteroids; (*E*) resolution of bilateral opacities and maintained partial metabolic response after cessation of oral steroids, and completion of 3 months of lorlatinib; and (*F*) most recent CT imaging. Apr, April; CT, computed tomography; FDG, fluorodeoxyglucose F^{18}; Feb, February; Jan, January; Nov, November; PET, positron emission tomography.

ALK-rearranged NSCLC, but because of concern that DI-ILD may be a class effect.[1] A systematic review of the literature was conducted (Supplementary Appendix), which only identified four cases reporting lorlatinib safety after *AKI*-TKI DI-ILD (Table 1).

Here, we report a patient who tolerated and responded to lorlatinib after the resolution of grade 3 DI-ILD secondary to alectinib.

Case Presentation

An 83-year-old Caucasian woman and ex-light smoker (less than 5 pack-year history) was diagnosed with *EML4-ALK* fusion–positive lung adenocarcinoma with widespread metastases including asymptomatic brain metastases (cT4N2M1c). Fluorescence in-situ hybridization detected an *ALK* rearrangement and whole exome sequencing revealed no additional variations of significance. Baseline respiratory function tests revealed preserved total lung capacity (90% predicted) and diffusion capacity for carbon monoxide (76% predicted); however, the patient was unable to perform acceptable spirometry.

The patient commenced alectinib 600 mg twice daily and achieved a partial response on computed tomography (CT) (Fig. 1*A* and *B*). After 4 months of therapy, she was admitted to the clinic with increasing dyspnea and a CT revealing extensive patchy ground-glass changes (Fig. 1*C*) but maintained partial response. There were no infectious or cardiac symptoms, nor occupational or other exposures associated with pneumonitis. Salient clinical findings included oxygen saturations of 94% on room air and bilateral lower zone crepitations.

Bronchoscopy revealed left lower lobe erythema and bronchoalveolar lavage (BAL) revealed elevated lymphocytes in a macrophage-predominant infiltration with negative cultures for infective etiology including atypical microorganisms.

The differential diagnoses of her pneumonitis were the following: (1) DI-ILD, (2) infectious etiology including pneumocystis, and (3) pulmonary edema. Given the distribution of changes, temporal correlation with the start of therapy, and the absence of infection, cardiac causes, or other precipitants, a consensus diagnosis of alectinib-induced ILD was made. She made a rapid clinical response to the cessation of alectinib and 50 mg of prednisone (0.5–1.0 mg/kg), further supporting this diagnosis.

Steroids were weaned by 10 mg per week initially under outpatient supervision and completely ceased by 8 weeks. CT imaging confirmed the resolution of

interstitial ground-glass changes (Fig. 1*D*). Given the patient and treating team's desire to maintain *ALK* inhibition and the low reported incidence of DI-ILD with lorlatinib, the patient was commenced on lorlatinib without any considerable adverse events. Our patient continues on lorlatinib after 9 months without progression or pneumonitis (Fig. 1*E* and *F*).

Discussion

The safety of novel third-generation TKIs after DI-ILD secondary to first- or second-generation TKIs has seldom been reported and represents an area of great clinical need given the efficacy and tolerability of these drugs compared with alternatives such as platinum-based chemotherapy. Here, we report the successful sequencing of lorlatinib after discontinuation of alectinib because of DI-ILD. After 9 months of therapy, lorlatinib exhibited continued efficacy without recurrent pneumonitis.

Whereas patients with a history of ILD or fibrosis were specifically excluded from registrational studies, rechallenge with first and second-generation *ALK* TKIs after DI-ILD has been reported in a small case series.[3] A systematic review of the literature (Appendix A) only identified four cases with reported safety of lorlatinib after DI-ILD from second-generation TKIs (Table 1).

Myall et al.[3] reported two patients who tolerated lorlatinib after DI-ILD secondary to alectinib. In contrast with our case, both remained on corticosteroids during the introduction of lorlatinib, and it is not known whether concurrent steroids may have a mitigating role in early-onset pneumonitis. Furthermore, one patient had been recently exposed to pembrolizumab before their commencing alectinib, and this may have potentiated their initial TKI lung toxicity.[3] Kashizaki et al.[6] reported one patient with pretreated NSCLC who experienced DI-ILD after 3 months of alectinib and eventually went on to tolerate lorlatinib for a significant period without lung toxicity or steroid exposure. A strength of this study was the reporting of BAL findings of lymphocyte-predominant infiltrate, and a lung biopsy reporting overlapping organizing pneumonia and nonspecific interstitial pneumonia pattern.

Finally, Monzonís et al.[7] reported an unusual case of rapid-onset DI-ILD secondary to lorlatinib in a woman with heavily pretreated NSCLC who had a previous early-onset brigatinib-associated lung toxicity. The BAL was bland. Whereas the authors appropriately raised concerns regarding potential cross-reactivity leading to rapid hypersensitivity pneumonitis, it is interesting to note that the patient had previously been successfully rechallenged with brigatinib.

A strength of our case was the exclusion of infectious etiologies and having prompt, albeit noncontributory, bronchoscopic evaluation. The delayed onset of progressive dyspnea, widespread radiographic pulmonary infiltrates, and rapid response to corticosteroids all supported the original diagnosis of DI-ILD. The authors also acknowledge the limited follow-up period, as previous reports of pneumonitis have been documented several months after initiation of *ALK* TKIs. However, it stands to reason that cross-reactivity with a hypersensitivity pneumonitis would present early, similar to previous case reports of rechallenge with earlier TKIs.

This case study contributes to a small but clinically important body of evidence suggesting that lorlatinib is a feasible option for patients who have been intolerant to earlier-generation TKIs because of pulmonary adverse events. Interruption of therapy to treat pneumonitis did not seem to result in a disease flare in the cases reported to date. In at least two cases, lorlatinib was introduced during steroid tapering, suggesting that it may be an alternative to chemotherapy if disease flare is encountered in this context. However, data are scarce, and significant questions remain regarding the absolute rate of pneumonitis in this setting, the risk of potential cross-reactivity reactions, and whether strategies such as concurrent steroids might be mitigating factors.

Conclusion

Lorlatinib is a third-generation *ALK* TKI associated with substantial clinical efficacy. Limited case reports suggest that it remains an important treatment consideration in patients who have experienced DI-ILD to earlier-generation *ALK* TKIs.

Informed Consent

Written informed consent was provided by the patient for this case report.

CRediT Authorship Contribution Statement

James A. Fletcher: Study concepts, Study design, Data acquisition, Data analysis and interpretation, Manuscript preparation, Manuscript editing.

William J. Mullally: Study concepts, Study design, Data acquisition, Data analysis and interpretation, Manuscript preparation, Manuscript editing.

Rahul Ladwa: Study concepts, Study design, Manuscript editing.

Kenneth J. O'Byrne: Study concepts, Study design, Manuscript editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO*

Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100591.

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