An Unusual Case of Lorlatinib-Induced Pneumonitis: A Case Report

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Abstract
The discovery of tyrosine kinase oncogenic driver mutations, including anaplastic lymphoma kinase (ALK), has changed the face of non-small cell lung cancer (NSCLC) treatment. Whilst the development of tyrosine kinase inhibitors has improved survival, with their increasing use, it is important to be aware of the risks of rare yet serious adverse events, such as drug-induced pulmonary toxicity. Whilst little is known in regard to drug-induced pneumonitis in the setting of ALK inhibitors, such reactions carry a high morbidity and mortality rate, impacting greatly upon options for further treatment and management. We describe the case of a 73-year-old female with metastatic ALK-positive NSCLC who developed subacute dyspnoea 3 weeks after commencing \textit{lorlatinib}. She was diagnosed with drug-induced pneumonitis, from which she recovered clinically following the cessation of her targeted therapy. Pneumonitis related to \textit{lorlatinib} is a rare pulmonary toxicity, and early recognition and intervention is critical to reduce the associated risks of respiratory failure and death.

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Introduction

Lorlatinib is a novel third-generation TKI designed to target advanced, ALK-positive NSCLC. Although pneumonitis secondary to epidermal growth factor receptor (EGFR) inhibitors is a commonly recognized entity, it is far less well-described in regard to ALK inhibitors. In this setting, drug-induced pneumonitis has been most frequently associated with brigatinib, a second-generation ALK inhibitor, whilst the incidence amongst patients receiving lorlatinib has been documented at <2% in clinical trials [1, 2]. This report reviews a case of lorlatinib-induced pneumonitis, a potentially fatal, yet poorly understood adverse reaction, which is not widely documented in the current literature.

Case Report

A 73-year-old Caucasian female with a past medical history of asthma, depression, and atrial fibrillation was diagnosed with stage IV lung adenocarcinoma in March 2020. Her only regular medication was escitalopram. She was a lifelong nonsmoker with no known history of asbestos or mineral dust exposure. At diagnosis, she was found to have extensive disease involving mediastinal and intra-abdominal lymph nodes and metastases to the pericardium, bone, and liver. Molecular testing revealed a high programmed death ligand-1 (PDL-1) tumour proportion score of 55% and positive ALK immunohistochemistry. ALK translocation was subsequently confirmed with fluorescent in situ hybridization.

The patient was commenced on alectinib as the first-line therapy in March 2020, to which she had a partial but uncharacteristically short-lived response. In July, she reported progressive dysphagia and was found to have bulky mediastinal disease. She received palliative radiation therapy 20 Gy/5 fractions using a volumetric arc therapy technique, limiting high-dose isodoses to the mediastinum, as shown in Figure 1. Radiation therapy was completed in August 2020 following which the patient demonstrated a good symptomatic response. Repeat imaging studies in November 2020 demonstrated progressive extrathoracic disease, and second-line therapy with lorlatinib 100 mg daily was initiated.

Within 3 weeks of commencement of lorlatinib, the patient presented dyspnoeic at rest with a new dry cough and associated malaise. On examination, she was afebrile but hypoxaemic, with an oxygen saturation of 86% on room air. She was in rapid atrial fibrillation. Her blood pressure was stable, and there were no signs of cardiac decompensation. Fine inspiratory crepitations were auscultated bilaterally, most predominant in the right midzone. Initial blood tests revealed elevated inflammatory markers (CRP 103 [<5.0 mg/L]
and WCC 15.4 [4.0–11.0 × 10⁹/L]) and a haemoglobin level of 85 g/L [115–165 g/L]. Thoracic echocardiogram was largely unremarkable. A CT angiogram excluded a pulmonary embolism; however, it did demonstrate widespread patchy bilateral consolidation and associated pleural effusions, not present when compared to a CT chest performed 1 month before (shown in Fig. 2). Differential diagnoses of an underlying infective process, a delayed presentation of radiation toxicity, or an adverse drug event secondary to lorlatinib were considered.

The patient was admitted to the hospital and commenced on supplemental oxygen, broad-spectrum intravenous antibiotics, and systemic corticosteroid therapy. Lorlatinib was discontinued. An infective workup, including COVID-19 testing and blood cultures, was negative. Bronchoscopy was not pursued given the unacceptably high anaesthetic risk.

Within days of initiating the above interventions, the patient showed rapid clinical and radiological improvement and was discharged home on a steroid weaning course of oral prednisone. Follow-up imaging performed 1 month later showed significant improvement in the region of pneumonitis, as shown in Figure 2. During the steroid wean, third-line palliative chemotherapy was planned. Anti-PD1 immunotherapy was not considered given the risk of recurrent pneumonitis. Unfortunately, she re-presented to the hospital 2 months later with a bowel obstruction secondary to widespread intra-abdominal metastases. Surgical intervention was not pursued, and she died 1 week later. Figure 3 provides an overview of her treatment algorithm.

**Fig. 2.** Serial CT images of the chest demonstrating extensive parenchymal abnormalities observed after commencing lorlatinib, and evident improvement following its cessation. The first CT angiogram, performed 3 weeks after commencing lorlatinib, demonstrates diffuse, bilateral ground glass opacity and consolidation (a). Follow-up imaging, performed 1 month after the cessation of lorlatinib, demonstrates near-complete resolution of these radiographic abnormalities, with some focal scarring at the sites of previous active pneumonitis (b).
Identification of oncogenic driver mutations, such as ALK and EGFR, has helped revolutionize the treatment of NSCLC [3]. Isolated in around 3–5% of patients with NSCLC, ALK-positive tumours have a stronger association with younger patients, nonsmokers, and those with a histological diagnosis of adenocarcinoma [4]. Detecting ALK gene rearrangements is critical as these tumours are highly sensitive to targeted tyrosine kinase therapy, improving survival [1].

A third-generation TKI, lorlatinib, has recently received FDA approval for first-line use in advanced ALK-positive NSCLC in March 2021. It is also employed for patients whose disease burden has progressed despite treatment with one or more of the first (crizotinib) or second (ceritinib, brigatinib, and alectinib)-generation ALK-TKIs [1, 4, 5]. It potently targets most known acquired resistance mutations which invariably develop during treatment with first- and second-generation TKIs and also exhibits strong antitumour activity in patients with intracranial metastases, even after previous ALK-targeted therapy [1].

All of the TKIs have been associated with drug-induced respiratory disease [1, 6]. Brigatinib is the agent most frequently linked to pneumonitis (4–9.1%) and is associated with early onset of respiratory symptoms (<48 h), whilst longer exposure periods have been typically observed amongst the other ALK inhibitors [6]. There is a paucity of information available on pneumonitis specifically associated with lorlatinib therapy; however, in a systematic review of the literature, pulmonary toxicity was encountered in 1.8% of exposed patients [6]. Whilst bronchoscopic and further histopathological evaluation was not pursued in this patient due to her clinical instability and risk of hypoxia, the absence of fevers and the rapid clinical recovery observed once lorlatinib was discontinued favours the diagnosis of drug-induced pneumonitis. Moreover, the acute bilateral radiographic changes observed on chest imaging were characteristic of ALK inhibitor pneumonitis, where the underlying pathological processes of exudative oedema and hyaline membrane formation in the lung correlate with diffuse alveolar damage, seen radiographically as bilateral ground glass opacities such as those shown in Figure 2 [7].

There is one reported case of cross-reactivity where a patient who had recovered from brigatinib-induced interstitial lung disease re-developed pneumonitis shortly after commencing lorlatinib [8]. Interestingly, in this case, the patient developed severe dyspnoea and fever just 1 day after lorlatinib therapy was initiated [8]. In a more recently reported fatal
case, the patient tolerated lorlatinib for 3 months before acute respiratory decompensation led to her emergency presentation and death. With a similar treatment sequence to our case, this patient had progressive disease whilst on alectinib and had been commenced on lorlatinib after a course of radiation therapy [9]. It is important to acknowledge that whilst our patient did receive thoracic radiation therapy, she had received a low palliative dose completed >3 months prior to the onset of her respiratory symptoms and the diffuse bilateral ground glass opacities. The consolidation demonstrated on imaging involved lung parenchyma beyond the irradiated field, when the diagnostic scan was re-fused with her original radiation therapy field. This strongly favoured ALK inhibitor-associated pneumonitis over a radiation pneumonitis.

There are 2 accounts in the literature where lorlatinib has been successfully tolerated in individuals who had recovered from alectinib-induced pneumonitis. Both patients showed no evidence of further respiratory decompensation, and lorlatinib was proposed as a reasonable alternative therapy to be considered following recovery from drug-induced pneumonitis precipitated by other TKIs [7].

Pulmonary toxicity secondary to ALK-targeted therapy is classified as a grade 3 or 4 adverse event in 65% of cases, with an associated mortality rate of 9% [6]. Recognizing this, prompt investigation is necessitated for any patient who presents with new respiratory symptoms suggestive of pneumonitis in the setting of tyrosine kinase therapy. The risk of progression to life-threatening disease calls for discontinuation of the offending drug in every suspected case, regardless of graded severity. Indeed, determining what constitutes safe and effective therapy for patients who wish for further treatment following resolution of the respiratory illness is difficult. Whilst the permanent discontinuation of lorlatinib, or other implicated ALK-TKIs (with the exception of brigatinib), is agreed upon as a critical step to decrease the risk of life-threatening pneumonitis, this course of action leaves limited treatment options available.

Conclusion

This case describes a patient with ALK-positive NSCLC who developed pneumonitis 3 weeks after the commencement of lorlatinib. Although pulmonary toxicity associated with this ALK-TKI is rare, it carries the risk of life-threatening respiratory failure. Particularly, as new-generation agents such as lorlatinib come into increasing use, it is important to be aware of TKI-inhibitor-induced pneumonitis and to highlight the need for prompt investigation and early intervention to reduce morbidity and mortality.

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Statement of Ethics

The patient described in this manuscript provided written informed consent for the reporting of her case and use of clinical imaging. The treating teams also approved of her case being published, and as an individual case report, this study is exempt from ethics committee approval.
Conflict of Interest Statement

The authors report no existing conflicts of interest.

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Author Contributions

P.K.H. and D.J.P. conceived the case report, P.K.H. wrote the initial draft of the manuscript, and all authors contributed to the editing and revising of the manuscript. All authors agree to be accountable for all aspects of the work.

Data Availability Statement

No data were utilized for the purpose of this case report.

References

1. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018;19(12):1654–67.
2. Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol. 2017;35(22):2490–8.
3. Akamine T, Toyokawa G, Tagawa T, Seto T. Spotlight on lorlatinib and its potential in the treatment of NSCLC: the evidence to date. Onco Targets Ther. 2018;11:5093–101.
4. Nagasaka M. A user’s guide to lorlatinib. Crit Rev Oncol Hematol. 2020;151:102969.
5. Shaw AT, Ou SH, Felip E, Bauer TM, Besse B, Gadgeel SM, et al. Efficacy and Safety of lorlatinib in ALK+ non-small cell lung cancer (NSCLC) patients (pts) with >1 prior ALK tyrosine kinase inhibitor (TKI): a phase 1/2 Study. J Clin Oncol. 2017;35(15 Suppl 1) (no pagination). Conference: 2017 annual meeting of the american society of clinical oncology, ASCO United states.
6. Pellegrino B, Facchinetti F, Bordi P, Silva M, Gnetti L, Tiseo M. Lung toxicity in non-small-cell lung cancer patients exposed to ALK inhibitors: report of a peculiar case and systematic review of the literature. Clin Lung Cancer. 2018;19(2):e151–61.
7. Myall NJ, Lei AQ, Wakelee HA. Safety of lorlatinib following alectinib-induced pneumonitis in two patients with ALK-rearranged non-small cell lung cancer: a case series. Transl Lung Cancer Res. 2021;10(1):487–95.
8. Monzonís X, Arriola E. Early onset pulmonary toxicity with lorlatinib in a patient with previous pulmonary toxicity from brigatinib. J Thorac Oncol. 2019;14(11):e247–8.
9. Sharma S, Kommineni K, Mehta SS, Singh H. Lorlatinib-associated acute respiratory distress syndrome. Am J Ther. 2020;27(6):e698–9.