CASE REPORT

Successful Lorlatinib Rechallenge After Severe Drug-Induced Psychosis in ALK-Positive Metastatic NSCLC: A Case Report

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ABSTRACT

Neurocognitive adverse events (NAEs) have been reported in up to 60% of patients on lorlatinib, a potent central nervous system–active ALK inhibitor. Manifestations may include psychotic, mood, speech, and cognitive symptoms. Current guidance recommends permanent discontinuation of lorlatinib in cases of grade IV NAEs. Here, we report a case of successful rechallenge of dose-reduced lorlatinib after recovery of grade IV psychosis in a patient with ALK-positive NSCLC.

Keywords: Adverse event; ALK; Lorlatinib; Non–small cell lung cancer; Psychosis; Case report

Introduction

Lorlatinib is a U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)–approved, potent, central nervous system (CNS)–penetrant ALK inhibitor. Its clinical efficacy was first found in a multicohort phase 2 trial of patients with pretreated and untreated stage 4 ALK-positive NSCLC, the first-line results of which were corroborated in the phase 3 CROWN trial. This revealed a considerable improvement in progression-free survival, overall and intracranial response rates, and duration of response, in comparison with crizotinib in patients with untreated ALK-positive NSCLC.[1,2]

Neurocognitive adverse events (NAEs), including psychotic, cognitive, mood, and speech changes, have been observed as unique toxicities of lorlatinib in comparison with earlier generation ALK inhibitors, partly explained by greater CNS drug accumulation. Risk factors for development of NAEs may include brain metastases, brain radiation, psychiatric illness, and neurotropic medications.[3]

The FDA prescribing information and EMA summary of product characteristics for lorlatinib recommends withholding drug for grade II to III (moderate–severe) NAEs until improved to less than or equal to grade I in severity and permanent discontinuation in cases of grade IV (life-threatening or urgent intervention indicated) NAE. Here, we report a case of successful rechallenge of dose-reduced lorlatinib in a patient with ALK-positive NSCLC who developed grade IV lorlatinib-induced psychosis.

Case Presentation

A 47-year-old man of South Asian ethnicity with a never-smoking history and background medical history of type 2 diabetes and pulmonary embolism was diagnosed in October 2017 with de novo metastatic lung adenocarcinoma with nodal (cervical, thoracic) and bilateral pulmonary nodular metastases, without

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baseline CNS metastases. Core biopsy result of a cervical lymph node was ALK positive by immunohistochemistry.

The patient commenced first-line crizotinib in December 2017 but was switched to brigatinib in February 2018 due to grade II rise of alanine transaminase level. He remained on brigatinib until August 2022 (approximately 4.5 y), with a dose reduction from 180 mg to 120 mg daily in July 2020 due to recurrent grade III rise of creatine kinase level. In August 2022, the patient developed new intracranial (innumerable small lesions) and leptomeningeal metastases on routine gadolinium-enhanced magnetic resonance imaging (MRI) brain surveillance with stable extracranial disease. He remained entirely asymptomatic with no neurologic signs, with performance status of 0, and with ability to continue work full time. He was subsequently commenced on lorlatinib 100 mg daily, having been counseled on risks, including the potential for NAEs.

Concomitant medications at the time of commencing lorlatinib were (doses of all unknown) doxazosin, ramipril, edoxaban, metformin, insulin, amlodipine, allopurinol, and rosuvastatin, which he had been taking for approximately 4.5 years for management of hypercholesterolemia.

The patient was reviewed fortnightly for the first two months, per institutional protocol. Two days after commencing lorlatinib, the patient developed grade I visual and olfactory hallucinations, seeing bright colors rotating on his room wall overnight and reporting an abnormal smell emanating from his TV that was not corroborated by family. These episodes were self-limiting, resolving after two days, and were not reported to the clinical team on cycle 1 week 2 review of systems.

At week 3 of treatment, the patient was apprehended by police and subsequently hospitalized after a psychotic episode. This first manifested as a delusion in which he was convinced that the King was intent on marrying his daughter and was followed by an alcohol binge and physical violence at home, prompting his family to contact the police.

During hospitalization, lorlatinib was withheld, other causes of psychosis (e.g., sepsis, electrolyte derangement) were excluded, albeit without cerebrospinal fluid analysis being performed, and result of gadolinium-enhanced MRI brain revealed complete response in parenchymal brain and leptomeningeal metastases. No acute intracranial abnormalities accounting for the presentation were detected. The patient was admitted for just over four weeks in total. On review, there were no prior risk factors, with no history of mental health problems, no neuromodulating drug use, no substance abuse, and no prior CNS radiotherapy. After review by the psychiatric team, he was commenced on risperidone 4 mg daily with concurrent procyclidine 5 mg, and lorlatinib was withheld.

Four weeks post-discharge, at his next clinic review, he remained on risperidone and procyclidine and had partial insight into the psychotic episode, noting that he had not been himself but still believed the events that occurred to him were real. His psychiatry team diagnosed ongoing delusions, without major clinical impact.

On review in the clinic six weeks post-discharge, his psychiatric status had largely improved, with good insight, although mild delusions were still present. After discussions with the patient's psychiatrist and noting the natural history of post-psychosis delusions that may take weeks to fully resolve, alongside the intracranial response found on MRI result, discussion was done with the patient and family about the risks and benefits of lorlatinib rechallenge (including risk of psychotic relapse and its management), the lack of data on lorlatinib rechallenge after a grade IV psychiatric adverse event, and optimal timing of rechallenge, if at all. Hence, after agreement with all parties including the patient, who was believed to have capacity at the time, he was recommenced on lorlatinib at 50 mg daily with ongoing risperidone and reviewed fortnightly, initially in the clinic, alongside ongoing review by his psychiatric team. Lorlatinib dosing was initially administered and supervised by his wife to prevent unreported aberrant self-dosing to a higher level.

In January 2024, approximately 14 months post-lorlatinib rechallenge, the patient remains on 50 mg daily of lorlatinib, with maintained intra- and extracranial complete response on routine three-monthly brain MRI and computed tomography extracranial staging. His NAEs have completely resolved with no relapse from time of rechallenge, with current minimal input from the community psychiatric service and a gradual wean of risperidone dose (currently 2 mg daily).

Apart from fluctuant rise of creatine kinase level (transiently grade III, but mostly normal or grade I) and fluctuant grade I hypercholesterolemia on rosuvastatin, he has otherwise tolerated lorlatinib well, continues with performance status of 0, and is back at work full time (Figs. 1 and 2).

Discussion

Lorlatinib-induced NAEs are common, being reported in up to 60% of patients in retrospective studies, and heterogeneous, ranging from mood effects to forgetfulness, but are usually of low grade and generally managed by dose delay or dose reduction.[3] Our case reveals that lorlatinib-induced NAEs can be life threatening, potentially lead to deleterious physical consequences not only to patients but also caregivers and the general public, and occur in patients without a prior history of any

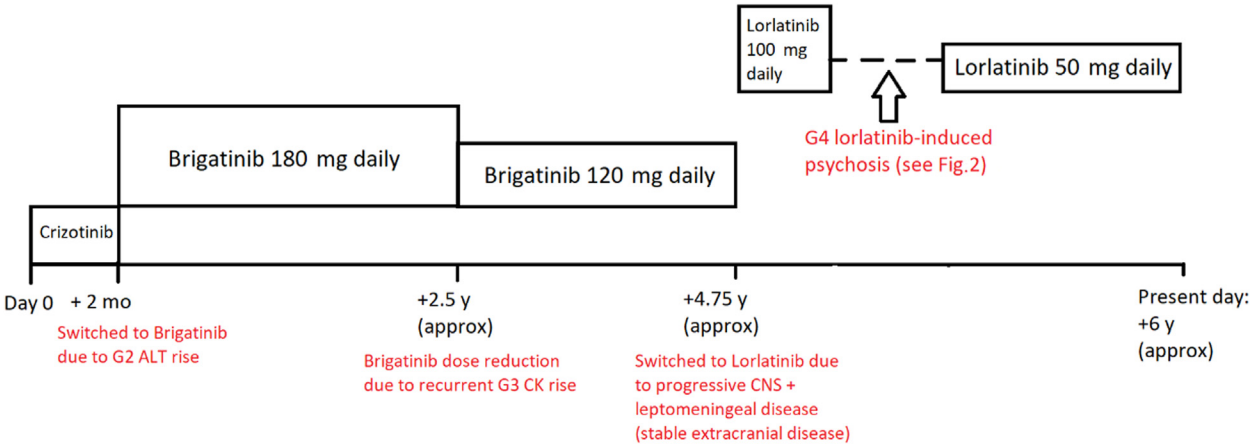

Figure 1. Overall timeline of events. ALT, alanine transaminase; CK, creatine kinase; CNS, central nervous system; G2, grade II; G4, grade IV.

mental illness or other established risk factors, making them difficult to screen for. Moreover, significant NAEs can rapidly appear from low-grade NAEs, which themselves may not be reported.

As per FDA and EMA guidance, lorlatinib should be withheld in the event of greater than or equal to grade II NAEs. Though permanent drug discontinuation is generally recommended in any grade IV drug-induced toxicity, there are no data evaluating the safety of lorlatinib rechallenge in the context of grade IV NAE. Optimizing management of lorlatinib-induced NAEs is key to maximizing drug exposure, patient quality of life, and ultimately progression-free survival, particularly in the described case, where intracranial-only progression developed on a second-generation ALK inhibitor and stereotactic radiosurgery was deemed unsuitable due to intracranial disease extent.

After lorlatinib-induced grade IV NAE in our reported case, introduction of an alternative second-generation ALK inhibitor to which the patient was not previously exposed (e.g., alectinib) could have been considered, because tumour genotyping was not performed at the time of progression on brigatinib to reveal on-target resistance to second-generation ALK inhibitors (e.g., G1202R, L1196M *ALK* mutations). Nevertheless, rechallenge with lorlatinib was favored for pragmatic reasons due to nonreimbursement of other ALK inhibitors in England. Moreover, rechallenge with lorlatinib than platinum-based chemotherapy was favored given its known potent intracranial activity in pretreated patients; the global phase II trial reported intracranial response rates of 50% to 60% in patients pretreated with multiple ALK inhibitors, including those treated with a non-crizotinib ALK inhibitor.[1]

We note that, in preclinical studies, lorlatinib inhibits several targets other than ALK and ROS1, including TRKB, and that reduced levels of TRKB are associated with CNS disorders, including schizophrenia and mood

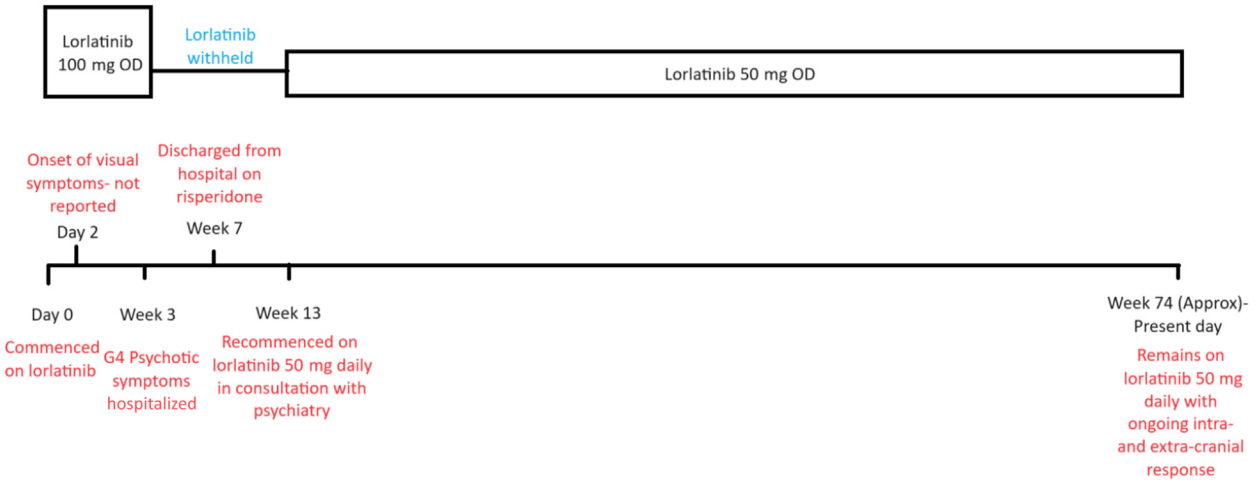

Figure 2. Timeline of lorlatinib-induced psychosis. G4, grade IV; OD, once daily.

disorders; hence, NAEs are likely mediated as a nontarget TRKB effect.[4] Moreover, in preclinical models, lorlatinib causes a dose-dependent neurocognitive deterioration at doses of greater than or equal to 3 mg/kg in rats. In brain metastasis xenograft studies, lorlatinib resulted in a dose-dependent intracranial response at 5, 10, and 20 mg/kg/d.[5]

In the phase I dose-finding trial, no clinical responses were observed at lower doses (35 mg twice a day), doses greater than 100 mg daily were not tolerable, and 100 mg daily was identified to be recommended phase 2 dose, giving adequate exposure against *ALK* G1202R.[6] Comprehensive neuropsychiatric evaluation was performed using multiple validated scales only in the phase 2 portion of the trial, reporting 54% of patients with CNS effects (grades III–IV: 6%) and effective management of toxicities through dose reductions.[4] In our case, the decision to rechallenge with level 2 dose reduction (50 mg daily) was primarily based on clinical judgment to minimize risk and maintain efficacy after significant NAE in a patient with no other ALK inhibitor options. Although we have not planned dose escalation currently, this may be considered on the basis of individualized risk:benefit assessments, if there is future evidence of intracranial relapse.

The importance of reviewing drug interactions before initiation of lorlatinib must also be underscored, as use of concomitant medications such as CYP3A inhibitors can increase plasma concentrations of lorlatinib and consequently increase the potential for lorlatinib-associated NAE and other AEs.[7] None of the concomitant medications described in our case are known to affect concentrations of lorlatinib, although lorlatinib can decrease plasma concentrations of amlodipine and edoxaban.

Choice of lipid-lowering therapy is of particular relevance, as hypercholesterolemia requiring pharmacologic management is observed in approximately 70% of patients on lorlatinib, typically occurring early after lorlatinib initiation.[8] Some lipid-lowering agents such as atorvastatin and simvastatin are known to interact with lorlatinib due to CYP450 pathway modulation, whereas rosuvastatin, pravastatin, and pitavastatin have been recommended in cases of lorlatinib-induced hyperlipidemia due to low potential for drug interaction.[8]

After 14 months of post-psychosis follow-up and ongoing lorlatinib treatment with ongoing response to leptomeningeal disease, our case reveals that patients can be safely rechallenged with dose-reduced lorlatinib after recovery from a grade IV NAE, with appropriate input from both oncology and psychiatric services, with safe concomitant use of risperidone.

The generalizability of this strategy must, of course, be interpreted with caution given this individual case, but it does suggest that this strategy is plausible. We emphasize to both patients and caregivers that NAEs can occur and that these may occur suddenly and rapidly and may require timely referral for specialist psychological support services at identification if mild to mitigate against propagation, alongside lorlatinib dose interruption or reduction.

Conclusion

We report a case of grade IV lorlatinib-induced psychosis which was safely rechallenged with dose-reduced lorlatinib, initially under spouse supervision, in conjunction with close specialist nursing monitoring and support, psychiatric input, and antipsychotic therapy. Although this approach should be pursued with caution, it may be appropriate if no other meaningfully efficacious treatment choices exist, thereby maximizing lorlatinib exposure and durable intracranial benefit.

CRediT Authorship Contribution Statement

Alexius John: Conceptualization, Writing—Original Draft.

Joanna Vick: Writing—Review and Editing.

Sarah Sarker: Writing—Review and Editing.

Elizabeth Middleton: Writing—Review and Editing.

Elizabeth Cartwright: Writing—Review and Editing.

Thubeena Manickavasagar: Writing—Review and Editing.

David McMahon: Writing—Review and Editing.

Nadza Tokaca: Writing—Review and Editing.

Sanjay Popat: Conceptualization, Supervision, Writing—Review and Editing.

Disclosure

Mrs. Vick reports receiving honoraria from Amgen, AstraZeneca, Pfizer, and Takeda. Mrs. Middleton reports receiving honoraria from AstraZeneca, Bristol-Myers Squibb, and Takeda. Dr. McMahon reports receiving travel fees from Takeda. Prof. Popat reports receiving consulting fees and honoraria from Amgen, AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi EQRx, Sankyo, GlaxoSmithKline, Guardant Health, Incyte, Janssen, Lilly, Merck Serono, SD, Novartis, Roche, Takeda, Pfizer, Seattle Genetics, and Turning Point Therapeutics. The remaining authors declare no conflict of interest.

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The patient reported gave informed consent authorizing the use and disclosure of his health information. All adverse events were reported to the relevant regulatory pharmacovigilance systems.

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