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CASE REPORT

Olanzapine enabled rechallenge after lorlatinib-induced psychosis: A case report

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Abstract

Background: Lorlatinib is a third-generation tyrosine kinase inhibitor for anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC). While it has a high intracranial lesion control rate, it can also cause central nervous system complications, including psychotic symptoms. We present a case of lorlatinib-induced psychosis successfully managed with olanzapine, enabling lorlatinib rechallenge.

Case Presentation: A 32-year-old woman with *ALK*-positive NSCLC and brain metastases was started on lorlatinib. After 18 months, she developed hallucinations and delusions. Despite treatment with risperidone, her psychotic symptoms persisted, leading to hospitalization. Her symptoms resolved upon lorlatinib discontinuation while risperidone was continued. Given the critical role of lorlatinib in controlling brain metastases, rechallenge was considered. To mitigate concerns regarding drug interactions, risperidone was replaced with olanzapine. Following lorlatinib rechallenge with olanzapine, no recurrence of psychiatric symptoms was observed, allowing continued lorlatinib treatment. Additionally, no progression of lung cancer was noted.

Conclusion: Lorlatinib is an essential drug for controlling brain metastases in *ALK*-positive NSCLC. However, it can induce psychotic symptoms. When psychiatrists are involved in managing adverse effects during cancer treatment, close collaboration among oncologists, psychiatrists, and patients is essential.

KEYWORDS
psycho-oncology, lorlatinib, lung cancer, medication-induced psychosis

BACKGROUND

Anaplastic lymphoma kinase (*ALK*) gene rearrangements occur in 3%–5% of non-small cell lung cancer (NSCLC) cases. Lorlatinib, a third-generation tyrosine kinase inhibitor (TKI), is approved for *ALK*-positive NSCLC. Because of its high central nervous system penetration, lorlatinib is particularly effective in cases involving brain metastases.[1] However, neurologic adverse events, including hallucinations, were observed in 39% of patients,[1] and severe psychotic symptoms have been reported, sometimes leading to treatment discontinuation.[2,3] Here, we present a case of lorlatinib-induced psychosis successfully managed with olanzapine, enabling lorlatinib rechallenge. Written informed consent for publication was obtained from the patient.

CASE PRESENTATION

A 32-year-old woman with no smoking history or prior psychiatric disorders was diagnosed at 28 years of age with NSCLC (*ROS1*+, *ALK*+), brain metastases, and bone metastases (Stage IV, performance Status 1). Entrectinib 600 mg/day was initiated, but because of tumor progression, the therapy was switched to alectinib 600 mg/day, and radiation therapy was administered for intracranial lesions. At 31 years of age, carcinoembryonic antigen tumor marker levels increased, leading to a change to lorlatinib (100 mg). Brain metastases in both occipital lobes and the right temporal lobe regressed after lorlatinib initiation, with regular magnetic resonance imaging confirming lesion control. No opioids or steroids were used concurrently.

Four months later, the patient began experiencing emotional instability and impaired concentration. One year later, the lorlatinib dose was reduced to 75 mg, but her symptoms persisted, and auditory hyperesthesia gradually emerged. Eighteen months after starting lorlatinib, at the age 32 of years, she exhibited delusions of being targeted by electromagnetic attacks and auditory hallucinations commenting on her actions. Because of persecutory delusions, she could no longer live alone and had to move in with her mother. Suspecting lorlatinib-induced psychotic symptoms classified as "Grade 3" under the Common Terminology Criteria for Adverse Events (which categorizes all adverse events observed during treatment, regardless of causality, on a five-grade severity scale ranging from Grade 1 [mild] to Grade 5 [death]), the oncologist instructed discontinuation during an outpatient visit. The psychotic symptoms persisted even after 2-week cessation, leading to a referral to our neuropsychiatry department. Risperidone 2 mg/day was initiated, but after 2 weeks there was no improvement in symptoms, resulting in hospitalization in our psychiatric ward.

On admission, the patient's Brief Psychiatric Rating Scale score was 48, vital signs were normal, and she was fully conscious, with no signs of neurological abnormalities. Blood tests were unremarkable. Cerebrospinal fluid analysis demonstrated an elevated protein level of 111 mg/dL but no autoimmune encephalitis-related autoantibodies or oligoclonal bands. Because the case did not meet the criteria by Graus et al.,[4] autoimmune encephalitis was unlikely. Contrast-enhanced brain magnetic resonance imaging revealed the resolution of metastatic lesions, and negative cerebrospinal fluid cytology suggested tumor-related neuropsychiatric symptoms were unlikely. It was discovered that she had been taking lorlatinib (75 mg) irregularly of her own accord. Lorlatinib was formally discontinued, and risperidone was continued. One week later, hallucinations and delusions were resolved. After discussions with the oncologist, the patient, and her family, a decision was made to resume lorlatinib at a reduced dose of 50 mg, considering its superior efficacy in controlling brain metastases, especially given the patient's young age and the development of resistance to two prior TKI therapies. To avoid drug interactions, risperidone was replaced with 5 mg of olanzapine, increased to 7.5 mg after 1 week to address persistent hyperacusis. Emotional instability improved, but mild subjective difficulty in concentration persisted. There was no recurrence of psychotic symptoms, and the patient was discharged on Day 28 of hospitalization. Figure 1 shows the clinical course. At the 1-month follow-up after discharge, she remained in psychiatric remission. The patient was able to continue lorlatinib treatment, with no signs of lung cancer progression. After discharge, she was able to live alone and resume enjoying outdoor activities.

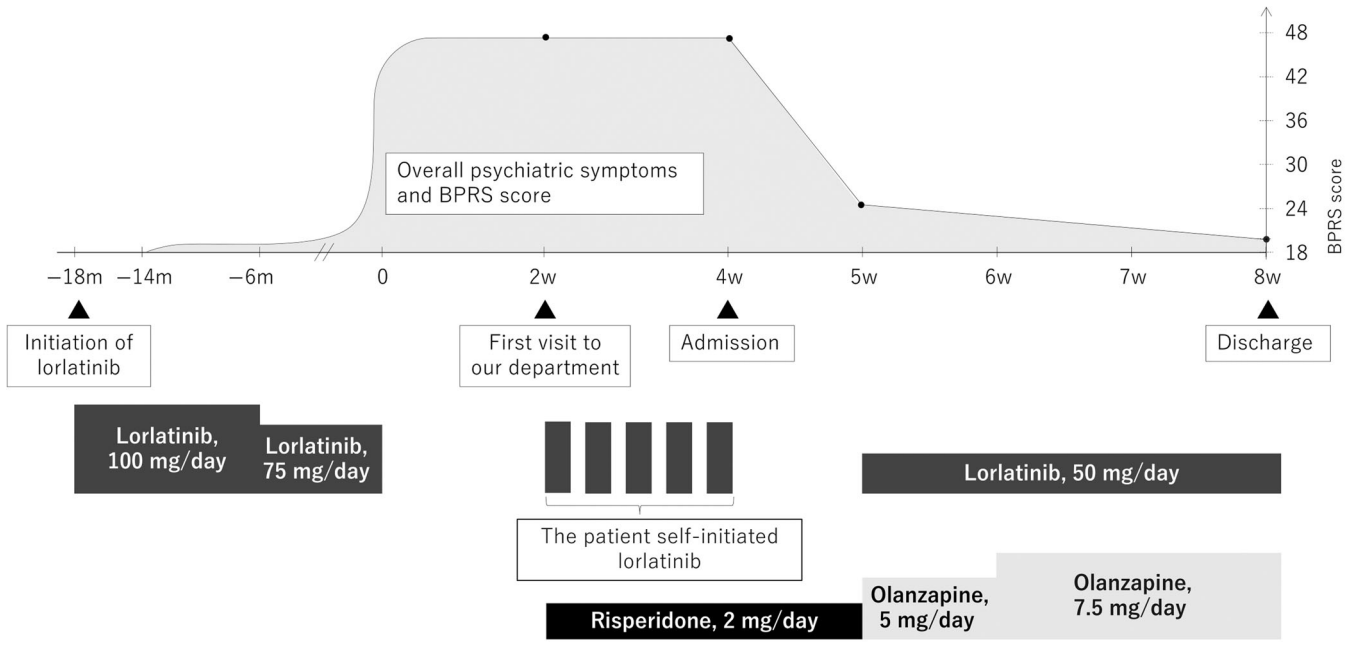

FIGURE 1 Clinical course of the patient. BPRS, Brief Psychiatric Rating Scale; w, week; m, month.

DISCUSSION

In this case, lorlatinib rechallenge was successfully achieved with the concomitant use of antipsychotics. Continuing lorlatinib treatment was particularly meaningful for this patient, given her resistance to multiple TKIs. To the best of our knowledge, there have only been two reported cases of rechallenge with antipsychotics,[3,5] and this is the first report in Japan.

Psychotic symptoms have been reported in approximately 5% of patients receiving lorlatinib therapy.[1] The mechanism of these symptoms is thought to involve lorlatinib's central nervous system penetrance and its inhibition of ALK tyrosine kinase, which suppresses D2 receptor internalization.[6] Most cases can be managed with dose reduction or interruption.[1] However, some cases require the discontinuation of lorlatinib or the use of antipsychotics.[2,3,5,7,8] Additionally, there have been reports of cases presenting with severe psychotic symptoms, including jumping and violent behavior.[2,3] There are two case reports where antipsychotic use enabled lorlatinib rechallenge, including risperidone[3] and quetiapine following haloperidol.[5] Lorlatinib is a moderate inducer of cytochrome P450 3A4, and experts recommend cautious risperidone use because of interactions, identifying olanzapine as the preferred option for its lower susceptibility to concentration reductions.[9] We initially administered risperidone, referencing the re-administration case.[3] However, during intermittent lorlatinib use, risperidone appeared ineffective, prompting a switch to olanzapine. This ineffectiveness might have been influenced by irregular lorlatinib intake.

CONCLUSION

Lorlatinib, essential for treating NSCLC with brain metastases, has a dose adjustment recommendation based on Common Terminology Criteria for Adverse Events grading for central nervous system side-effects.[10] For Grade 3, it is recommended that treatment be paused until symptoms improve to Grade 1, before resuming at a reduced dose. Because lorlatinib can cause psychotic side-effects, concurrent antipsychotic use may help manage symptoms and allow continued treatment. Close collaboration between psychiatrists, oncologists, and patients is crucial to integrating psychiatric care with cancer treatment plans.

AUTHOR CONTRIBUTION

Akiyoshi Yokode: Conceptualization; literature search; data curation; visualization; and writing (original draft). **Masaki Fujiwara:** Conceptualization; project administration; supervision; and writing (review and editing). **Yuko Nakamura, Kadoaki Ohashi,** and **Shinji Sakamoto:** Conceptualization and writing (review and editing). **Manabu Takaki:** Conceptualization; supervision; writing (review and editing).

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CONFLICT OF INTEREST STATEMENT

Akiyoshi Yokode has no conflict of interest. Masaki Fujiwara reports honoraria from Mochida and Eisai outside of the submitted work. Yuko Nakamura has no conflict of interest. Kadoaki Ohashi has received grants or honoraria from Chugai Pharmaceutical Co. Ltd., Novartis, and Pfizer unrelated to the submitted work. Shinji Sakamoto reports honoraria from Yoshitomi Yakuhin, Otsuka, Meiji Seika Pharma, Eisai, Viatris, Tsumura, Sumitomo Pharma, Lundbeck, and Takeda. Manabu Takaki reports honoraria from Otsuka, Sumitomo Pharma, Tsumura, Lundbeck, Merck Sharp & Dohme, Eisai, Meiji Seika Pharma, Viatris, Mitsubishi Tanabe Pharma, Janssen, Yoshitomi Yakuhin, Boehringer-Ingelheim, and Takeda. He has received unrestricted research funding from Otsuka, Sumitomo Pharma, Eisai, and Mochida. Manabu Takaki is an Editorial Board member of *Psychiatry and Clinical Neurosciences Reports* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

N/A.

ETHICS APPROVAL STATEMENT

Written informed consent was obtained from the patient to publish the case report. This is a case report which does not require ethics committee approval.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient to publish the case report.

CLINICAL TRIAL REGISTRATION

N/A.

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