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Psychiatric symptoms in patients with metastatic ALK-positive NSCLC treated with third-generation ALK-inhibitors: a brief review and case series

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ABSTRACT

People treated with anaplastic lymphoma kinase (ALK) inhibitors, especially lorlatinib, have had problems with their central nervous system (CNS). According to a real-world pharmacovigilance study, the most frequent psychiatric symptoms were mood disorders, psychotic disorders, anxiety, agitation, and irritability. Still, it is not clear how ALK tyrosine kinase inhibitors (ALK-TKIs) might cause psychiatric adverse effects. However, ALK seems involved in the endocytosis of dopamine D2 receptors in response to long-term dopamine stimulation. Here, we report three cases of patients treated with ALK inhibitors in a single Italian Centre who developed psychiatric disorders.

Introduction

3–7% of non-small cell lung cancer (NSCLC) has ALK rearrangements, which are very sensitive to ALK-TKIs [1]. Crizotinib was the first TKI approved for treating advanced *ALK*-rearranged NSCLC [2]. However, observation of acquired resistance led to the development of second-generation (ceritinib, alectinib, and brigatinib) and third-generation (lorlatinib) ALK inhibitors. These drugs produced high response rates in patients who had not received treatment before and in patients who had not responded to crizotinib [3–6]. Patients treated with ALK-TKIs, especially lorlatinib, have shown occurrences of central nervous system (CNS) disorders. These include hallucinations, cognitive symptoms, mood changes, and alterations in mental status and speech [7].

Patients treated with ALK-TKIs, especially with lorlatinib, have experienced CNS disorders, including hallucinations, cognitive symptoms, mood changes, alterations in mental status, and speech problems. Nevertheless, detailed data regarding identifying the population at risk, the onset time of cognitive symptoms, or the persistence of these symptoms after discontinuing ALK-TKIs are still lacking.

Here, we report three cases of patients treated with ALK inhibitors in a single Italian Centre who developed psychiatric disorders.

This brief review and case series aims to discuss the mechanisms through which lorlatinib can cause neurocognitive side effects and how to identify and manage them promptly in clinical practice.

The intracranial efficacy of lorlatinib

Lorlatinib is a powerful third-generation ALK inhibitor designed to overcome first- and second-generation ALK-TKIs resistance mutations, including the most common G1202R mutation. Phase I and II trials have widely demonstrated the efficacy of lorlatinib in patients with brain metastases (BM) and leptomeningeal disease who experienced progression after first- or second-generation ALK-TKIs. Specifically, the phase 1 trial included 55 patients with pre-treated NSCLC with *ALK* and *ROS1* rearrangements. Among them, 39 patients (72%) had BM, with 12 out of the 39 having received no prior local treatment to the CNS. Additionally, 24 patients (19 ALK-rearranged and 5 ROS1-rearranged) had target BM. Among patients with measurable disease, the intracranial–objective response rate (IC-ORR) was 42% for *ALK*-positive and 60% for *ROS1*-positive patients [8]. In the single-arm phase 2 trial, 228 TKI-naïve or TKI-pre-treated patients with ALK-rearranges NSCLC were enrolled. Among untreated patients, 3 out of 8 had target BM, and an IC-ORR of 66.7% was achieved. Similarly, among 133 pre-treated patients, 81 had target BM, whose IC-ORR was 63% [9]. Updated results of this study showed an IC-ORR of 66.7% in those treated with one prior second-generation ALK-TKI and 54.2% in those treated with two or more second-generation TKIs [10]. Thus, the updated analysis confirms the second-line and CNS activity of lorlatinib. The phase III CROWN trial directly compared lorlatinib with crizotinib as first-line treatment in patients with *ALK*- and *ROS1*-positive metastatic NSCLC. BM were present in 38 patients treated with lorlatinib and 40 treated with crizotinib. Among those patients with measurable BM, the IC-ORR was 82% in the lorlatinib arm and 23% in the crizotinib arm, and 71% of patients who received lorlatinib had an intracranial complete response (CR) [6]. According to the recent, updated results of the CROWN trial, with a median follow-up duration of 36.7 months, lorlatinib continued to show better overall and intracranial activity compared to crizotinib. In particular, lorlatinib did not reach a median progression-free survival (PFS), while crizotinib had a median PFS of 9.3 months. The 3-year PFS rate in the lorlatinib and crizotinib groups was 64% in the lorlatinib group and 19% in the crizotinib group. The confirmed IC-ORR in those with baseline measurable BM was 83.3% and 23.1%, respectively [11].

Lorlatinib and the blood-brain barrier

To better clarify the distribution of lorlatinib in the brain, cytological experiments were performed on different cell lines (human umbilical vein endothelial cells [HUVEC], human microvascular endothelial cells [HMEC-1], and human neuroblastoma cells [HCMEC/D3]).

Lorlatinib and crizotinib both demonstrated effects on endothelial cells, although lorlatinib inhibited the growth of HCMEC/D3 better than crizotinib. Furthermore, lorlatinib significantly downregulated the expression of SPP1, VEGF, TGF-β, and Claudin, increasing the permeability of the BBB. In particular, osteopontin expressed by the SPP1 gene is a neuroprotective glycoprotein that plays a crucial role in the maintenance of the BBB structure, leading to the destruction of tight junctions [12,13]. In non-human primates, a radioisotope of lorlatinib demonstrated significant and rapid brain distribution. To measure the intracranial concentrations of lorlatinib, 11C and 18F-isotopologues were prepared, and whole-body dosimetry assessments by positron emission tomography (PET) were performed. The 11C-labelled lorlatinib achieved the highest

concentrations in the cerebellum, frontal cortex and thalamus, intermediate levels in other cortical grey matter, and lowest values in the white matter [14]. Furthermore, in the abovementioned phase 1 trial investigating lorlatinib in pre-treated patients with *ALK*-positive NSCLC, four patients underwent lumbar puncture for cerebrospinal fluid (CSF) sampling. The mean concentration of lorlatinib in CSF corresponded to 75% of unbound plasma concentrations, demonstrating the high availability of the drug in the CNS [8].

Case summary

Case 1

In August 2019, a 46-year-old female patient with no history of psychiatric disorders was diagnosed with *ALK*-positive metastatic lung adenocarcinoma (bilateral lung metastases, mediastinal pathologic lymph nodes, single brain metastases, bone metastases). Initially, the BM localised in the left frontal lobe (≈ 1 cm) was surgically excised, and adjuvant radiotherapy on the surgical site was administered (30 Gy in 3 fractions). In September 2019, a first-line treatment with alectinib 600 mg/twice daily was started, achieving a partial response. In March 2020, a magnetic resonance imaging (MRI) revealed new lesions in CNS (right cerebellum and right frontal lobe, <5 mm) (**Figure 1A**), and the computed tomography (CT) scan evidenced progression in mediastinal lymph nodes. The treatment with alectinib was interrupted, and a second-line therapy with lorlatinib 100 mg/daily was started. Lorlatinib induced an extracranial partial response, reducing all mediastinal lymph nodes and an intracranial stable disease (**Figure 1B**).

After two months of treatment, the patient experienced a manic disorder with persecutory ideation, requiring hospitalisation in a psychiatric ward from 15th to 25th May 2020. Laboratory analyses were normal, and no other organic symptom causes were found. Although an analysis of the CSF was not performed, a correlation with BM was discarded due to the stability of the intracranial disease.

Lorlatinib was interrupted during hospitalisation and resumed on 26th May at 75 mg/daily dose. At the same time, an antipsychotic therapy with valproic acid 750 mg/twice daily and haloperidol decanoate 75 mg every four weeks was started. Despite the lorlatinib dose reduction, the patient was hospitalised again four days later, and a psychiatric rehabilitation program was commenced. This intervention led to a stabilisation of symptoms, and lorlatinib was continued at the same dose. In September 2020, the patient experienced

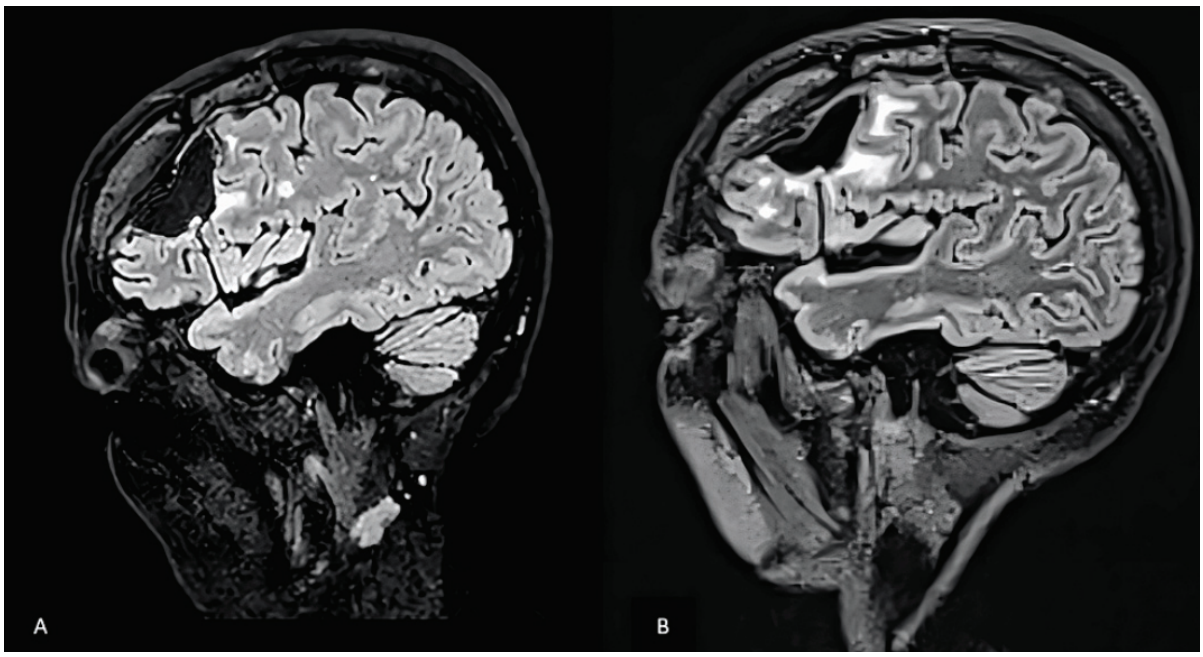

Figure 1. A: A brain MRI of case 1 was performed in March 2020, confirming a new lesion in the right frontal lobe. **B**: Brain MRI performed in May 2020 with evidence of intracranial stable disease. MRI – magnetic resonance imaging.

disease progression with the appearance of subcutaneous nodes, mediastinal lymph nodes and new BM, leading to the definitive discontinuation of lorlatinib. In December 2020, a third-line therapy with Carboplatin (AUC5) and Pemetrexed (500 mg/m^2 D1, D1=D21) was started. Unfortunately, the general conditions of the patient rapidly worsened, leading to death in February 2021.

It is noteworthy that the psychotic symptoms never resolved, and the antipsychotic therapy was never interrupted until death.

Case 2

In February 2013, a 60-year-old female patient with no history of psychiatric disorders was diagnosed with *ALK*-positive metastatic lung adenocarcinoma (bilateral lung, bone and liver metastases, two brain metastases – right frontal lobe of 1 cm, left parietal lobe of 6 mm). A first-line chemotherapy with Cisplatin (75 mg/m^2) plus Pemetrexed (500 mg/m^2 D1, D1=D21) for six cycles was administered from February to June 2013, achieving a stable disease. During the chemotherapy period, the patient underwent whole brain irradiation (WBRT; 35 Gy in 14 fractions).

In October 2013, a CT scan evidenced multisite progression, and a second-line therapy with crizotinib 250 mg/twice daily was started, achieving a stable disease as the best response. In November 2014, a single brain lesion < 1 cm in the left parietal lobe appeared, and a gamma-knife treatment was performed. In November 2015, due to a bilateral lung progression, the patient was enrolled in a phase I trial evaluating ceritinib 300 mg/daily and ribociclib 200 mg/daily, obtaining extracranial partial response and intracranial stable disease. In January 2018, an intracranial progression occurred (multiple BM < 1 cm), and a new treatment with brigatinib 180 mg/daily was started, achieving a stable disease. In October 2018, an MRI revealed diffuse brain parenchymal and leptomeningeal progression (**Figure 2: A** and **B**). Brigatinib was interrupted, and lorlatinib was started at a dose of 100 mg/daily. After 15 days of treatment with lorlatinib, the patient experienced auditory hallucinations with a suicide attempt, and she was hospitalised in a psychiatric ward from 31st December 2018 to 8th January 2019. No laboratory discrepancies were noted, and the MRI did not show evidence of progressive disease in the CNS, although an analysis of the CSF was not performed. Lorlatinib was interrupted for two months and resumed on 22nd February at a dose of 75 mg/daily. A therapy with quetiapine 25 mg

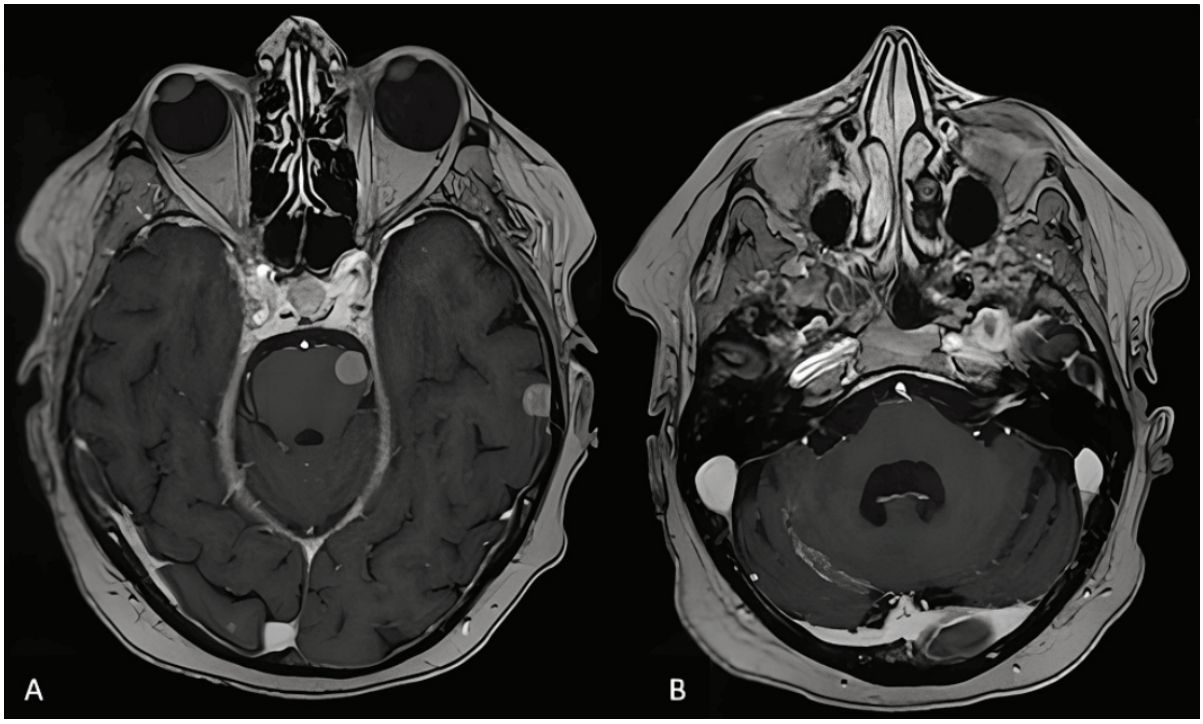

Figure 2. A: A brain MRI of case 2 was performed in October 2018 before starting lorlatinib, with evidence of pontine and left temporal brain metastases. **B**: MRI scan with evidence of cerebellar leptomeningeal carcinomatosis.

was started as well, obtaining a mild improvement of psychotic symptoms, especially auditory hallucinations. In May 2019, a new MRI showed a complete intracranial response, both parenchymal and leptomeningeal (**Figure 3: A** and **B**). Despite the lorlatinib dose reduction, the patient experienced two new psychotic episodes with visual hallucinations in May 2019 and June 2019, both requiring hospitalisation. For this reason, lorlatinib was administered at a lower dose (50 mg/daily), obtaining a stabilisation of psychotic symptoms. The antipsychotic therapy was kept unchanged and never interrupted until death, which occurred in March 2020.

Case 3

In April 2013, a 47-year-old female patient with a silent psychiatric history was diagnosed with an ALK-FISH-negative resectable NSCLC. She underwent surgery (right inferior lobectomy + lymphadenectomy; EI: pT1bN0) in June 2013. In October 2013, a pleural relapse occurred, and first-line chemotherapy with Cisplatin (80 mg/m^2 D1, D1=D21) and Gemcitabine (1250 mg/m^2 D1 and D8, D1=D21) was administered, obtaining a partial response. In February 2015, the patient experienced multisite and second-line chemotherapy with Pemetrexed (500 mg/m^2 D1, D1=D21) was administered. The benefit was maintained until October 2015, when an isolated progression on the left ovary occurred. A laparoscopic bilateral ovariectomy was performed, and the histological examination confirmed the diagnosis of *ALK*-positive lung adenocarcinoma. Two further therapies were administered: Nivolumab (240 mg flat dose D1, D1=D15) for only three months, with progressive hepatic disease as the best response, and then – from November 2016 to January 2017 – Docetaxel (75 mg/m^2 D1, D1=D21) plus Nintedanib (200 mg/twice daily on D2 to D21) for six cycles. In February 2017, a multisite progression occurred, and a Next Generation Sequencing (NGS) analysis was performed on surgical tissue from ovariectomy, confirming an EML4-ALK fusion (Variant 1).

In March 2017, a fourth-line therapy with crizotinib 250 mg/twice daily was started, achieving a partial response. In October 2017, a brain CT scan showed multiple parenchymal lesions (**Figure 4A**). New treatment with alectinib 600 mg/twice daily was initiated, obtaining a partial extracranial response and a complete intracranial response (**Figure 4B**).

In April 2018, after five months of treatment with alectinib, the patient experienced a type I bipolar disorder, necessitating hospitalisations in April 2018, October 2018, and January 2019.

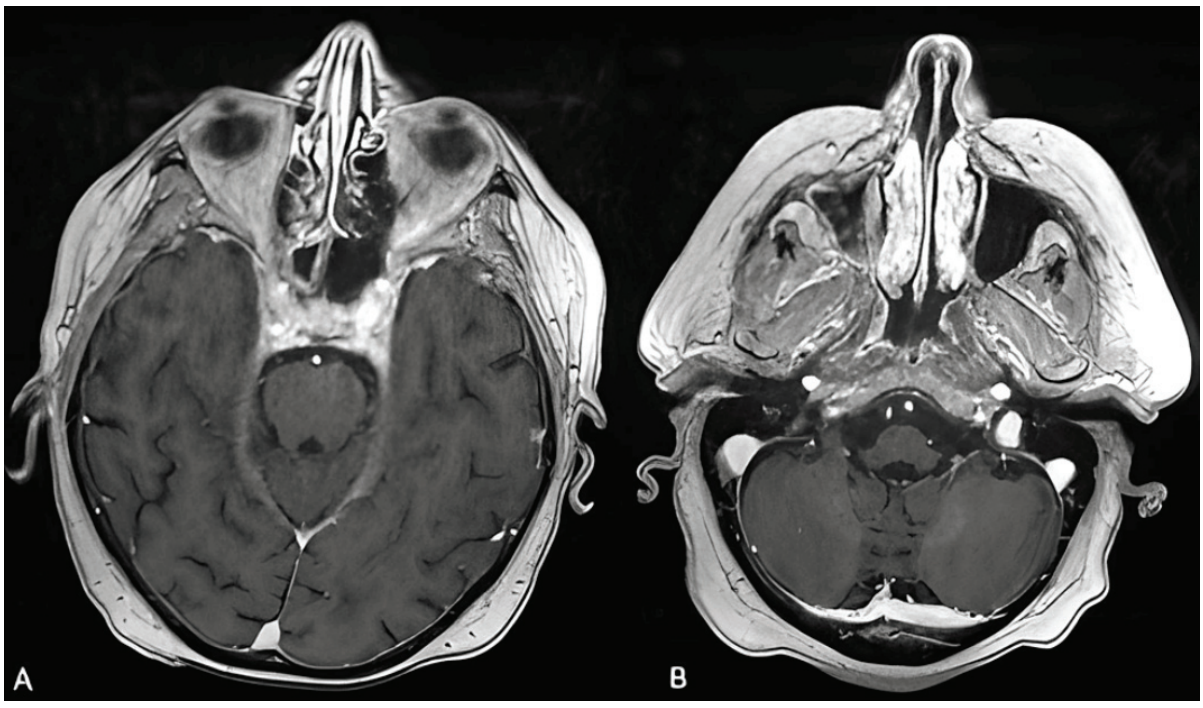

Figure 3. A: A brain MRI of case 2 with evidence of complete intracranial parenchymal response. **B**: Brain MRI scan with evidence of complete leptomeningeal response.

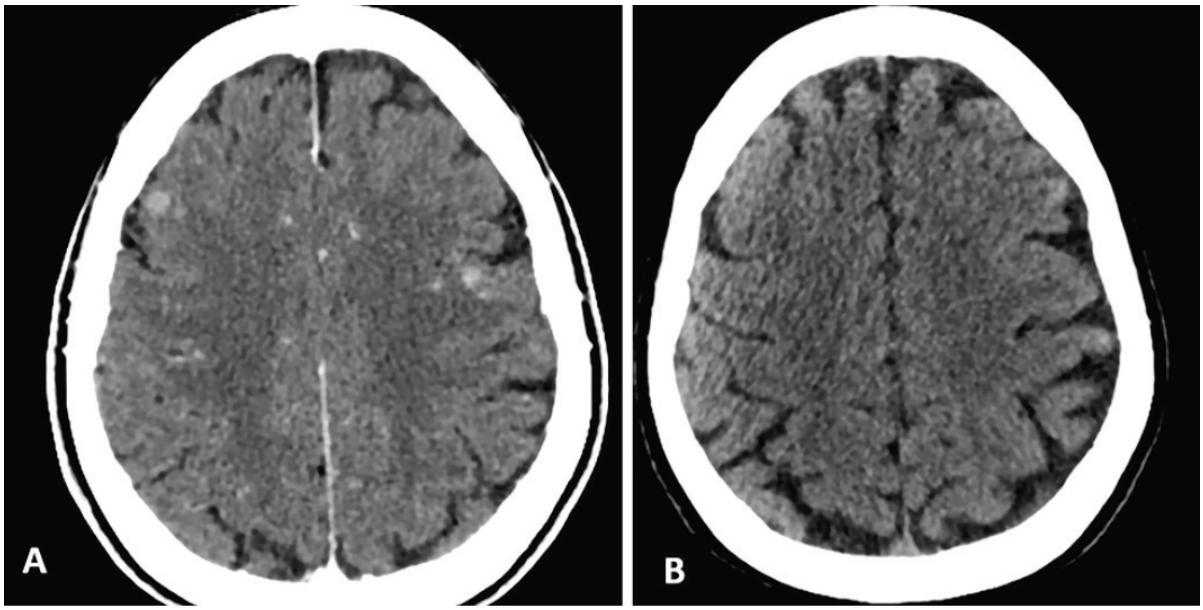

Figure 4. A: A brain CT scan of case 3 performed in October 2017 confirmed multiple parenchymal lesions. **B**: Brain CT scan performed in June 2018 with evidence of intracranial complete response. CT scan – computed tomography scan.

No laboratory discrepancies were noted, and the MRI did not indicate a progressive CNS disease. Alectinib was interrupted in February 2019, and an antipsychotic therapy with aripiprazole 30 mg and haloperidol 10 mg/ml 25 oral drops daily was set, resulting in a beneficial effect on psychiatric symptoms. In August 2019, after evidence of brain progression, a further line with brigatinib 180 mg/daily was initiated, but no other psychotic symptoms were observed. The benefit was maintained until February 2021, when a new CNS progression occurred, and therapy with lorlatinib 100 mg/daily was set. After two months of treatment, the patient experienced an exacerbation of bipolar disorder with a mild maniac episode, which required hospitalisation. Lorlatinib was reduced at a dose of 50 mg/daily with mild benefit on psychiatric symptoms. In June 2022, an isolated progression in the left parietal lobe occurred, and a surgical exeresis was performed. In February 2023, the patient experienced a new episode of bipolar disorder with manic decompensation and restless leg syndrome, requiring hospitalisation in a psychiatric ward. A different antipsychotic therapy was started, including olanzapine 7,5 mg/daily, diazepam 5 mg/ml 15 drops/daily and pramipexol 0,26 mg/daily, while lorlatinib was continued at the same dose of 50 mg daily. The patient is still alive, and the antipsychotic therapy was never interrupted.

Discussion

Lorlatinib represents a promising therapy for patients with *ALK*-positive advanced NSCLC. However, it is correlated with increased psychiatric and neurocognitive symptoms not seen as commonly with other TKIs.

As specified by pivotal trials, the most common adverse events (AEs) observed with lorlatinib were diarrhoea (up to 67%), nausea (up to 83%), vomiting (up to 67%), increased alanine and aspartate aminotransferase (up to 60%) and fatigue (up to 43%) [15].

Based on a real-world pharmacovigilance study, the most frequent psychiatric symptoms were mood disorders, psychotic disorders, anxiety, agitation, and irritability [16]. Notably, these symptoms appear to be more frequent in the female sex. According to this report, the preponderance of psychiatric reports is 2.3% for lorlatinib, 1.2% for brigatinib, 0.6% for ceritinib and 0.3% for crizotinib. A safety analysis of the phase I/II trial of lorlatinib (n = 295) reported a spectrum of CNS adverse events in 23.1% of patients, including memory impairment, confusion, and hallucinations (1.7% of grade 3–4). According to the same analysis, among the CNS disorders caused by lorlatinib, the median time to onset of mood effects was 43 days (range: 1–452 days), cognitive effects 53 days (range: 1–423) and

speech effects 42 days (range: 1–404) [17]. Furthermore, a recent case report reported the onset of paranoia and hallucinations in a 45-year-old woman with no prior psychiatric history [18].

Table 1 reports all the AEs for administering different ALK—TKIs in cases 1, 2, and 3.

was administered. It is worth noting that, in all three mentioned cases, reducing the dose of lorlatinib resulted in a mild improvement of psychotic symptoms without ever achieving resolution. Furthermore, according to the pharmacovigilance study by Sisi et al., psychotic disorders are more

Table 1: Reported adverse events after administration of first – (crizotinib), second – (ceritinib, brigatinib, and alectinib) and third-generation ALK inhibitors in cases 1, 2 and 3.

	CASE 1	CASE 2	CASE 3
Crizotinib	NA	NR	NR
Ceritinib	NA	Hypertransaminasemia G2, diarrhea G2	NA
Brigatinib	NA	Hyperlipasemia G3, hyperamylasaemia G2	NR
Alectinib	Hypertransaminasemia G2	NA	Bipolar disorder G4
Lorlatinib	Manic disorder G4	Visual hallucinations G4, auditory hallucinations G4, suicide attempt G4, hypertriglyceridemia G2, hypercholesterolemia G1	Bipolar disorder G4, restless leg syndrome G3

NA – not administered; NR – not reported.

The mechanism through which ALK-TKIs may cause psychiatric AEs remains unclear. However, there is a suggestion that ALK might be involved in dopamine D2 receptor (D2R) endocytosis in response to prolonged dopamine stimulation [19]. D2R is a G-protein-coupled receptor that regulates many CNS aspects, including cognition, mood, and reward systems [20]. This receptor is widely distributed in the brain, particularly in the striatum and nucleus accumbens. Furthermore, D2R serves as one of the primary therapeutic targets for typical and atypical antipsychotic drugs commonly employed in the treatment of neuropsychiatric disorders, including schizophrenia [21,22]. To the best of our knowledge, ALK-TKIs block the activation of ALK, increasing the expression of D2R in firing dopaminergic neurons and arousing psychotic effects [11]. According to these data, ALK-TKIs have a reverse action mechanism on D2R if compared with typical and atypical antipsychotic drugs [14]. All the cases reported here were treated with both typical (haloperidol) and atypical antipsychotics (quetiapine). This treatment regimen restored regular cognitive activity and was consistently maintained if an ALK-TKI

frequent in patients treated with lorlatinib compared to other ALK-TKIs. This is likely attributed to its enhanced ability to cross the BBB, leading to higher concentrations in the CNS [9]. Nevertheless, in patients with BM, it is challenging to attribute the onset of psychotic symptoms either to CNS involvement (brain or leptomeningeal) or to a pharmacologic class effect.

A recent study analysed safety outcomes from two large cohorts comprising more than 350 patients with ALK- and ROS1-positive NSCLC. The aim was to describe the potential association between baseline clinical characteristics (comorbidities, disease localisation and treatment, baseline medications) and the risk of developing neurocognitive adverse events (NAEs) during treatment with lorlatinib [23]. Records from patients who received lorlatinib through prospective studies at Massachusetts General Hospital (MGH, n 124) or in the phase 1/2 B7461001 (NCT01970865; n 248) study were reviewed. Most patients experienced an NAE (MGH: 60%, B7461001: 49%), although psychotic effects were infrequent (MGH: 3%, B7461001: 9%). All patients experiencing this toxicity in the MGH cohort

required dose interruption or reduction, and in all cases, the psychotic effects (specifically hallucinations) improved but did not resolve. Conversely, in the B7461001 cohort, dose interruption was needed in 27% of patients, whereas dose reduction was documented in 18%. Notably, BM ($p = 0.008$), brain radiation ($p = 0.033$), psychiatric illness ($p = 0.008$), psychiatric medications ($p = 0.001$), antiepileptics ($p = 0.001$), and stimulants ($p = 0.026$) were associated with developing cognitive effects in B7461001. These findings suggest that the presence of BM may contribute to the development of NAEs, but they are not the only factor which can justify the rise of lorlatinib-related NAEs. Particularly, a further disruption of the BBB resulting from surgery or radiation therapy may increase the risk of developing NAEs. Similarly, having a preexisting psychiatric illness is associated with a statistically significant increase in developing lorlatinib-related mood disorders in the MGH cohort [15].

Conclusions

In conclusion, in patients with BM, determining whether the onset of psychotic symptoms is correlated with CNS involvement or the use of lorlatinib is very challenging. Furthermore, a synergic effect between BM and lorlatinib cannot be excluded.

A lumbar puncture with CSF analysis should be performed to completely discard a CNS involvement, particularly a leptomeningeal spread. Unfortunately, in the three cases reported here, none of the patients underwent lumbar puncture, and attributing the onset of psychotic symptoms strictly to a pharmacological class effect remains an unresolved issue. It is worth noting that a disruption of the BBB resulting from surgery or radiation therapy may increase the risk of developing psychotic symptoms.

Possible effects on mood should be discussed with patients and caregivers before lorlatinib administration, and particular attention should be paid to patients with a history of psychiatric illness. Probably, assessing the risk of developing psychotic symptoms with a psychiatric team before initiating treatment with lorlatinib could be beneficial. This approach aims to promptly detect psychotic symptoms and initiate antipsychotic therapy at an early stage.

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Conflict of interest statement
The authors declare no conflict of interest.

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