CASE REPORT

Severe Psychiatric Symptoms in a Patient With *EGFR* Exon-20 Insertion Mutation Receiving Mobocertinib: A Case Report

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ABSTRACT

Tyrosine kinase inhibitor therapy is an established standard of care for patients with NSCLC with *EGFR* mutations, but a worse prognosis has been observed in patients with specific *EGFR* exon-20 insertion mutations. Mobocertinib (TAK-788) is a novel tyrosine kinase inhibitor developed to target *EGFR* exon-20 insertion and has exhibited promising response rates and acceptable safety in phase 1 and 2 trials. We report a case of a 59-year-old woman with metastatic NSCLC and *EGFR* exon-20 mutation responsive to mobocertinib therapy, who developed severe depression and catatonia approximately 4 months after mobocertinib initiation, ultimately necessitating its permanent discontinuation. Given the observed severe depression in this case report, we recommend that, for patients on mobocertinib who develop neuropsychiatric adverse effects, strong consideration should be given for dose interruption or discontinuation.

Keywords: Tyrosine kinase inhibitors; Non–small cell lung cancer; Exon-20 insertion; Mobocertinib; CNS neurotoxicity; Case report

Introduction

Although treatment with an EGFR tyrosine kinase inhibitor (TKI) in patients with *EGFR*-mutated lung cancer has a response rate of 40% to 70%, therapy for patients who have exon-20 mutations exhibits a response rate of only 3% to 8%.[1] *EGFR* exon-20 insertion (EGFRex20ins) mutations represent about 4% to 12% of all *EGFR*-mutated NSCLC.[1] Mobocertinib (TAK-788) is an investigational TKI with Food and Drug Administration breakthrough designation (April 2020) and accelerated approval (September 2021) developed to target EGFRex20ins.[2] Ongoing phase 1 and 2 trials (N = 28) of mobocertinib reported an acceptable safety profile with an overall response rate of 43% (n = 12 of 28) with a median progression-free survival of 7.3 months.[2] Here we report a case of a 59-year-old woman with EGFRex20ins metastatic NSCLC treated with mobocertinib who developed severe depression and catatonia (Supplementary Fig.1).

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Case Presentation

A 59-year-old woman presented for management of newly diagnosed lung adenocarcinoma. Next-generation sequencing revealed an EGFRex20in (EGFR p.N771_H773dup; variant allele frequency = 12.81%), AGK(e2)–BRAF(e8) fusion, and other somatic mutations including (NBN, POLE, SETD2, SLX4, and SMAD). The tumor was negative for *ALK, ROS1, RET*, and *MET* amplification. Programmed death ligand-1 expression was greater than 1%. Brain magnetic resonance imaging was negative for metastatic disease. A positron emission tomography-computed tomography (CT) revealed clinical stage IVA (T2aN3M1b) disease (Supplementary Fig. 2*A* and *B*). At the time of staging, her patient health questionnaire-9 revealed a score of 11, corresponding to moderate depression. The patient was started on first-line chemotherapy with carboplatin, pemetrexed, and pembrolizumab. For the next month, the patient continued to endorse anxiety and depression. Her symptoms waxed and waned at subsequent appointments, with patient health questionnaire-9 scores fluctuating between 0 and 7. She was started on escitalopram 20 mg daily with symptom improvement.

After four cycles of chemoimmunotherapy, a chest CT revealed a new pleural-based lesion consistent with disease progression (Supplementary Fig. 2*C*). The patient was then started on mobocertinib (TAK-788) 160 mg daily. One month later, she was hospitalized owing to intractable nausea and vomiting (grade 3 treatment-related adverse events), which improved with antiemetics. She also reported anxiety and was tearful on examination with poor eye contact. She was discharged 2 days later with instructions to continue mobocertinib as prescribed. Two days after discharge, she presented with generalized weakness after a fall at home. She was noted to be tremulous and minimally responsive with a severely depressed affect. Mobocertinib was put on hold until resolution of symptoms and restarted on a reduced dose of 80 mg daily.

Subsequently, the patient had four more hospitalizations owing to grade 3 nausea and vomiting. Mobocertinib was again put on hold because of suspected toxicity. Imaging performed after 6 weeks of mobocertinib treatment revealed a partial response (Supplementary Fig. 2*D*). Evaluation 5 days after mobocertinib cessation revealed no considerable distress or depression. She was more talkative without tearfulness or tremors as noted on the previous examination. After 3 weeks, the patient presented to the clinic with complete resolution of her depression. Given her durable response to mobocertinib, resolution of nausea and vomiting, and the paucity of data citing TKI-induced depression, mobocertinib 80 mg was restarted.

After 1 month, the patient was admitted for confusion and suicidal ideation. She was tearful and catatonic. Head CT and magnetic resonance imaging were negative for acute hemorrhage or metastatic disease. N-methyl-D-aspartate receptor antibody levels were obtained to evaluate for paraneoplastic syndrome and were not detected. Her catatonia and depression did not improve despite combined therapy with lorazepam, amantadine, sertraline, and mirtazapine, and on day 6 of hospitalization, the patient was initiated on electroconvulsive therapy (ECT). Mobocertinib was put on hold because of concern for possible contribution to her psychiatric symptoms. Repeat chest CT revealed sustained tumor response (Supplementary Fig. 2*E*). The patient slowly improved on three ECT treatments weekly. Ten days after holding mobocertinib, she had a notable resolution of catatonia and became more interactive with increased energy and oral intake. Mobocertinib was reinitiated at a 75% dose reduction of 40 mg daily.

One day after reinitiation, the patient became restless and confused. By day 2, she developed a coarse resting tremor. She was withdrawn, responding to internal stimuli, had increased rigidity and posturing with myoclonus, and had multiple episodes of crying, confusion, and delusions. Because of her acute deterioration, mobocertinib was permanently discontinued. She continued ECT without significant improvement. Her course was complicated by hyperammonemia with a peak of 107 μg/dL. Owing to a poor prognosis, the patient and family elected hospice care.

Discussion

An association between depression and TKIs was previously reported in hematologic malignancies and gastrointestinal stromal tumors. A few case reports implicating TKI neurotoxicity are summarized in Table 1. The average time to symptom onset was 5.3 months. Cessation of TKIs resulted in near-resolution of symptoms within 1 to 2 weeks and recurrence after TKI rechallenge in most patients.[3,4] Although our patient had preexisting anhedonia, her worsening symptoms necessitated psychiatric hospitalization after 4 months of treatment. Per the 1981 Naranjo algorithm for adverse drug reaction probability, our patient's score was 5, corresponding to a probable likelihood.

One possibility is that the patient's severe vomiting resulted in hyponatremia with decreased absorption of her antidepressants. However, she did not have hyponatremia throughout her course making malabsorption unlikely. A second consideration is a possible hyperammonemia-induced encephalopathy. However, our patient did not have sustained hyperammonemia, and precipitation of her psychotic symptoms predated metabolic abnormalities.

Table 1. Summary of Case Reports Implicating Tyrosine Kinase Inhibitors in Precipitation of Psychiatric Symptoms

Case	Year	Number of Patients	Age, Sex	Malignancy	Chemotherapy Agent	History of Depression	Duration Before Onset of Symptoms, mo	Management	Outcome
Sami et al.[3]	2014	1	62, M			Yes, but latent for 30 years	12		Rechallenged with dasatinib 25 with venlafaxine and mirtazapine with no precipitation of symptoms.
Quek et al.[4]	2009	7	Patient 1: 55, M	GIST	Imatnib 800 mg/d	No	5	Refractory to standard therapy	Symptoms resolved with drug cessation; challenged five times with the return of depressive symptoms; depressive symptoms diminished or resolved completely with dose interruption in 4/5 instances.
			Patient 2: 45, M	GIST	Imatinib 400 mg/d	No	6	Declined treatment	
			Patient 3: 42, M	GIST	Imatinib 400 mg/d	No	6	Venlafaxine, methylphenidate, trazadone	Responded to velafaxine, methylphenidate, and trazodone.
			Patient 4: 59, M	GIST	Imatinib 400 mg/d	No	4	Citalopram, methylphenidate, nortriptyline	Imatinib dose reduced from 400 to 300 mg/d with partial relief. Depression was completely resolved with citalopram, methylphenidate, and nortriptyline therapy.
			Patient 5: 64, F	GIST	Imatinib 400 mg/d	No	4	Citalopram, venlafaxine, mirtazapine, clonazepam, and desipramine, and psychotherapeutic management	Depression progressed through treatment, culminating in suicidal ideation. The trial drug was discontinued because of grade 4 toxicity. Depressive symptoms began to decrease 2 weeks after imatinib cessation.

(continued)

Table 1. Continued

Case	Year	Number of Patients	Age, Sex	Malignancy	Chemotherapy Agent	History of Depression	Duration Before Onset of Symptoms, mo	Management	Outcome
			Patient 6: 58, M	GIST	Dasatinib	No	3	Drug holiday and then drug discontinuation	Depressive symptoms dramatically resolved after 1 week of drug holiday and then recurred within 1 week of drug rechallenge. Drug discontinued and symptoms resolved.
			Patient 7: 22, M	Metastatic epithelioid sarcoma	Dasatinib	No	2	Drug discontinued because of lack of sarcoma response	Depressive symptoms dramatically improved within 2 weeks despite a worsening prognosis.
Our patient	2021	1	59, F	NSCLC	Mobocertinib 160 mg/d	Yes (after the cancer diagnosis, on Lexapro; PHQ9 score = 1 1 day before mobocertinib initiation)	4	Depression: sertraline, mirtazapine, discontinued mobocertinib	

F, female; GIST, gastrointestinal stromal tumor; M, male; PHQ9, patient health questionnaire-9.

To best of our knowledge, there is no established mechanism to explain why patients receiving TKIs may develop depression. One hypothesis may be the impairment of HER2 signaling. In addition to the selectivity profile for EGFR, some TKIs including mobocertinib also target oncogenic ERBB2-HER2, which activates ErbB2 tyrosine kinase receptors and subsequently inhibits dopamine transport activity and modulates neural differentiation, myelination, and synapse formation.[5] Thus, nonspecific inhibition of ERBB2 receptor by TKIs such as mobocertinib may have an effect in precipitating neuropsychiatric symptoms through its inhibition on neurotransmission; however, further research in this area is needed.

Conclusions

We report the case of a 59-year-old woman with EGFRex20ins metastatic NSCLC who had worsening severe depression and catatonia while taking mobocertinib that ultimately required permanent discontinuation of this medication. We suggest continuous psychiatric monitoring of patients on mobocertinib.

CRediT Authorship Contribution Statement

Josette Kamel, Natalie Meeder: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Investigation.

Sandra Cuellar, David Chan, Michael Huber, Mary Pasquinelli, Alicia Hulbert: Writing - review & editing.

Karam Khaddour: Conceptualization, Investigation, Writing – review & editing, Supervision.

Lawrence Feldman: Writing – review & editing, Supervision.

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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.2021.100241.

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