Case Reports in Oncology

Case Rep Oncol 2024;17:1289–1293
DOI: 10.1159/000541988
Received: August 16, 2024
Accepted: October 8, 2024
Published online: November 12, 2024

Case Report

Polyradiculitis as a Neurological Complication Associated with Adagrasib: A Case Report

Kristofoor E. Leeuwenberg[a] Rob ter Heine[b] Johanna M.M. Gijtenbeek[a] Michel M. van den Heuvel[c]

[a]Department of Neurology, Radboud Research Institute for Medical Innovation, Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands; [b]Department of Pharmacy, Research Institute for Medical Innovation, Radboud University Medical Center, Nijmegen, The Netherlands; [c]Department of Pulmonary Diseases, Radboud Research Institute for Medical Innovation, Nijmegen, The Netherlands

Keywords
Adagrasib · Polyradiculitis · Non-small cell lung cancer · Toxicity · Neuro-oncology

Abstract
Introduction: Adagrasib is an upcoming anticancer treatment for KRAS G12C-mutated non-small-cell lung carcinoma, colorectal cancer and potentially other solid tumors harboring this mutation. It is generally well-tolerated and reports of neurological adverse events so far have been limited. ***Case Presentation:*** We present to our best knowledge the first case of a 70-year-old woman who was admitted with polyradiculitis as a treatment-related complication of adagrasib. Symptoms resolved after treatment with prednisone and therapy interruption of adagrasib followed by a permanent dose reduction. After the dose reduction, there was an ongoing effective tumor response at follow-up, and serum concentrations of adagrasib remained within the therapeutic index. ***Conclusion:*** Through this case report, we aim to bring attention to the possibility of this side effect, as we believe it is important to be aware of it for future patients undergoing treatment with adagrasib.

Introduction

Adagrasib is a novel KRAS G12C inhibitor that has demonstrated clinical activity in patients with non-small-cell lung cancer and colorectal cancer harboring this mutation [1, 2]. It is currently being evaluated in the KRYSTAL-1 study, a phase 1–2 multiple expansion cohort

Correspondence to:
Kristofoor E. Leeuwenberg, kris.e.leeuwenberg@radboudumc.nl

trial (NCT03785249). Adagrasib is generally well-tolerated. Neurological adverse events reported so far were uncommon and non-specific [1–4]. This case report describes to our best knowledge the first patient with polyradiculitis as a neurological complication of adagrasib, which appeared to be dose-related and resolved after treatment with prednisone and dose reduction of adagrasib.

Case Presentation

A 70-year-old woman attended our hospital with a 4-day history of severe radiating lower back pain with nausea and vomiting, without headache. She had a diagnosis of pulmonary adenocarcinoma with a solitary brain metastasis 2 years prior to the current presentation, for which she previously underwent pulmonary lobectomy, brain stereotactic radiotherapy, and chemo-immunotherapy. The biopsy from her previous pulmonary lobectomy showed a KRAS G12C mutation. Five weeks before presentation she started treatment with adagrasib in the KRYSTAL-1 study (NCT03785249). Her starting dose was 600 mg twice daily, which was reduced 2 weeks after start to 400 mg twice daily because of grade 1 blood creatinine increase (an increase from 124 μmol/L to 173 μmol/L, with recovery after dose adjustment).

The pain was located in the thoracolumbar region radiating toward the ventrolateral side of both legs. On neurological examination hypesthesia of left upper leg and bilateral reduced distal vibratory sensation were found. Deep tendon reflexes were reduced in the upper extremities and absent in lower extremities with a normal plantar reflex. Muscle strength of ankle extensors was slightly reduced on both sides, otherwise muscle strength was intact. Vital signs were normal. There were no signs of urinary or fecal incontinence.

Laboratory testing showed elevated liver enzymes (alanine aminotransferase 102 U/L, aspartate aminotransferase 102 U/L, γ-glutamyltransferase 95 U/L, alkaline phosphatase 240 U/L), infection parameters were low. MRI neuraxis showed contrast-enhancement of cauda equina (shown in Fig. 1), suspected for either inflammation or leptomeningeal metastases. There was no indication of contrast enhancement at the cervical level (shown in online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000541988). Cerebrospinal fluid analysis was performed twice with both times showing a mild pleocytosis (15 and 7 cells/μL), elevated total protein (783 and 816 mg/L) and normal glucose. Infectious causes including Varicella Zoster, Borrelia and Lues were ruled out. Cerebrospinal fluid cytology showed no atypical cells indicating metastasis.

Differential diagnosis at this point consisted of leptomeningeal metastasis or neurotoxicity of adagrasib. Adagrasib was withheld and prednisone was started at 60 mg per day and the patient was discharged. Follow-up 3 weeks later showed gradual clinical improvement and reduced contrast-enhancement of cauda equina on MRI (shown in Fig. 2), advocating for an inflammatory reaction and against leptomeningeal metastasis. Adagrasib was resumed at a lower dose (200 mg twice daily), and prednisone was tapered over a total period of 2 months.

At the 200 mg twice daily dose, the observed trough and peak plasma concentrations were 1,078 and 1,377 ng/mL, respectively, corresponding with an estimated AUC of 8,291 ng*h/mL, translating to an extrapolated AUC of 24.873 ng*h/L in the approved dose of 600 mg twice daily. As reference, the geometric mean of the AUC at the approved dose as reported by the license holder is very similar at 31.600 ng*h/L, showing that the observed exposure to adagrasib was normal and as expected for the 200 mg twice daily dose [5]. It is known that the systemic exposure required in preclinical models for adequate KRAS inhibition should be approximately 750 ng/mL to 1,750 ng/mL [5]. The observed plasma concentrations at the 200 mg dose were in this range.

Case Rep Oncol 2024;17:1289–1293
DOI: 10.1159/000541988

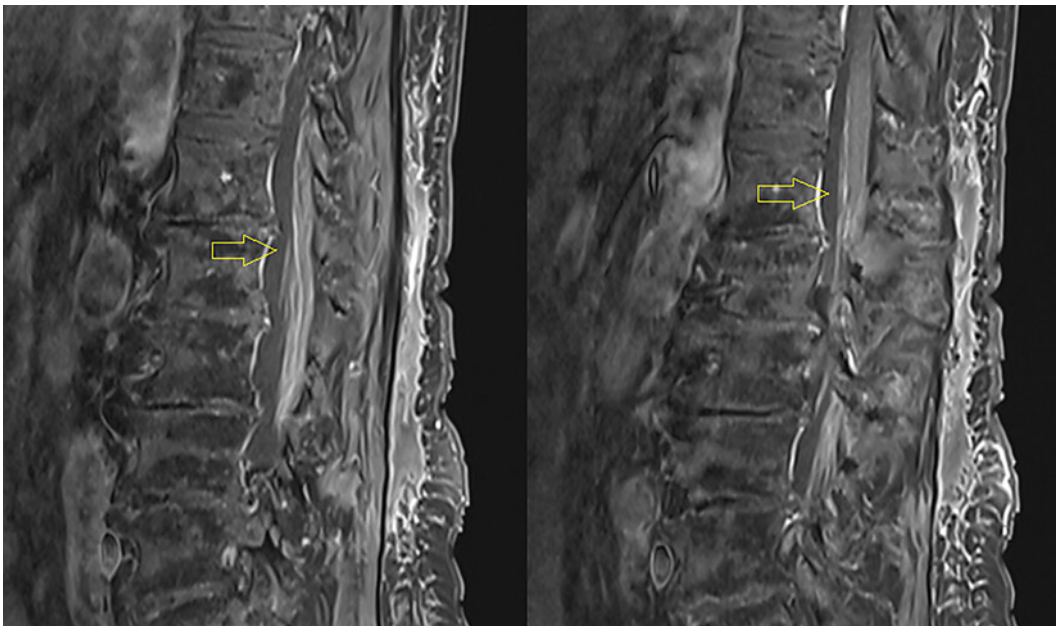

Fig. 1. Two sagittal images from the MRI of thoracolumbar spine at time of presentation (contrast-enhanced T1-weighted sequence with fat suppression), showing contrast-enhancement of the cauda equina.

At 2- and 5-month follow-up, patient showed ongoing effective tumor response and further improvement of her neurological symptoms at the 200 mg twice daily adagrasib dose. The adagrasib area under the plasma concentration time curve during a dosing interval was estimated at the 200 mg dose, by sampling a trough and peak concentration and subsequent Bayesian estimation of the AUC using the population pharmacokinetic model as reported in the FDA multidiscipline review [6].

Discussion

To the best of our knowledge, this is the first case of a patient with polyradiculitis as a result of neurotoxicity of adagrasib. In previous studies, hepatotoxicity and gastrointestinal toxicity were the most common reported adverse events of adagrasib and neurological complications were uncommon and not very specific. In a phase 2 cohort of 116 patients with non-small-cell lung cancer, dizziness (20.7%), back pain (19.8%), headache (14.7%), muscular weakness (11.2%), mental status change (4.3%), delirium (3.4%), and seizure (2.6%) were reported [1]. Similar reports of neurological complications were made in cohorts with colorectal cancer or other solid tumors [2–4]. Polyradiculitis has also not been previously reported in cohorts of other KRAS G12C inhibitors such as sotorasib and garsorasib [7–9].

The exact pathophysiological mechanism resulting in neurotoxicity attributed to adagrasib is uncertain, and our patient's analysis did not reveal a specific explanation. We have assumed the relationship between the polyradiculitis and adagrasib based on the timing of symptom onset in relation to the initiation of therapy and the improvement of neurological symptoms following dose adjustment, along with the exclusion of other causes. Adagrasib is recognized for its capacity to penetrate the central nervous system [4], which may be linked to the development of neurotoxicity. Although the CSF analysis did not offer specific insights into

Case Rep Oncol 2024;17:1289–1293
DOI: 10.1159/000541988

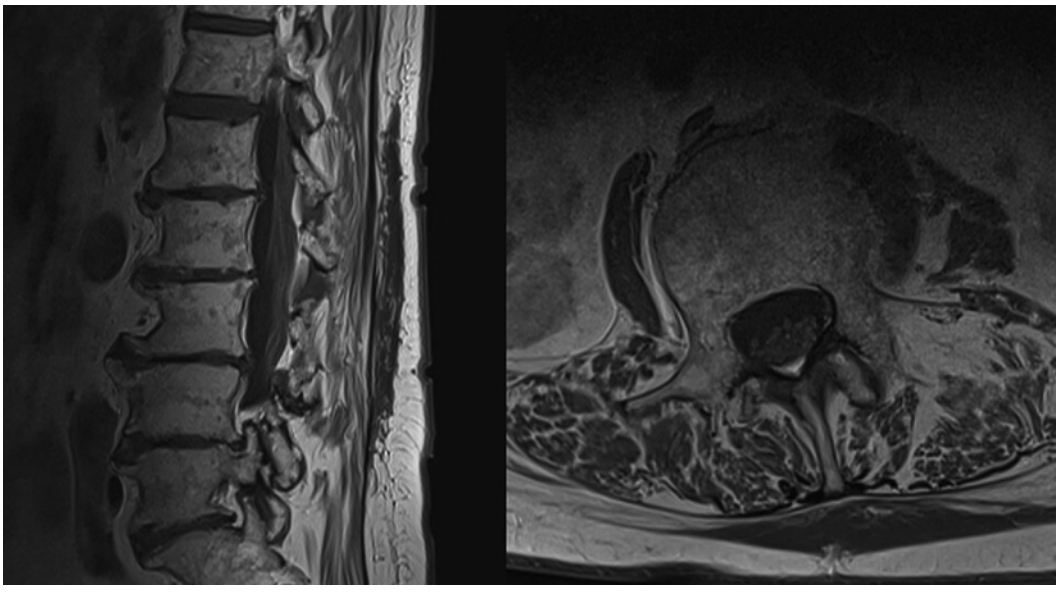

Fig. 2. Sagittal and axial images from the MRI of thoracolumbar spine at the 3-week follow-up (contrast-enhanced T1-weighted sequence without fat suppression), showing resolution of the previous contrast-enhancement. The axial image is at the level of the L2 vertebral body.

the underlying mechanism, it did show a mild pleocytosis and elevated protein levels, suggesting a mild inflammatory response.

Currently, there is practical guidance available for management of adverse events in adagrasib, specifically for the most common problems such as diarrhea, nausea, fatigue, liver enzyme or blood creatinine changes and electrocardiogram abnormalities [10]. Generally, it is advised to interrupt treatment and, if permitted, continue at a lower dose due to its dose-dependent pharmacokinetics. In our case, we additionally treated with prednisone because of a presumed auto-inflammatory underlying process.

This case report demonstrates that polyradiculitis is a potential complication of adagrasib and that symptoms may resolve after temporary treatment interruption with reintroduction at a lower dose. After the dose reduction, our patient still had an effective tumor response. In future cases with a similar presentation, we recommend to consider the same treatment strategy. Through this case report, we aim to bring attention to the possibility of this side effect, as we believe it is important to be aware of it for future patients undergoing treatment with adagrasib. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material.

Statement of Ethics

Written informed consent for publication of this case report and any accompanying images was obtained from the patient. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

No funding was received.

Author Contributions

K.E.L. was involved in patient care, reviewed the literature, collected patient data, and prepared the manuscript. R.H. was involved in interpretation of results and prepared and revised the manuscript. J.M.M.G. was involved in patient care and revised the manuscript. M.M.H. initiated the project, was involved in patient care and revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou S-HI, Pacheco JM, et al. Adagrasib in non-small-cell lung cancer harboring a *G12C* mutation. N Engl J Med. 2022;387(2):120–31. https://doi.org/10.1056/NEJMoa2204619
2 Yaeger R, Weiss J, Pelster MS, Spira AI, Barve M, Ou S-HI, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. N Engl J Med. 2023;388(1):44–54. https://doi.org/10.1056/NEJMoa2212419
3 Bekaii-Saab TS, Yaeger R, Spira AI, Pelster MS, Sabari JK, Hafez N, et al. Adagrasib in advanced solid tumors harboring a $KRAS^{G12C}$ mutation. J Clin Oncol. 2023;41(25):4097–106. https://doi.org/10.1200/JCO.23.00434
4 Ou S-HI, Jänne PA, Leal TA, Rybkin II, Sabari JK, Barve MA, et al. First-in-human phase I/IB dose-finding study of adagrasib (MRTX849) in patients with advanced $KRAS^{G12C}$ solid tumors (KRYSTAL-1). J Clin Oncol. 2022;40(23):2530–8. https://doi.org/10.1200/JCO.21.02752
5 European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). EMA assessment report - KRASATI (adagrasib). Reference ID: EMA/552099/2023 [Internet]. 2023 [cited 2024 Aug 16]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/krazati-epar-public-assessment-report_en.pdf
6 Center for Drug Evaluation and Research. NDA/BLA multi-disciplinary review and evaluation - KRAZATI (adagrasib). Reference ID: 5092534. 2021 [Internet] [cited 2024 Aug 16]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216340Orig1s000MultidisciplineR.pdf
7 Luo W, Zhu J, Zhang W, Yu A, Zhou W, Xu K. Efficacy and toxicity of drugs targeting KRAS G12C mutation in non-small cell lung cancer: a meta-analysis. Expert Rev Anticancer Ther. 2023;23(12):1295–303. https://doi.org/10.1080/14737140.2023.2282606
8 Li Z, Song Z, Zhao Y, Wang P, Jiang L, Gong Y, et al. D-1553 (garsorasib), a potent and selective inhibitor of KRAS G12C in patients with NSCLC: phase 1 study results. J Thorac Oncol. 2023;18(7):940–51. https://doi.org/10.1016/j.jtho.2023.03.015
9 Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021;384(25):2371–81. https://doi.org/10.1056/NEJMoa2103695
10 Zhang J, Johnson M, Barve M, Bazhenova L, McCarthy M, Schwartz R, et al. Practical guidance for the management of adverse events in patients with KRASG12C-mutated non-small cell lung cancer receiving adagrasib. Oncologist. 2023;28(4):287–96. https://doi.org/10.1093/oncolo/oyad051