Complete remission of brain metastases in renal cell carcinoma treated with axitinib after failure with nivolumab and ipilimumab treatment

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Introduction: Complete remission of cerebral metastasis is a rare consequence of tyrosine kinase inhibitor monotherapy in patients with metastatic renal cell carcinoma.

Case presentation: A 68-year-old woman, who presented with dyspnea, was diagnosed with left renal cell carcinoma with multiple brain and pleural metastases. Although nivolumab and ipilimumab combination treatment was initiated, it was discontinued because of an immune-related adverse event. Two months after treatment cessation, brain metastases progressed regardless of shrinkage of primary renal tumor and pleural metastases. Therefore, axitinib was started as a second-line treatment, which resulted in the complete disappearance of the brain metastases along with the stable disease of the other tumor lesions.

Conclusion: This is the first report of complete remission of brain metastases in renal cell carcinoma treated by axitinib.

Key words: axitinib, brain metastasis, complete remission, renal cell carcinoma.

Keynote message

We report the first case of complete remission of brain metastases in renal cell carcinoma treated by axitinib. Early detection of brain metastasis would help in choosing the appropriate second-line treatment. Brain metastases progressed regardless of shrinkage of primary renal tumor and pleural metastases after nivolumab and ipilimumab combination treatment.

Introduction

In patients with metastatic renal cell carcinoma (mRCC), the incidence of brain metastasis has been increasing despite advances in treatment that have prolonged survival. A vascular endothelial growth factor receptor (VEGFR)—tyrosine kinase inhibitor (TKI) and an immune checkpoint inhibitor (ICI) have been reported to be beneficial in patients with mRCC. However, these treatments have failed to demonstrate efficacy in brain metastasis, which is known to have a poor prognosis.1 Brain metastasis is mainly treated with radiation therapy or neurosurgery for improving clinical symptoms. As complete remission (CR) of cerebral metastasis is rare in patients with mRCC (even with systemic therapy), early detection of cerebral metastasis and the development of an effective treatment strategy are crucial.

We report a case of CR of brain metastases in a patient with mRCC, who was treated with axitinib after treatment failure with nivolumab and ipilimumab.

Case presentation

A 68-year-old woman visited our hospital, complaining of dyspnea. The patient’s Karnofsky performance status was 100%, and the hemoglobin, corrected serum calcium, neutrophils, and platelets were within normal limits. Contrast-enhanced computed tomography (CT) scan showed a left renal tumor (45 mm × 35 mm) (Fig.1a) and pleural metastases with effusions (Fig.1b). Magnetic resonance imaging (MRI) of the brain revealed a small metastatic lesion.
We performed a left kidney biopsy and diagnosed the condition as clear cell RCC with metastases (cT3aN0M1). As the International Metastatic RCC Database Consortium risk was intermediate, nivolumab and ipilimumab treatment was started as the first-line treatment. However, this treatment was discontinued as the patient developed grade 3 thyrotoxicosis after two courses were administered. The patient presented with a high fever, severe fatigue, and dehydration. Laboratory tests showed low thyroid stimulating hormone (0.03 μIU/L, Reference range: 0.500–5.00 μIU/L), high free triiodothyronine of 6.67 pg/mL (Reference range: 2.30–4.00 pg/mL), and free thyroxine of 3.68 ng/dL (Reference range: 0.90–1.70 ng/dL). The patient was hospitalized for a week and treated with antipyretics and intravenous fluids. Two months after the discontinuation of nivolumab and ipilimumab treatment, a CT scan revealed shrinkage of the left renal tumor and pleural metastases (Fig. 2a and b). Further, MRI revealed the progression of multiple brain metastases (Fig. 2c and d). And, 2 months later, MRI revealed the same brain metastases without any changes (Fig. 3a and b). Altogether, brain metastases were evaluated for progression after nivolumab and ipilimumab treatment. Therefore, axitinib was initiated as a second-line treatment at a dose of 5 mg twice daily. Three months after axitinib initiation, the renal tumor, and pleural metastases showed stable disease (Fig. 4a and b), and the multiple brain metastases disappeared totally (Fig. 4c and d). Axitinib treatment was continued for 26 months, and the patient currently remains in good condition with the disease under control.

**Discussion**

In this case, a heterogeneous response was observed between intracranial regions and extra-cranial regions during combined ICI treatment. The early diagnosis of brain metastasis contributed to the appropriate choice of second-line treatment. We switched systemic therapy to VEGFR-TKI, expecting a different mechanism from that of ICIs. The brain metastases shrank and then disappeared without any neurological symptoms, after initiating axitinib, an effect beyond our expectations.

The role of VEGFR-TKIs, including axitinib, for treating brain metastasis of RCC remains unclear, because patients with this condition have often been excluded from prospective clinical trials due to their poor prognosis. Several retrospective analyses and case reports have documented the...
limited effect of VEGFR-TKIs on brain metastases, and only two cases reported the clinical benefit of these drugs in patients with brain metastasis. Medioni et al. demonstrated for the first time that sunitinib achieved CR of brain metastasis of clear cell RCC.2 Uche et al. described a case of a patient with mRCC with brain metastases, who achieved a CR of cerebral lesions with cabozantinib treatment.3 In the present case, combined ICI therapy was initiated to treat mRCC, resulting in the progression of brain metastases. Afterward, the patient was treated with axitinib, which brought about a favorable response in brain metastases. To the best of our knowledge, this is the first report of CR of brain metastasis achieved by axitinib in patients with mRCC. Axitinib is known to be a more potent VEGFR inhibitor than other VEGFR-TKIs.4 In addition to the anti-angiogenesis, this class of drugs is known for modulating cancer immunity by the following mechanisms: (1) normalization of tumor vessels, promoting T cell infiltration into the tumor; (2) maturation of dendritic cells, enhancing the presentation of tumor-specific antigen; (3) inhibition of myeloid-derived suppressor cells, resuscitating immune surveillance mechanisms.5 Based on our radiological images, this case might allow us to speculate that the administration of axitinib, a VEGFR-TKI, in a state of enhanced T-cell activation and priming after ICI treatment, may have resulted in inhibition of angiogenesis and restoration of immune tolerance in the tumor microenvironment, thus reinducing an antitumor effect.

The rate of brain metastases is not low in patients with mRCC. However, the current guidelines recommend brain imaging only in individuals with central nervous system symptoms.6–8 Bianchi et al. analyzed the difference in rates of brain metastases with different metastatic organs.9 The high-risk group consisted of patients with concomitant thoracic (including lung, pleura, and other thoracic organs) and bone metastases. The rate of brain metastases in these patients was 14–16%. Moreover, a patient with lung metastasis was at an increased risk of brain metastasis, as reported from a single-center retrospective analysis (hazard ratio, 9.61; 95% confidence interval, 2.97–31.1; P < 0.001).10 Notably, in a case series of patients with brain metastases of mRCC, one-third of the patients were asymptomatic.11 Overall, these reports suggest the need for brain imaging in mRCC, even in patients with only lung metastases. Early detection of cerebral metastasis would help in choosing a more effective and appropriate treatment option.

Conclusions

We report the first case of CR of brain metastases in a patient with mRCC treated with axitinib after the failure of nivolumab and ipilimumab treatment. Further research is needed to evaluate the effect of VEGFR-TKI treatment in these patients.

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Author contributions

Koichiro Takayama: Writing – original draft; writing – review and editing. Kazuyuki Numakura: Writing – review and editing. Ryoma Igarashi: Writing – review and editing. Tomonori Habuchi: Writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Review Board

Not applicable.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Registry and the Registration No. of the study/trial

Not applicable.

References

1 Sun M, De Velasco G, Brasianos PK et al. The development of brain metastases in patients with renal cell carcinoma: epidemiologic trends, survival, and clinical risk factors using a population-based cohort. Eur Urol Focus 2019; 5: 474–81.
2 Medioni J, Cojocarasu O, Belcaceres JL, Halimi P, Oudard S. Complete cerebral response with sunitinib for metastatic renal cell carcinoma. Ann. Oncol. 2007; 18: 1282–3.
3 Uche A, Sila C, Tanoura T et al. Brain complete response to cabozantinib prior to radiation therapy in metastatic renal cell carcinoma. Case Rep. Urol. 2019; 2019: 6769017.
4 Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. Drugs R D 2011; 11: 113–26.
5 Roland CL, Lynn KD, Toombs JE, Dineen SP, Udugamasooriya DG, Brekken RA. Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer. PLoS One 2009; 4: e7669.
6 Ljungberg B, Albiges L, Abu-Ghanem Y et al. European Association of Urology Guidelines on renal cell carcinoma: the 2019 update. Eur. Urol. 2019; 75: 799–810.
7 Motzer RJ, Jonasch E, Boyle S et al. NCCN guidelines insights: kidney cancer, version 1.2021. J. Natl. Compr. Canc. Netw. 2020; 18: 1160–70.
8 Escudier B, Porta C, Schmidinger M et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2019; 30: 706–20.
9 Bianchi M, Sun M, Jeldres C et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann. Oncol. 2012; 23: 973–80.
10 Verma J, Jonasch E, Allen P, Tannir N, Mahajan A. Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. Cancer 2011; 117: 4958–65.
11 Shuch B, La Rochelle JC, Klatte T et al. Brain metastasis from renal cell carcinoma: presentation, recurrence, and survival. Cancer 2008; 113: 1641–8.