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Case Report

Contemplation of the Effect of Nivolumab Plus Cabosantinib Therapy on Cerebral Hemorrhage in Patients with Brain Metastasis of Renal Cell Carcinoma: A Case Report

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Keywords
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Abstract
Although the response to combination therapy has been reported in patients with brain metastases from advanced renal cancer, treatment-related cerebral hemorrhage has not been adequately studied. The CheckMate 9ER clinical trial of nivolumab and cabozantinib excluded patients with brain metastases. Therefore, the associated treatment outcomes in these patients with brain metastases are unclear. Herein, we report a case of bleeding from brain metastases in a patient with advanced renal cancer after gamma knife combination therapy with nivolumab and cabozantinib. Fortunately, the cerebral hemorrhage of the patient was alleviated by conservative treatment. Despite treatment interruption, the metastatic lesions reduced in size, and treatment was gradually resumed. In this case study, we report the risk of cerebral hemorrhage in combination therapy for brain metastasis cases, how to manage hemorrhage cases, and their prognosis.

Introduction

Combination therapy with immune checkpoint inhibitors has been used to treat renal cell carcinoma (RCC), and more cases of long-term response have been observed. Although these drugs have shown some efficacy, which patients are more likely to respond to treatment

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remains unclear. The CheckMate 9ER trial excluded patients with central nervous system metastases who were considered to have short life expectancies. In this case report, we discuss the bleeding risk, response, and prognostic relevance of nivolumab plus cabozantinib therapy for advanced renal cancer with brain metastasis.

Case Report

A 72-year-old woman underwent a laparoscopic nephrectomy for right RCC at our facility with no recurrence for 14 years. She had no history of alcohol consumption or smoking; her pre-existing medical history included hypertension and ureteral stones, and she was taking calcium channel blockers, xanthine oxidase inhibitors, and AT1 receptor blocker medications. However, the patient was admitted to our hospital for urinary incontinence and forgetfulness. Computed tomography (CT) without contrast showed two high-density lesions with surrounding edematous changes in the right frontal and parietal lobes, suspected to be brain metastases of the RCC (shown in Fig. 1a). Contrast-enhanced magnetic resonance imaging (MRI) of the head revealed two tumors in the right frontal and left parietal lobes (shown in Fig. 1b). Contrast-enhanced CT showed multiple nodules in the lower lobe of the right lung and a 7 mm nodule with a contrast effect on the outer side of the right psoas muscle, which was determined to be recurrent RCC (shown in Fig. 1c, d). Based on these findings, the patient was diagnosed with advanced RCC with favorable risk according to the International Metastatic RCC Database Consortium classification of brain metastases, multiple lung metastases, and local recurrence.

One week after treatment with stereotactic irradiation at 35 Gy/5 fractions for brain metastases, the patient began combination therapy with nivolumab and cabozantinib. The treatment had no obvious side effects, and the patient was discharged 1 week after starting combination therapy. However, on the day of discharge, she was transported to the emergency room by ambulance because of generalized convulsions and disturbances of consciousness. At that time, her level of consciousness was as follows: Glasgow coma scale eye-opening 1, best verbal response 1, and best motor response 4 (GCS E1V1M4). Her vital signs were: temperature, 36.4°C; blood pressure, 152/92 mm Hg; and SpO_2, 92% (room air). Various laboratory tests were also performed with the following results: blood count, WBC 11,100/μL; Hb, 12.5 g/dL; PLT, 346,000/μL; clotting time: PT, 140.5%; APTT, 21.1 s; chemistries: T-bil, 0.5 mg/dL; AST, 36 U/L; ALT, 37 U/L; Cre, 0.89 mg/dL; TP, 7.4 g/dL; Alb, 4.1 g/dL; Na, 140 mmol/L; K 4.2, mmol/L; Cl, 102 mmol/L; Ca, 9.1 mg/dL; and Glu 155 mg/dL. CT showed the emergence of bleeding from the brain metastasis in the left parietal lobe (shown in Fig. 2), which was determined to be a generalized seizure and a decreased level of consciousness. Conservative treatment for the cerebral hemorrhage was initiated immediately with glycerin, prednisolone, and lacosamide, and consciousness improved within 2 weeks of the hemorrhage (Glasgow Coma Scale: E4V5M6).

One month after hemorrhage, CT demonstrated no increase in the hematoma, MRI showed shrinkage of the brain metastases, and the patient restarted nivolumab. Five months after hemorrhage, MRI and CT revealed that the brain metastases continued to shrink (shown in Fig. 3a), but multiple lung metastases and local recurrence progressed (shown in Fig. 3b, c); therefore, we restarted combination therapy with cabozantinib.

Six months later, the patient showed no progression, without bleeding from the brain metastases, after resuming combination therapy with nivolumab and cabozantinib. The authors have completed the CARE Checklist for this case report which is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533785).

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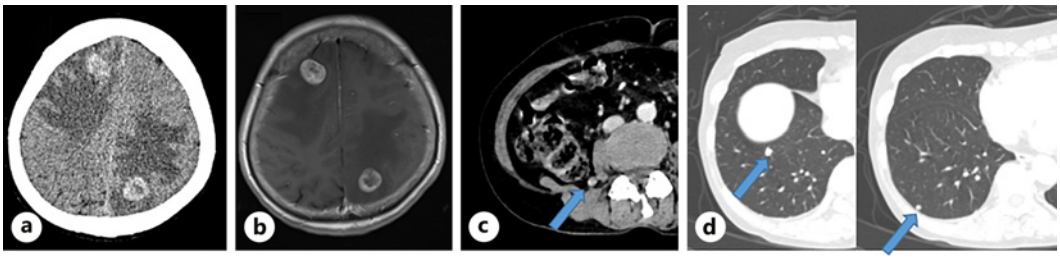

Fig. 1. a Computed tomography (CT) demonstrated two high-density lesions with surrounding edematous changes in the right frontal and parietal lobes. **b** Magnetic resonance imaging (MRI) demonstrated two tumors in the right frontal and left parietal lobes. **c** CT demonstrated a 7 mm nodule with a contrast effect on the outer side of the right psoas muscle. **d** CT demonstrated multiple nodules in the lower lobe of the right lung.

Discussion

The CheckMate 9ER trial demonstrated the benefits of combination therapy with nivolumab and cabozantinib. The study also showed prolonged progression-free survival and overall survival in previously untreated patients with advanced RCC [1]. However, patients with central nervous system metastases were excluded, and the efficacy of the combination therapy in patients with brain metastases and the risk of cerebral hemorrhage was not determined. Clinical trials on combination therapies with other immune checkpoint and tyrosine kinase inhibitors have also excluded patients with brain metastases [2–4]. Screening for brain metastases is important in patients with advanced-stage RCC because some reports suggest that 40% of patients with brain metastases have no symptoms [5].

Cabozantinib is an inhibitor of tyrosine kinases, including mesenchymal-epithelial transition (MET), vascular endothelial growth factor receptors (VEGFRs), and growth arrest-specific 6 receptors [6]. Several clinical trials of cabozantinib alone have reported its efficacy in treating brain metastases by crossing the blood-brain barrier [7, 8], and several case reports have suggested that combination therapy including nivolumab or combination therapy with nivolumab and cabozantinib is effective for advanced RCC with brain metastases [9–11]. As a reason for its effectiveness, it has been suggested that MET expression is higher in brain metastases in patients with RCC [7]. Therefore, we chose combination therapy with cabozantinib in this case. However, there is a known risk of bleeding with cabozantinib, which is thought to result from disruption of the tumor vasculature and inhibition of angiogenesis due to VEGFR blockade [12]. There have been case reports of bleeding from brain metastases at high frequencies when sunitinib or sorafenib, which resembles cabozantinib, were used [13]. When immunotherapy has been administered, cabozantinib reportedly enhanced angiogenesis inhibition in a mouse model with hepatocellular carcinoma. However, when administered to patients with advanced RCC, nivolumab alone did not increase the risk of hemorrhagic adverse events [14, 15]. With a long half-life, cabozantinib takes time to stabilize the blood levels of patients, and the first week of administration is insufficient to detect cerebral hemorrhage. In the present case, cerebral hemorrhage occurred 1 week after starting cabozantinib treatment.

The initiation of cabozantinib therapy requires further investigation; therefore, it is important to consider the irradiation timing. Radiosurgery can decrease hemorrhagic events by blunting angiogenesis and normalizing the tumor vasculature [16–18]; moreover, it has been reported that the effect of radiation can be observed in approximately 1 month [19]. The timing of cabozantinib administration after irradiation is unclear; however, if there is sufficient time before treatment, it may be preferable to wait approximately 1 month after

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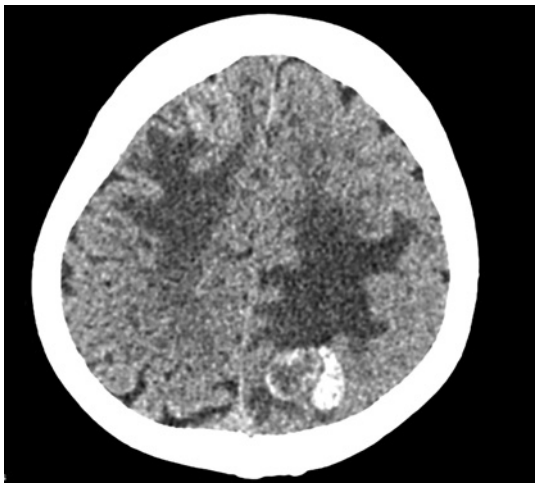

Fig. 2. CT demonstrated the emergence of bleeding from brain metastasis on the left parietal lobe.

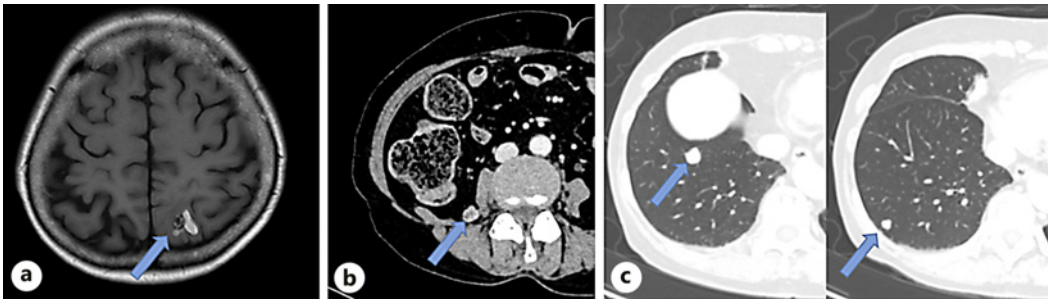

Fig. 3. a Brain metastases decreased by >50%. **b** Progression of local recurrence. **c** Progression of multiple lung metastases.

irradiation. Because of the use of drugs that are prone to adverse events related to elevated blood pressure, the importance of daily blood pressure control for reducing the risk of cerebral hemorrhage should be noted [20]. In this case, the systolic blood pressure after cabozantinib administration was 150–160 mm Hg at the higher end of the range, which may have required stricter blood pressure monitoring to reduce the risk of a cerebral hemorrhage.

One month after the hemorrhage, nivolumab was resumed because of the risk of re-bleeding with cabozantinib. Four months after nivolumab resumption, the brain metastases continued to shrink to 50%; however, the progression of multiple lung metastases and local recurrence were observed. We decided to restart cabozantinib treatment because the antitumor effect of nivolumab as a single agent was insufficient, and the combination with cabozantinib was necessary. Six months after the resumption of combination therapy, the patient showed no disease progression or bleeding from the brain metastases.

As in the present case, steroids and glycerin are generally used as conservative treatments for edema or bleeding caused by brain tumors [21, 22]. Antiepileptic drugs are also used to treat seizures resulting from edema caused by bleeding [23]. Surgery for hematoma removal is required when conservative treatment is inadequate if compression findings are observed. Treatment decisions for hemorrhages caused by brain metastases should be made on a case-by-case basis for hemorrhage caused by brain metastases [24]. Cabozantinib is effective in patients with RCC and brain metastases but carries a risk of cerebral hemorrhage. Patients should be fully informed of the risk of a cerebral hemorrhage when receiving combination therapy that includes cabozantinib. Administering radiotherapy before

combination therapy can reduce this risk. Therefore, the timing of cabozantinib administration after irradiation should be noted; it may be preferable to wait until approximately 1 month after irradiation.

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Statement of Ethics

The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Hospital (approval number: 30967). The study was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yasufumi Sato and Yoshihide Kawasaki wrote the manuscript. Yoshihide Kawasaki, Hiromichi Katayama, Yohei Satake, Shuichi Shimada, Takuma Sato, Naoki Kawamorita, Shinichi Yamashita, and Akihiro Ito served as attending physicians for the presented patient. Yoshiteru Shimoda and Masayuki Kanamori provided conservative treatment for edema or bleeding caused by brain tumors. All authors agree to be accountable for all aspects of this study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Data supporting the findings of this study are available from the corresponding author, Yoshihide Kawasaki, upon request.

References

1 Motzer RJ, Powles T, Burotto M, Escudier B, Bourlon MT, Shah AY, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. Lancet Oncol. 2022;23(7):888–98.

2 Powles T, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. 2020;21(12):1563–73.
3 Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1103–15.
4 Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med. 2021;384(14):1289–300.
5 Parmar A, Ghosh S, Sahgal A, Lalani AKA, Hansen AR, Reaume MN, et al. Evaluating the impact of early identification of asymptomatic brain metastases in metastatic renal cell carcinoma. Cancer Rep Hob. 2023;6(3):e1763.
6 Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1814–23.
7 Hirsch L, Martinez Chanza N, Farah S, Xie W, Flippot R, Braun DA, et al. Clinical activity and safety of cabozantinib for brain metastases in patients with renal cell carcinoma. JAMA Oncol. 2021;7(12):1815–23.
8 Peverelli G, Raimondi A, Ratta R, Verzoni E, Bregni M, Cortesi E, et al. Cabozantinib in renal cell carcinoma with brain metastases: safety and efficacy in a real-world population. Clin Genitourin Cancer. 2019;17(4):291–8.
9 Abid H, Watthanasuntorn K, Shah O, Gnanajothy R. Efficacy of pembrolizumab and nivolumab in crossing the blood brain barrier. Cureus. 2019;11(4):e4446.
10 Négrier S, Moriceau G, Attignon V, Haddad V, Pissaloux D, Guerin N, et al. Activity of cabozantinib in radioresistant brain metastases from renal cell carcinoma: two case reports. J Med Case Rep. 2018;12(1):351.
11 Nakagawa T, Kijima T, Imasato N, Nagoshi A, Nakamura G, Uematsu T, et al. Efficacy of cabozantinib therapy for brain metastases from renal cell carcinoma. IJU Case Rep. 2022;5(4):293–6.
12 Al-Salama ZT, Keating GM. Cabozantinib: a review in advanced renal cell carcinoma. Drugs. 2016;76(18):1771–8.
13 Pouessel D, Culine S. High frequency of intracerebral hemorrhage in metastatic renal carcinoma patients with brain metastases treated with tyrosine kinase inhibitors targeting the vascular endothelial growth factor receptor. Eur Urol. 2008;53(2):376–81.
14 Esteban-Fabró R, Willoughby CE, Piqué-Gili M, Montironi C, Abril-Fornaguera J, Peix J, et al. Cabozantinib enhances anti-PD1 activity and elicits a neutrophil-based immune response in hepatocellular carcinoma. Clin Cancer Res. 2022;28(11):2449–60.
15 McFarlane JJ, Kochenderfer MD, Olsen MR, Bauer TM, Molina A, Hauke RJ, et al. Safety and efficacy of nivolumab in patients with advanced clear cell renal cell carcinoma: results from the phase IIIb/IV CheckMate 374 study. Clin Genitourin Cancer. 2020;18(6):469–76.e4.
16 Sneed PK, Mendez J, Vemer-van den Hoek JG, Seymour ZA, Ma L, Molinaro AM, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. J Neurosurg. 2015;123(2):373–86.
17 Yan DF, Yan SX, Yang JS, Wang YX, Sun XL, Liao XB, et al. Hemorrhage of brain metastasis from non-small cell lung cancer post gefitinib therapy: two case reports and review of the literature. BMC Cancer. 2010;10:49.
18 Ali M, Mooi J, Lawrentschuk N, McKay RR, Hannan R, Lo SS, et al. The role of stereotactic ablative body radiotherapy in renal cell carcinoma. Eur Urol. 2022;82(6):613–22.
19 Angelov L, Mohammadi AM, Bennett EE, Abbassy M, Elson P, Chao ST, et al. Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases ≥ 2 cm. J Neurosurg. 2018;129(2):366–82.
20 Zuo PY, Chen XL, Liu YW, Xiao CL, Liu CY. Increased risk of cerebrovascular events in patients with cancer treated with bevacizumab: a meta-analysis. PLoS One. 2014;9(7):e102484.
21 Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, Asher AL, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neuro Oncol. 2010;96(1):103–14.
22 Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, et al. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. Eur J Neurol. 2006;13(7):674–81.
23 Mikkelsen T, Paleologos NA, Robinson PD, Ammirati M, Andrews DW, Asher AL, et al. The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neuro Oncol. 2010;96(1):97–102.
24 Boissonneau S, Graillon T, Rolland A, Botella C, Pallud J, Dufour H. Management of patients suffering from hemorrhagic intracranial metastases: propositions to help the neurosurgeon in emergency situations based on a literature review. Neurochirurgie. 2021;67(4):369–74.