



## Oncology

# A case of cabozantinib therapy leading to complete remission for massive intra-intestinal bleeding and worsening metastatic sites following nivolumab and ipilimumab therapy

Kyohei Ishida<sup>a</sup>, Go Hasegawa<sup>b</sup>, Yohei Ikeda<sup>c</sup>, Noboru Hara<sup>a</sup>, Tsutomu Nishiyama<sup>a,\*</sup>

<sup>a</sup> Department of Urology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Minamiuonuma, Niigata, Japan

<sup>b</sup> Department of Pathology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Minamiuonuma, Niigata, Japan

<sup>c</sup> Department of Diagnostic Radiology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Minamiuonuma, Niigata, Japan



## ARTICLE INFO

## Keywords:

Recurrent renal cell carcinoma  
Massive intra-intestinal bleeding  
Cabozantinib  
Complete remission

## ABSTRACT

A woman in her 50s had recurrent renal cell carcinoma six years after nephrectomy. The patient was treated with nivolumab plus ipilimumab therapy starting in May 2022. She was rushed to hospital due to melena and severe anemia in September 2022. CT showed massive leakage of contrast medium into the gastrointestinal tract and mild enlargement of the metastatic tumors. Nivolumab was discontinued and she was started on cabozantinib as second-line therapy. After cabozantinib therapy, the anemia subsided. The metastatic tumors have shrunk significantly, with no further recurrence being observed as of September 2023.

## 1. Introduction

VEGF inhibiting TKIs have significantly improved outcomes for patients with advanced RCC. However, these agents, besides the known progression-free survival benefits, are associated with a risk of potentially life-threatening and contrasting toxicities of thrombosis and bleeding.<sup>1</sup> The safety of TKIs for the treatment of advanced RCC patients with bleeding is unknown. We encountered a case of cabozantinib therapy leading to complete remission for massive intra-intestinal bleeding and worsening metastatic sites following nivolumab and ipilimumab therapy.

## 2. Case presentation

A woman in her 50s underwent laparoscopic right nephrectomy in October 2016, and pathological findings were clear cell renal cell carcinoma, G1 and G2, Fuhrman grade 2, pT3aN0M0. The patient was under surveillance at 3-month intervals for the first two years and at 6-month intervals thereafter using CT and whole-body Magnetic Resonance Imaging. In April 2022, follow-up CT revealed multiple mass lesions of the abdominal wall and multiple pelvic lymph nodes, and findings suggestive of peritoneal dissemination (Fig. 1). She was also

pointed out as having severe anemia (Hb 6.0g/dl). The biopsy result of the recurrent tumor was similar to the pathology at the time of nephrectomy (Fig. 2). Her clinical status was intermediate risk (Hemoglobin < lower limit of normal; Platelets > upper limit of normal) based on the International Metastatic RCC Database Consortium (IMDC) Risk Model for Metastatic RCC. Considering her age and benefits regarding long-term survival based on a reported clinical trial, the patient was treated with nivolumab plus ipilimumab therapy starting in May 2022.<sup>2</sup> She improved in anemia temporarily (Hb 9.3g/dl). Even after starting treatment, her anemia worsened (Hb 7.3g/dl), and she received repeated blood transfusions as necessary. The patient was rushed to hospital due to melena and severe anemia (Hb 6.1g/dl) in September 2022. CT showed massive leakage of contrast medium into the gastrointestinal tract and mild enlargement of the metastatic tumors (Fig. 3). Nivolumab treatment was discontinued after eight doses. Although the patient showed severe anemia and leakage of contrast medium into the gastrointestinal tract, cabozantinib (40 mg/day) was started as second-line therapy after she gave informed consent regarding the risk of life-threatening bleeding. After starting cabozantinib therapy, the anemia subsided, and blood transfusions were no longer required. CT showed that the metastatic lesions were reduced and leakage of contrast medium into the gastrointestinal tract disappeared in October 2022 (Fig. 3). As severe diarrhea continued in October 2022, the dose of

\* Corresponding author. Department of Urology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Urasa 4132, Minamiuonumashi, Niigata, 949-7302, Japan.

E-mail address: [nishiyama@med.niigata-u.ac.jp](mailto:nishiyama@med.niigata-u.ac.jp) (T. Nishiyama).

URL: <http://www.uonuma-kan-hospital.jp/> (T. Nishiyama).

<https://doi.org/10.1016/j.eucr.2023.102603>

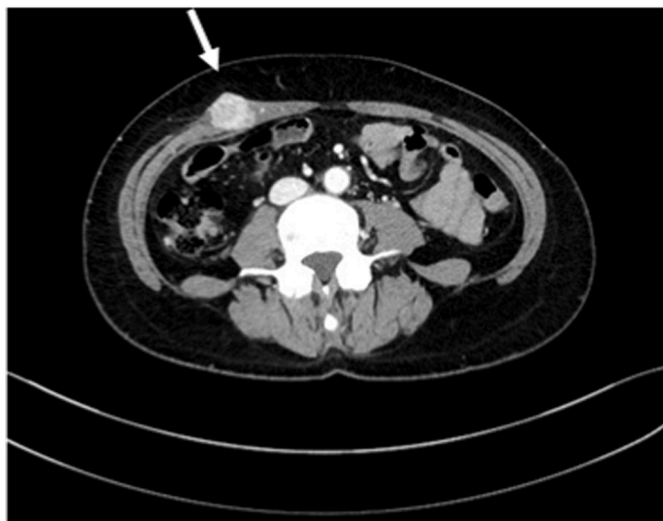
Received 23 September 2023; Received in revised form 17 October 2023; Accepted 23 October 2023

Available online 30 October 2023

2214-4420/© 2023 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### Abbreviations

VEGF	Vascular endothelial growth factor
TKIs	kinase inhibitors
RCC	renal cell carcinoma
CT	computed tomography



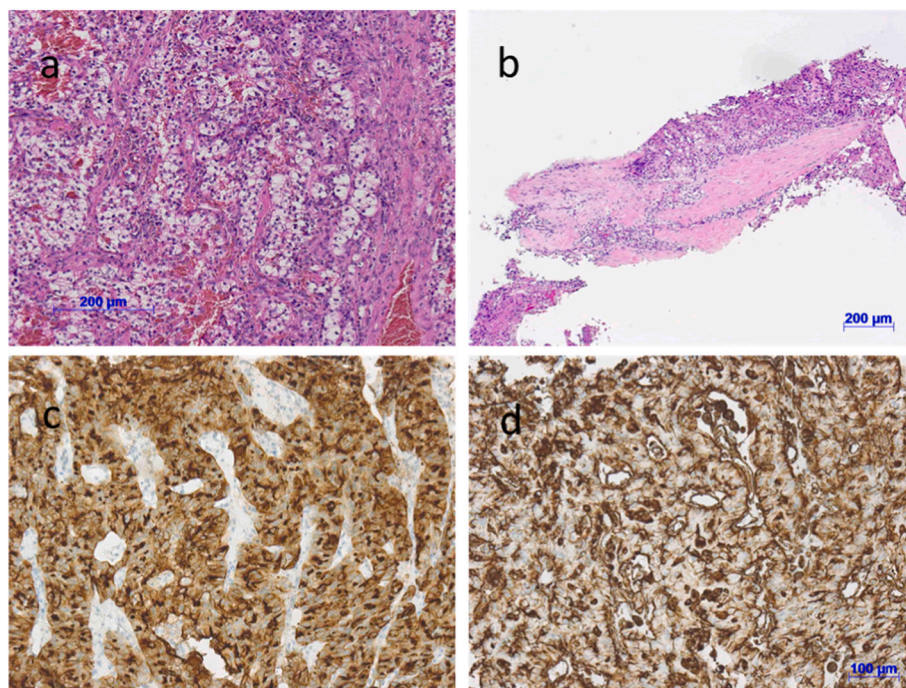
**Fig. 1.** CT at recurrence shows a contrast medium-enhanced mass lesion on the abdominal wall. (arrow).

cabozantinib was reduced to 20 mg and continued. The metastatic tumors have shrunk significantly, with no further recurrence being observed as of September 2023.

### 3. Discussion

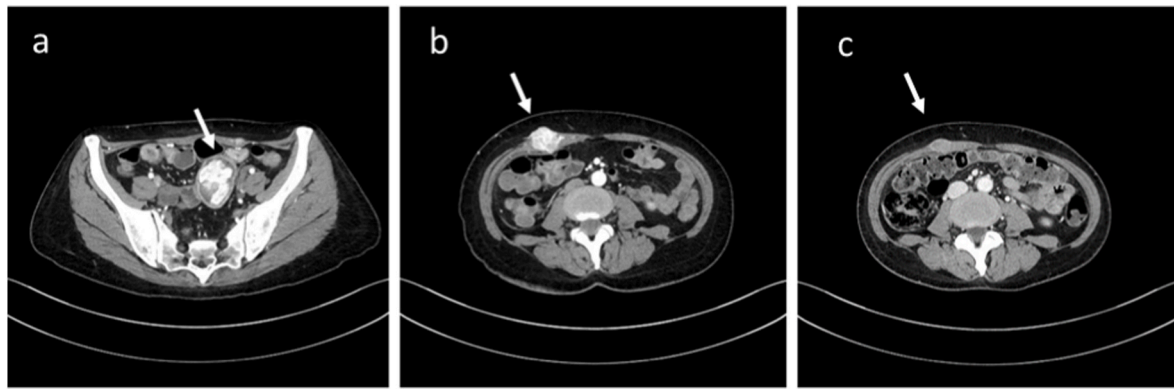
Treatments for advanced RCC mainly involve immune-checkpoint inhibitors and VEGF inhibiting TKIs, such as cabozantinib.<sup>3</sup> Over the past few years, the treatment landscape for patients with advanced RCC has been revolutionized. Combination therapy relying on immune-checkpoint inhibitors has become the standard of care. However, optimal second-line treatment approaches remain to be defined.<sup>3</sup> One potential treatment approach is the use of cabozantinib, a multi-target TKI originally approved as second-line treatment after first-line target therapy.<sup>4</sup> The present patient, considering her age and benefits regarding long-term survival based on a reported clinical trial, was treated with nivolumab plus ipilimumab therapy.<sup>2</sup>

VEGF inhibiting TKIs may be associated with an increased risk of bleeding incidence.<sup>1</sup> However, their safety for the treatment of advanced RCC patients with bleeding is unknown. Interventions for bleeding events may include palliative radiation, embolization, or surgery. The present patient had severe intra-intestinal bleeding and severe anemia, but achieved hemodynamic stability. Therefore, we judged that interventions for bleeding were not necessary and cabozantinib was started as second-line therapy. In the present patient, after cabozantinib therapy, the anemia subsided, and blood transfusions were no longer required. The antitumor effect of cabozantinib overcame the bleeding tendency, and the tumor size was reduced without exacerbation of bleeding. If the present patient had been treated with nivolumab plus cabozantinib therapy as first-line therapy, she may have achieved remission without bleeding.<sup>5</sup> If there were effective markers for selecting first-line treatment for advanced RCC, it may be possible to provide more effective treatment for advanced RCC patients.



**Fig. 2.** Pathological findings.

Pathological findings of the recurrent tumor are renal clear cell carcinoma, G1 and G2, similar to the pathology at the time of nephrectomy: renal clear cell carcinoma, G1 and G2, Fuhrman grade 2. a: hematoxylin-eosin staining of the nephrectomy specimen, b: hematoxylin-eosin staining of the recurrent tumor, c: recurrent tumor positive for CD10, d: recurrent tumor positive for vimentin.



**Fig. 3.** a. CT at emergent hospital admission shows massive leakage of contrast medium into the gastrointestinal tract in September 2022. (arrow) b. CT shows mild enlargement of the metastatic tumors in September 2022. (arrow) c. CT shows the reduced metastatic lesion of the abdominal wall in October 2022. (arrow).

#### 4. Conclusion

VEGF inhibiting TKIs may be associated with an increased risk of bleeding incidence; however, cabozantinib therapy was started as second-line therapy in the present patient. Cabozantinib therapy was very effective. Following cabozantinib therapy the anemia did not progress, and the tumor shrank significantly. Effective markers for selecting first-line treatment for advanced RCC may make it possible to provide more effective treatment for advanced RCC patients.

#### Disclosure statement

No competing financial interest exists.

#### Approval of the research protocol by an institutional reviewer board

Not applicable.

#### Informed consent

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

#### Registry and registration no. of the study/trial

Not applicable.

#### Disclosure instructions

The authors did not use AI and AI-assisted technologies in the writing process in the manuscript.

#### Author contributions

Kyohei Ishida: Writing – original draft; writing.

Go Hasegawa: Writing – review and editing.

Yohei Ikeda: Writing – review and editing.

Noboru Hara: Writing – review and editing.

Tsutomu Nishiyama: Writing – original draft; writing – review and editing.

#### Declaration of competing interest

None.

#### Acknowledgment

This research project received no specific grant from funding agencies in public or commercial sectors.

#### References

1. Crist M, Hansen E, Chablani L, Guancial E. Examining the bleeding incidences associated with targeted therapies used in metastatic renal cell carcinoma. *Crit Rev Oncol Hematol.* 2017 Dec;120:151–162. <https://doi.org/10.1016/j.critrevonc.2017.10.014>.
2. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open.* 2020 Nov;5(6), e001079. <https://doi.org/10.1136/esmoopen-2020-001079>.
3. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Kidney Cancer Version 1.2024* — June 21; 2023. [https://www.nccn.org/professionals/physician\\_gls/pdf/kidney.pdf](https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf).
4. Santoni M, Massari F, Bracarda S, et al. Cabozantinib in patients with advanced renal cell carcinoma primary refractory to first-line immunocombinations or tyrosine kinase inhibitors. *Eur Urol Focus.* 2022 Nov;8(6):1696–1702. <https://doi.org/10.1016/j.euf.2022.02.004>.
5. Motzer RJ, Powles T, Burotto M, 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 Jul;23(7):888–898. [https://doi.org/10.1016/S1470-2045\(22\)00290-X](https://doi.org/10.1016/S1470-2045(22)00290-X).