3: 124-129 (2023)

Pathological Complete Response to Preoperative Nivolumab Plus Cabozantinib for Renal Cell Carcinoma With Inferior Vena Cava Thrombus: A Case Report

ARISA MACHIDA¹, DAIKI IKARASHI¹, NAOKI YANAGAWA², MASAMICHI SUZUKI², TATSUYA KAWAMURA¹, KIE SEKIGUCHI¹, KENTA TAKAHASHI¹, RENPEI KATO¹, TOMOHIKO MATSURA¹, SHIGEKATSU MAEKAWA¹, MITSUGU KANEHIRA¹, RYO TAKATA¹, TAMOTSU SUGAI² and WATARU OBARA¹

Departments of ¹Urology and ²Pathology, School of Medicine, Iwate Medical University, Iwate, Japan

Abstract. Background/Aim: Surgical treatment of renal cell carcinoma (RCC) with inferior vena cava (IVC) thrombus is associated with high morbidity and mortality rates, therefore presurgical systemic therapies are required in order to improve the safety and feasibility of the surgical procedure by decreasing the thrombus level and burden. The efficacy of presurgical combination therapy of immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors (TKI) for advanced renal cell carcinoma with IVC thrombus remains unclear. Case Report: We report a case of a 69-year-old male with cT3bN0M0 locally advanced RCC. We successfully performed a less invasive nephrectomy with thrombectomy, because nivolumab plus cabozantinib administration remarkably reduced the primary tumor and IVC thrombus, resulting in complete pathological response, as assessed with perioperative immunohistochemistry. Conclusion: To the best of our knowledge, this is the first report showing that nephrectomy could be safely performed for RCC with IVC thrombus after presurgical nivolumab plus cabozantinib therapy, leading to pathological complete response.

Correspondence to: Arisa Machida, Department of Urology, School of Medicine, Iwate Medical University, 2-1-1, Yahaba, Shiwa-gun, Iwate 028-3695, Japan. Tel: +81 196515111, Fax: +81 196231527, e-mail: ar.machida@gmail.com

Key Words: Nivolumab, cabozantinib, renal cell carcinoma, inferior vena cava thrombus, pathological complete response, case report.

©2023 International Institute of Anticancer Research www.iiar-anticancer.org



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (https://creativecommons.org/licenses/by-nc-nd/4.0).

Surgical treatment of advanced renal cell carcinoma (RCC) with tumor thrombus extending into the inferior vena cava (IVC) requires careful management due to the high risk of operation-related deaths (1). Presurgical therapy, using tyrosine kinase inhibitors (TKI) or immune checkpoint inhibitors (ICI), for RCC with tumor thrombus is expected to shrink the tumor size and reduce surgical risks (2, 3). Currently, ICI-based therapy has been the standard first-line treatment for unresectable or metastatic RCC (4). In a recent study, Yoshida, et al. reported the efficacy of ICI-based therapy in the patients with RCC and IVC tumor thrombus in terms of primary tumor shrinkage and decrease of the tumor thrombus extent, resulting in reduced surgical risk (5). Herein, we report a case of RCC with IVC thrombus treated with nivolumab plus cabozantinib as presurgical therapy and subsequent safe nephrectomy, resulting in a pathological complete response (pCR). To the best of our knowledge, this is the first case in which a combination of nivolumab and cabozantinib as presurgical therapy resulted in shrinkage of the renal tumor and thrombus while achieving pCR.

Case Report

A 69-year-old male was referred to our Hospital (Iwate Medical University Hospital) for surgical treatment of a left renal tumor without any symptoms. He had a medical history of hypertension and diabetes mellitus. Abdominal enhanced computed tomography (CT) revealed a 30-mm left renal tumor (cT1aN0M0) with low-density enhancement (Figure 1A). We initially planned a robot-assisted partial nephrectomy, but the tumor grew rapidly during the 3-month waiting period, as per the patient's preference. Follow-up CT revealed an expanding left renal tumor with a tumor thrombus in the left renal vein and IVC (Figure 1B). The International metastatic RCC Database Consortium (IMDC) prognostic risk scores were favorable. The clinical diagnosis



Figure 1. Contrast-enhanced computed tomography (CT) showing (A) the left renal cell carcinoma at initial diagnosis. At 3 months after initial diagnosis, CT showed a rapid progression of the primary tumor with inferior vena cava (IVC) thrombus (B).

was cT3bN0M0 advanced RCC. We first performed CTguided biopsy of the primary tumor. Pathological findings revealed RCC without sarcomatoid differentiation. However, biopsy specimens could not confirm the histological subtype diagnosis, including clear or non-clear cell carcinoma. Immunohistochemistry findings were positive for PAX8, CD10, AMACR, and E-cadherin and were negative for CK7. These results were not typical of renal clear cell carcinoma and diagnosis by needle biopsy did not lead to histological subtyping. We provided systemic therapy instead of immediate surgery because the tumor growth progressed rapidly, and we aimed to reduce the size of the primary tumor and thrombus. Therefore, we administered nivolumab 240 mg every 2 weeks and cabozantinib 40 mg once daily. The patient's medical course was uneventful without drug withdrawal or dose reduction because of adverse events.

After 10 courses of nivolumab, CT revealed primary tumor and thrombus shrinkage (Figure 2). IVC thrombus level was downstaged from level II to I according to the Neves and Zincke's classification system (6). We then planned curative surgery because the tumor had shrunk sufficiently for a safer surgery. We withdrew cabozantinib for one month and placed a temporary IVC filter immediately before surgery. Thereafter, we performed an open left nephrectomy and thrombectomy without mobilizing the liver and artificial vascular replacement of the IVC (Figure 3A). Histological findings revealed expanded necrosis and infiltration of foamy histiocytes with no viable cells in the surgical specimen, including in the thrombus (Figure 3B and C). Moreover, we investigated the expression levels of CD4, CD8, and CD20 in biopsy and surgical specimens by immunohistochemical examination (Figure 4). CD4⁺ and CD8⁺ cells were sparsely found in the biopsy specimens but were remarkably increased in the surgical specimens. In contrast, even though CD20⁺ cells were not found in the biopsy specimen, they were observed surrounded by CD4⁺ cells in the surgical specimen, which suggested that the formation of tertiary lymphoid structures (TLS) was recognized in the surgical specimens.

The perioperative course was uneventful, and the patient was discharged 10 days after surgery. No local recurrence or metastasis was observed 3 months after the discontinuation of nivolumab plus cabozantinib therapy.

Discussion

The efficacy of nivolumab plus cabozantinib was demonstrated in the CheckMate 9ER trial for metastatic RCC (7), with an objective response rate of 55.7%, CR rate of 8%, and progression disease (PD) rate of 5.6%. In addition, the healthrelated quality of life was significantly better with nivolumab plus cabozantinib compared to sunitinib at nearly all time points during treatment (7). Furthermore, the combination of nivolumab and cabozantinib showed promising efficacy in the treatment of patients with papillary, unclassified, and translocation-associated histological type metastatic non-clear cell RCC in a phase 2 study (8). In the present case report, a definitive diagnosis could not be made by biopsy, but the possibility of non-clear RCC was suggested. In addition, the tumor grew rapidly and its progression required immediate control. Therefore, we selected a combination of ICI plus TKI therapy with nivolumab plus cabozantinib.

There have been several reports on achieving pCR with ICI combination therapy for RCC with IVC thrombus, such as iplimumab plus nivolumab (9-11), pembrolizumab plus axitinib (12), and avelumab plus axitinib (13). To our knowledge, this



Figure 2. Contrast-enhanced computed tomography (CT) showing shrinkage of the primary tumor and downstaging of the inferior vena cava IVC tumor thrombus: At pretreatment (A, B), after 10 cycles of immune checkpoint inhibitors (ICI) therapy (C, D), and after 15 cycles of combination therapy with nivolumab plus cabozantinib (E, F).

is the first case in which a combination of nivolumab and cabozantinib as presurgical therapy resulted in pCR.

In a recent review article, Topalian et al. (14). reported the presence of tumor-specific CD8+ T cells and TLS in pretreatment specimens as factors associated with the efficacy of neoadjuvant ICI therapy. In particular, CD20⁺ B cells were associated with survival and immunotherapy response. The prognostic significance of tumor-infiltrating CD20⁺ B cells was generally concordant with that of CD3⁺ and/or CD8⁺ T cells, and the prognostic effect of T cells was generally stronger when tumor-infiltrating CD20⁺ B cells were also present (15-17). Our results suggested that nivolumab promotes the immune activity of CD20⁺ B cells by stimulating CD4⁺ T cells and forming TLS or directly blocking PD-1 expression on CD20⁺ B cells, and the increased CD20⁺ B cells contribute to nivolumab response together with CD8⁺ cells. We also previously reported a similar case of achieving pCR in a patient treated with presurgical pembrolizumab for chemoresistant upper urinary tract urothelial carcinoma (18). In contrast, cabozantinib has been shown to enhance anti-tumor T cell immunity by increasing T cell infiltration into the tumor bed. Furthermore, tumor antigens released from necrotic tumor tissue by cabozantinib may trigger increased tumor antigen presentation and recognition by CD8⁺ T cells, leading to enhanced immune response (19).

The limitation of this single case report is that a conclusion cannot be drawn on the response of RCC with IVC thrombus to nivolumab plus cabozantinib, based on a single patient. While the shrinkage of tumor thrombus allowed the patient to undergo less invasive surgery without any perioperative complications via ICI combination therapy, we must always keep in mind the risk of pulmonary embolism or the risk of disease progression (20). Furthermore, nivolumab plus cabozantinib could cause severe adverse events (AEs) caused by TKIs or immune related AEs, therefore careful monitoring until surgery is required (7). In addition, the histological subtype, such as clear cell or non-clear cell RCC, could not be confirmed in this patient because the surgical specimen showed no viable cells. Nevertheless, we believe that the information presented herein will contribute further insight into new therapeutic methods, including the neoadjuvant setting of combined immunotherapy, for RCC patients with IVC thrombus.



Figure 3. Gross examination showing the left kidney and tumor thrombus protruding from the left renal vein (yellow arrow) (A). Hematoxylin and eosin (H&E) staining showing extended necrosis and infiltration of foamy histiocytes without viable cells in the surgical specimen (B) (×100 magnification) and the tips of the tumor thrombus (C) (×40 magnification).



Figure 4. Hematoxylin and eosin (H&E) staining (\times 200 magnification) (A), CD4 (B), CD8 (C), and CD20 (D) staining of the biopsy specimen. H&E staining (\times 100 magnification) (E), CD4 (F), CD8 (G), CD20 (H) staining of the surgical specimen. CD20 was not found in the biopsy specimen but was present in the surgical specimen.

In conclusion, we showed that nephrectomy could be safely performed in an RCC patient with IVC thrombus after presurgical nivolumab plus cabozantinib therapy, resulting in pCR. CD20⁺ lymphocyte infiltration after nivolumab plus cabozantinib treatment suggests the efficacy of immunotherapy, as assessed *via* immunohistochemistry. Presurgical nivolumab plus cabozantinib therapy may be a curative treatment option for RCC with IVC thrombus in selected patients.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Arisa Machida: Conceptualization, data curation, writing-original writing-reviewing, and editing. draft. Daiki Ikarashi: Conceptualization, data curation, supervision, writing-reviewing, and editing. Naoki Yanagawa: Visualization. Masamichi Suzuki: Visualization, Tatsuya Kawamura: Data curation, investigation. Kie Sekiguchi: Data curation. Kenta Takahashi: Data curation. Renpei Kato: Data curation. Tomohiko Matsuura: Data curation. Shigekatsu Maekawa: Data curation. Mitsugu Kanehira: Data curation, writingreviewing, and editing. Ryo Takata: Supervision. Tamotsu Sugai: Supervision. Wataru Obara: Supervision, writing-reviewing, and editing. All Authors read and approved the final version of the manuscript.

Acknowledgements

The Authors thank the patient for allowing the publication of this case report.

References

- Hirono M, Kobayashi M, Tsushima T, Obara W, Shinohara N, Ito K, Eto M, Takayama T, Fujii Y, Nishikido M, Kimura G, Kishida T, Takahashi M, Miyao N, Naya Y, Abe T, Fujioka T, Ito K, Naito S and Members of the Japanese Society of Renal Cancer: Impacts of clinicopathologic and operative factors on short-term and long-term survival in renal cell carcinoma with venous tumor thrombus extension: a multi-institutional retrospective study in Japan. BMC Cancer *13*: 447, 2013. PMID: 24083566. DOI: 10.1186/1471-2407-13-447
- 2 Tanaka Y, Hatakeyama S, Hosogoe S, Tanaka T, Hamano I, Kusaka A, Iwamura H, Fujita N, Yamamoto H, Tobisawa Y, Yoneyama T, Yoneyama T, Hashimoto Y, Koie T and Ohyama C: Presurgical axitinib therapy increases fibrotic reactions within tumor thrombus in renal cell carcinoma with thrombus extending to the inferior vena cava. Int J Clin Oncol 23(1): 134-141, 2018. PMID: 28752352. DOI: 10.1007/s10147-017-1169-z
- 3 Yoshida K, Hata K, Iizuka J, Kondo T, Ishihara H, Ishida H, Nagashima Y, Tanabe K and Takagi T: Immune checkpoint inhibitor combination therapy for renal cell carcinomas with concomitant inferior vena cava thrombi. In Vivo 36(2): 1030-1034, 2022. PMID: 35241567. DOI: 10.21873/invivo.12798

- 4 Rini BI, Battle D, Figlin RA, George DJ, Hammers H, Hutson T, Jonasch E, Joseph RW, McDermott DF, Motzer RJ, Pal SK, Pantuck AJ, Quinn DI, Seery V, Voss MH, Wood CG, Wood LS and Atkins MB: The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC). J Immunother Cancer 7(1): 354, 2019. PMID: 31856918. DOI: 10.1186/s40425-019-0813-8
- 5 Yoshida K, Hata K, Iizuka J, Kondo T, Ishihara H, Ishida H, Nagashima Y, Tanabe K and Takagi T: Immune checkpoint inhibitor combination therapy for renal cell carcinomas with concomitant inferior vena cava thrombi. In Vivo 36(2): 1030-1034, 2022. PMID: 35241567. DOI: 10.21873/invivo.12798
- 6 Neves RJ and Zincke H: Surgical treatment of renal cancer with vena cava extension. Br J Urol 59(5): 390-395, 1987. PMID: 3594097. DOI: 10.1111/j.1464-410x.1987.tb04832.x
- 7 Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, Oyervides Juárez VM, Hsieh JJ, Basso U, Shah AY, Suárez C, Hamzaj A, Goh JC, Barrios C, Richardet M, Porta C, Kowalyszyn R, Feregrino JP, Żołnierek J, Pook D, Kessler ER, Tomita Y, Mizuno R, Bedke J, Zhang J, Maurer MA, Simsek B, Ejzykowicz F, Schwab GM, Apolo AB, Motzer RJ and CheckMate 9ER Investigators: Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med *384(9)*: 829-841, 2021. PMID: 33657295. DOI: 10.1056/NEJMoa2026982
- 8 Lee CH, Voss MH, Carlo MI, Chen YB, Zucker M, Knezevic A, Lefkowitz RA, Shapnik N, Dadoun C, Reznik E, Shah NJ, Owens CN, McHugh DJ, Aggen DH, Laccetti AL, Kotecha R, Feldman DR and Motzer RJ: Phase II trial of cabozantinib plus nivolumab in patients with non-clear-cell renal cell carcinoma and genomic correlates. J Clin Oncol 40(21): 2333-2341, 2022. PMID: 35298296. DOI: 10.1200/JCO.21.01944
- 9 Okada T, Hamamoto S, Etani T, Naiki T, Sue Y, Banno R, Yamada K, Sakakura T and Yasui T: Complete response of renal cell carcinoma with an inferior vena cava tumor thrombus and lung metastases after treatment with nivolumab plus ipilimumab. Int Cancer Conf J 9(2): 88-91, 2020. PMID: 32257760. DOI: 10.1007/s13691-020-00403-9
- 10 Labbate C, Hatogai K, Werntz R, Stadler WM, Steinberg GD, Eggener S and Sweis RF: Complete response of renal cell carcinoma vena cava tumor thrombus to neoadjuvant immunotherapy. J Immunother Cancer 7(1): 66, 2019. PMID: 30857555. DOI: 10.1186/s40425-019-0546-8
- 11 Studentova H, Zemankova A, Spisarova M, Skanderova D, Tudos Z, Melichar B and Student V Jr: A pathological complete response to the combination of ipilimumab and nivolumab in a patient with metastatic renal cell carcinoma. Medicina (Kaunas) 58(3): 336, 2022. PMID: 35334512. DOI: 10.3390/medicina58030336
- 12 Tucker MD, Beckermann KE, Gordetsky JB, Giannico GA, Davis NB and Rini BI: Complete pathologic responses with immunotherapy in metastatic renal cell carcinoma: case reports. Front Oncol 10: 609235, 2020. PMID: 33415079. DOI: 10.3389/fonc.2020.609235
- 13 Hara T, Terakawa T, Hyodo T, Jinbo N, Nakano Y and Fujisawa M: Pathological complete response of renal cell carcinoma with vena cava tumor thrombus to neoadjuvant TKI/IO combination therapy. Urol Case Rep 39: 101800, 2021. PMID: 34430210. DOI: 10.1016/j.eucr.2021.101800
- 14 Topalian SL, Taube JM and Pardoll DM: Neoadjuvant checkpoint blockade for cancer immunotherapy. Science 367(6477): eaax0182, 2020. PMID: 32001626. DOI: 10.1126/science.aax0182

- 15 Helmink BA, Reddy SM, Gao J, Zhang S, Basar R, Thakur R, Yizhak K, Sade-Feldman M, Blando J, Han G, Gopalakrishnan V, Xi Y, Zhao H, Amaria RN, Tawbi HA, Cogdill AP, Liu W, LeBleu VS, Kugeratski FG, Patel S, Davies MA, Hwu P, Lee JE, Gershenwald JE, Lucci A, Arora R, Woodman S, Keung EZ, Gaudreau PO, Reuben A, Spencer CN, Burton EM, Haydu LE, Lazar AJ, Zapassodi R, Hudgens CW, Ledesma DA, Ong S, Bailey M, Warren S, Rao D, Krijgsman O, Rozeman EA, Peeper D, Blank CU, Schumacher TN, Butterfield LH, Zelazowska MA, McBride KM, Kalluri R, Allison J, Petitprez F, Fridman WH, Sautès-Fridman C, Hacohen N, Rezvani K, Sharma P, Tetzlaff MT, Wang L and Wargo JA: B cells and tertiary lymphoid structures promote immunotherapy response. Nature *577(7791)*: 549-555, 2020. PMID: 31942075. DOI: 10.1038/s41586-019-1922-8
- 16 Petitprez F, de Reyniès A, Keung EZ, Chen TW, Sun CM, Calderaro J, Jeng YM, Hsiao LP, Lacroix L, Bougoüin A, Moreira M, Lacroix G, Natario I, Adam J, Lucchesi C, Laizet YH, Toulmonde M, Burgess MA, Bolejack V, Reinke D, Wani KM, Wang WL, Lazar AJ, Roland CL, Wargo JA, Italiano A, Sautès-Fridman C, Tawbi HA and Fridman WH: B cells are associated with survival and immunotherapy response in sarcoma. Nature 577(7791): 556-560, 2020. PMID: 31942077. DOI: 10.1038/s41586-019-1906-8
- 17 Cabrita R, Lauss M, Sanna A, Donia M, Skaarup Larsen M, Mitra S, Johansson I, Phung B, Harbst K, Vallon-Christersson J, van Schoiack A, Lövgren K, Warren S, Jirström K, Olsson H, Pietras K, Ingvar C, Isaksson K, Schadendorf D, Schmidt H, Bastholt L, Carneiro A, Wargo JA, Svane IM and Jönsson G: Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature *577(7791)*: 561-565, 2020. PMID: 31942071. DOI: 10.1038/s41586-019-1914-8

- 18 Ikarashi D, Kitano S, Ishida K, Nakatsura T, Shimodate H, Tsuyukubo T, Tamura D, Kato R, Sugai T and Obara W: Complete pathological response to neoadjuvant pembrolizumab in a patient with chemoresistant upper urinary tract urothelial carcinoma: a case report. Front Oncol *10*: 564714, 2020. PMID: 33072593. DOI: 10.3389/fonc.2020.564714
- 19 Liu H, Sun S, Wang G, Lu M, Zhang X, Wei X, Gao X, Huang C, Li Z, Zheng J and Zhang Q: Tyrosine kinase inhibitor cabozantinib inhibits murine renal cancer by activating innate and adaptive immunity. Front Oncol *11*: 663517, 2021. PMID: 33954115. DOI: 10.3389/fonc.2021.663517
- 20 Manoharan A, Lugo-Baruqui A and Ciancio G: Radical nephrectomy and pulmonary lobectomy for renal cell carcinoma with tumor thrombus extension into the inferior vena cava and pulmonary arteries. Anticancer Res 40(10): 5837-5844, 2020. PMID: 32988913. DOI: 10.21873/anticanres.14602

Received August 24, 2022 Revised September 22, 2022 Accepted September 26, 2022