Case Series

Presurgical immune-oncology/tyrosine kinase inhibitor combination therapy for renal cell carcinoma with a vena cava tumor thrombus: a single-institution case series

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Background: Although current guidelines recommend administering adjuvant immunotherapy following resection of advanced primary renal cell carcinoma (RCC), the clinical benefit of presurgical immunotherapy for patients with RCC remains uncertain.

Case Description: We conducted a retrospective analysis of five patients diagnosed with RCC who developed inferior vena cava (IVC) tumor thrombus and were treated with radical nephrectomy following combined immunotherapy with a tyrosine kinase inhibitor. The median follow-up after nephrectomy was 23 months (range, 19–30 months). In all cases, the size of the IVC tumor thrombus decreased, and three of the cases demonstrated a decrease in the tumor thrombus level. Surgical margins were negative in all cases, and none of the patients experienced any major intraoperative complications. However, adhesions were encountered at the operative sites during surgery in all cases. One patient required a lymphatic intervention due to abdominal lymphatic leakage (Clavien IIIa) within 90 days after operation. Our case series demonstrated a median progression-free survival (PFS) of 11 months [95% confidence interval (CI)]: 5.5–22.5 months). No patient died during the follow-up period.

Conclusions: Presurgical therapy combined with immunotherapy and tyrosine kinase inhibitors warrants consideration. Nevertheless, surgeons should be mindful of the difficulties that may arise beyond the clinical stage.

Keywords: Presurgical therapy; renal cell carcinoma (RCC); combined immunotherapy with a tyrosine kinase inhibitor; case series

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Introduction

Current guidelines recommend administering adjuvant immunotherapy following resection of primary renal cell carcinoma (RCC) (1). However, no consensus exists regarding presurgical immunotherapy. In this case series, we present cases of RCC that developed an inferior vena cava (IVC) tumor thrombus (ITT) and discuss the potential role of presurgical immune-oncology/tyrosine kinase inhibitor (IO/TKI) therapy for these cases. We present this article in accordance with PROCESS (2) and AME Case Series reporting checklists (available at https://tau.amegroups.com/article/view/10.21037/tau-23-203/rc).

Case presentation

Patients were eligible for inclusion if they had RCC with ITT and underwent radical nephrectomy. We retrospectively reviewed the cases of five patients who received IO/TKI combination therapy as presurgical therapy. All patients underwent nephrectomy at The Jikei University Hospital (Tokyo, Japan) between August 2020 and July 2021. As treatment regimens, a combination of pembrolizumab (120 mg every 3 weeks) and axitinib (5 mg twice daily) was selected in 4 cases, while a combination of avelumab (10 mg per kilogram of body weight every 2 weeks) and axitinib (5 mg twice daily) was chosen in one case. The regimens and cycles were determined at the discretion of the treating physicians. To assess tumor and thrombus volume, the calculation of major axis multiplied by minor axis and height was performed using CT images. Postoperative complications were evaluated using the Clavien-Dindo classification scale. Progression-free survival (PFS) was defined as the time from the nephrectomy to disease progression or death. Treatment-free survival (TFS) was defined as the time from the nephrectomy to the first dose of subsequent systemic therapy or death. The clinical characteristics of the patients are shown in *Table 1*.

Highlight box

Key findings

- In the era of immune-oncological drugs, radical nephrectomy following presurgical therapy of combined immunotherapy with a tyrosine kinase inhibitor may be a useful therapeutic strategy for managing renal cell carcinoma with an inferior vena cava thrombus.

What is known and what is new?

- Current guidelines recommend administering adjuvant immunotherapy following resection of primary renal cell carcinoma.
- Nephrectomy following presurgical combined immunotherapy with a tyrosine kinase inhibitor could provide patients with a favorable oncological outcome and the opportunity to avoid systemic treatment.

What is the implication, and what should change now?

- A larger sample size and longer follow-up period are needed to determine the feasibility of presurgical IO/TKI combination therapy.

Responses and patient outcomes

The changes in the size of the primary tumor (PT) and ITT from pre-IO/TKI imaging to surgery are summarized in *Figure 1*, Figure S1, and Table S1. Pathological assessments of each case are provided in *Table 2*. Four cases were of clear cell histology, while one case was papillary type II. Two cases had multiple lung metastases, and they achieved a complete response before surgery. During the neoadjuvant IO/TKI therapy, all patients received the IO drugs at the recommended dosage. However, in the cases of adverse events, the oral administration of axitinib was adjusted to 1 mg twice daily (case 4), 2 mg twice daily (case 5), and 3 mg twice daily (case 6). Four patients underwent open radical nephrectomy with thrombectomy, and one patient underwent laparoscopic radical nephrectomy (LRNx) due to downstaging from cT3b to cT3a (case 2). In case 5, a level IV ITT shrank to level III, thus avoiding the need for an open sternotomy (Figure S1). The median operating time and estimated blood loss were 431 min and 3,100 mL, respectively (Table S2). Surgeons reported the presence of fibrosis and inflammatory changes at the surgical sites in all cases. The percentage of residual viable tumor cells in the ITT and primary RCC after presurgical therapy varied among the cases (*Table 2*). No major intraoperative complications were reported. One patient required a lymphatic intervention due to abdominal lymphatic leakage (Clavien IIIa) within 90 days after operation. The median total length of stay and follow-up was 10 and 691 days, respectively. The PFS curve was estimated using the Kaplan-Meier method (*Figure 2*). Our case series demonstrated a median PFS of 11 months (95% CI: 5.5–22.5 months). Excluding one patient who received IO within 1 month after surgery at the discretion of his physician, the median TFS was 10 months (95% CI: 5.8–18.7 months). No patient died during the follow-up period.

All procedures performed in this study were in

Table 1 Baseline clinical data of patients

Case	Age (y)	Gender	BMI (kg/m^2)	KPS	Laterality	cT stage	cN stage	Metastatic sites	Tumor thrombus (level per Mayo classification)	Regimen [No. cycles]	No. of days between IO and surgery	Any AE (≥ G2) prior to surgery
1	51	Male	22.5	0	Left	cT3b	cN0	Lung (multiple)	1	Pem [6] + Axitinib	33	None
2	71	Male	20.7	0	Right	cT3b	cN0	Lung (multiple)	1	Pem [4] + Axitinib	36	None
3	70	Male	27.9	0	Left	cT3b	cN2	None	2	Ave [20] + Axitinib	36	HFS (G2)
4	79	Male	22.7	0	Left	cT3b	cN1	None	1	Pem [3] + Axitinib	29	Constipation (G2)
5	72	Female	28.2	0	Right	cT3c	cN0	None	4	Pem [6] + Axitinib	24	Fatigue (G2)

y, years; BMI, body mass index; KPS, Karnofsky Performance Status; IO, immune-oncology therapy; AE, adverse event; Pem, pembrolizumab; HFS, hand-foot syndrome.

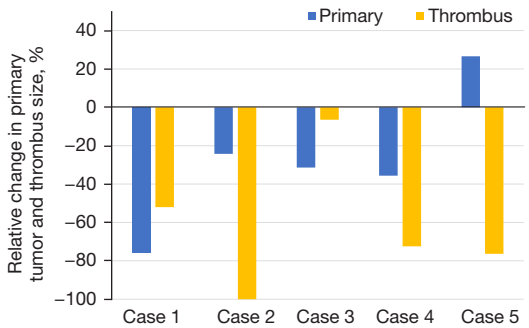

Figure 1 Relative change in primary tumor and thrombus size from pre-immunotherapy imaging to surgery.

accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). This study was approved by the Institutional Review Board of The Jikei University School of Medicine [No. 33-260(10878)]. Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This investigation was a case series carried out at a single institution, focusing on patients with ≥ cT3b RCC who were treated with presurgical combination therapy of IO/TKI and underwent nephrectomy. Presurgical therapy has been employed in various cancer types to reduce tumor size and improve surgical morbidity. Presurgical therapy has gained attention for its potential to reduce thrombus size and surgical risk in patients with RCC and ITT. Several reports have demonstrated the effectiveness of presurgical IO/TKI combination therapy for RCC with ITT (3-6). In previous case reports, presurgical IO/TKI combination therapy has resulted in the downstaging of ITT. In our case series, we observed a reduction in the volume of ITT in all cases, with 60% of cases (n=3/5) experiencing downstaging at the ITT level. One case was downstaged to cT3a, allowing for LRNx to be performed, and open sternotomy was avoided in another case.

Labbate *et al.* (7) reported on the differences in viable cells between PT and ITT. Similarly, we observed a difference in the percentage of viable tumor cells between PT and ITT in our study. This difference was attributed to the heterogeneity of the tumor microenvironment. Notably, Kim *et al.* (8) reported that clonal evolution contributes to genomic diversity between PT and ITT, which could explain why the relative change in the size of the PT and ITT is not always consistent.

Pignot *et al.* (9) reported that surgeons face difficulties finding dissection planes, due to fibrosis in the kidney and surrounding tissues. Graafland *et al.* (10) also reported on surgical complexity resulting from adhesions in 71% of cases, including 38% with major difficulties. In our cases, the surgeons reported fibrosis and inflammatory changes during the surgeries in all cases. One patient experienced lymphorrhea (Clavien IIIa), highlighting the potential

Table 2 Pathological findings on surgical specimens

Case	Histology	Primary tumor size (mm)	Grade	pT stage	pN stage	Tumor thrombus (level per Mayo classification)	Surgical margin	Viable tumor cells in IVC thrombus (%)	Viable tumor cells in primary RCC (%)
1	Clear cell	55×55×51	3	pT3b	pN0	1	Negative	5	0
2	Clear cell	110×110×90	3	pT3a	pN0	0	Negative	5	20
3	Papillary type II	70×50×30	3	pT3b	pNx	2	Negative	70	60
4	Clear cell	55×46×43	2	pT3b	pN0	1	Negative	80	70
5	Clear cell	53×43×35	2	pT3b	pNx	3	Negative	0	0

Size: height × major axis × minor axis. IVC, inferior vena cava; RCC, renal cell carcinoma.

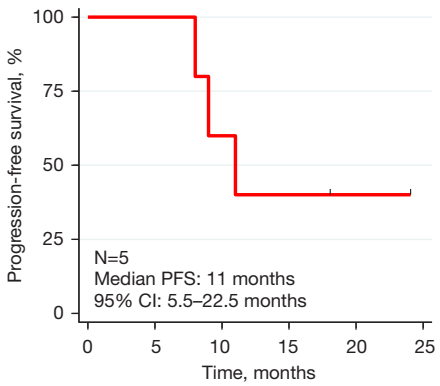

Figure 2 Kaplan-Meier curves of PFS. PFS, progression-free survival.

risks of the surgery beyond the clinical stage. Nevertheless, downstaging the thrombus level reduced the invasiveness of the surgery, and there was still the risk of dislodgement and pulmonary embolism after IO/TKI combination therapy. Furthermore, patients received a drug-free period after the surgery. Thus, radical nephrectomy following presurgical IO/TKI therapy for RCC with ITT should be considered.

The primary limitations of our study are its retrospective design and the small sample size derived from a single institution. Furthermore, we did not juxtapose the outcomes with those of neoadjuvant TKI treatments. In a recent publication, Klatte *et al.* (11) proposed a possible role for neoadjuvant TKI treatment in the management of RCC patients with ITT, whereas IO/TKI is a more modern systemic approach to RCC management. Thus, an imperative requirement exists for a prospective randomized trial to substantiate the survival benefits associated with neoadjuvant IO/TKI treatments for RCC patients with ITT.

Conclusions

We reviewed five patients with RCC and ITT who received IO/TKI combination therapy as presurgical therapy. Despite the potential challenges of the surgery, this approach could provide patients with favorable oncological outcomes and the opportunity to avoid systemic treatment. A larger sample size and longer follow-up period are needed to determine the feasibility of presurgical IO/TKI combination therapy.

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Footnote

Reporting Checklist: The authors have completed the PROCESS and AME Case Series reporting checklists. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-203/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-203/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-203/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). This study was approved by the Institutional Review Board of The Jikei University School of Medicine [No. 33-260(10878)]. Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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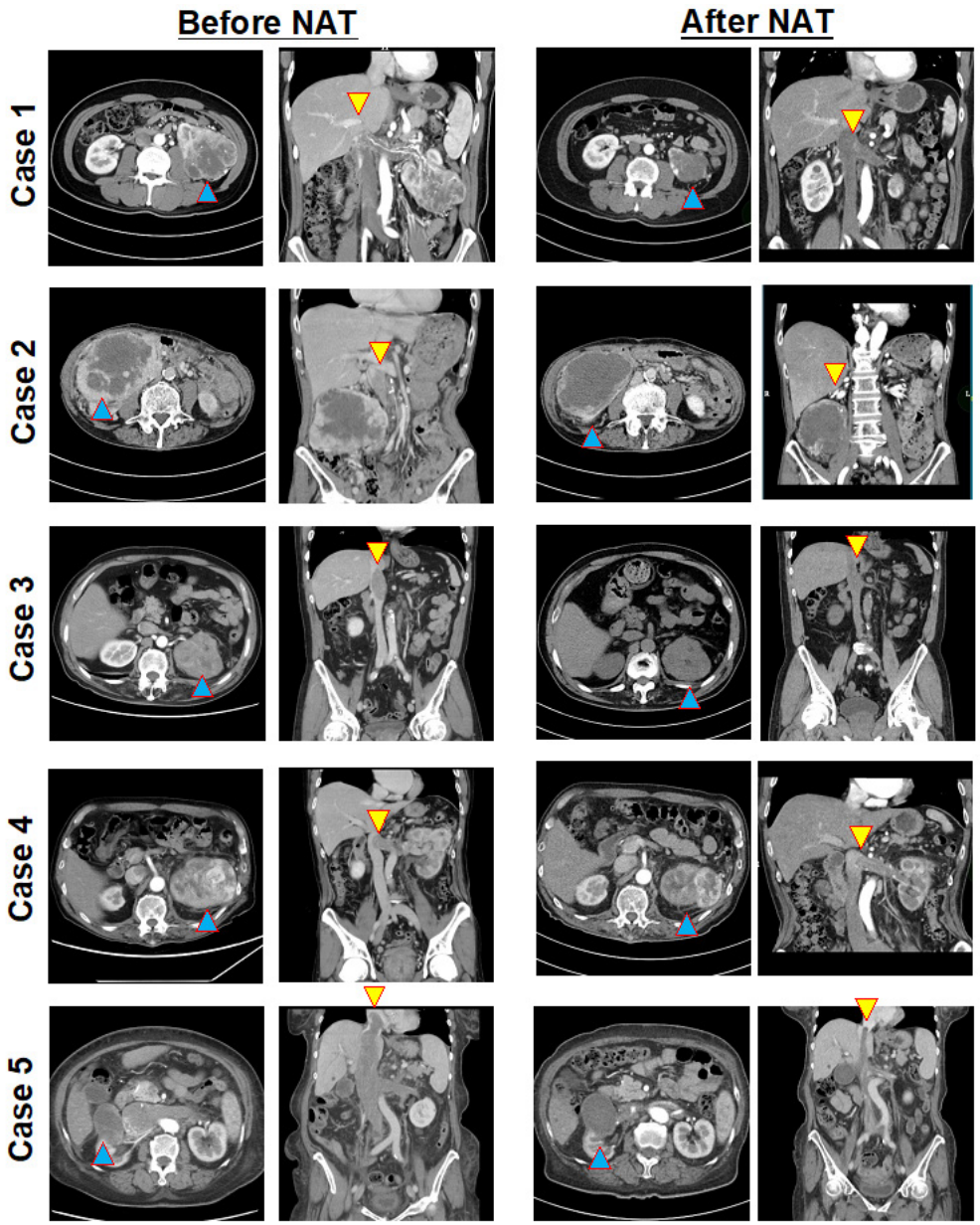

Figure S1 Axial and coronal images of the primary tumor and tumor thrombus pre- and post-NAT. Blue arrows indicate the primary tumor. Yellow arrows indicate the tips of the tumor thrombus. NAT, neoadjuvant therapy.

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Table S1 Tumor sizes before and after neoadjuvant IO/TKI evaluated by CT images

Case	Before neoadjuvant IO/TKI		After neoadjuvant IO/TKI	
	ITT size	PT size	ITT size	PT size
1	30×29×25	84×82×82	10.5×34×29.5	54.5×50.5×49.5
2	28×19×15	131×100×94	0	116×96×83
3	60×28×21	82×90×76.5	77×25.5×17	75×79×66
4	32×35×23	68×63×56	19×22×17	60×56.5×46
5	215×51×50	58×46×40	139×36×26	59×48×48

Size: height × major axis × minor axis (mm). IO/TKI, immune-oncology/tyrosine kinase inhibitor; CT, computed tomography; ITT, inferior vena cava tumor thrombus; PT, primary tumor.

Table S2 Feasibility and safety assessed by peri- and post-operative outcomes

Case	Procedure	OT (min)	EBL (mL)	LOS (days)	Detail of complications	Recurrence site	Time to last follow-up from surgery (days)
1	ORNx	431	4,380	9	None	Lung	891
2	LRNx	259	90	9	None	None	742
3	ORNx	460	3,100	10	None	Para aorta LN	691
4	ORNx	332	1,060	14	None	None	570
5	ORNx	687	8,590	56	Lymphorrhea	Bone	633

OT, operation time; EBL, estimated blood loss; LOS, length of stay; ORNx, open radical nephrectomy; LRNx, laparoscopic radical nephrectomy; LN, lymph node.

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