

Clinical and histopathological effects of presurgical treatment with sunitinib for renal cell carcinoma with inferior vena cava tumor thrombus at a single institution

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To evaluate the clinical and histopathological effects of presurgical treatment with sunitinib on inferior vena cava (IVC) tumor thrombus. Between 2010 and 2014, we treated seven patients with renal cell carcinoma and IVC tumor thrombus presurgically with sunitinib. We retrospectively evaluated primitive tumor size, the level of tumor thrombus according to Novick's classification, its distance above the renal vein, thrombus diameter at its widest segment, and histopathological change after sunitinib treatment. Three patients were diagnosed histologically. Percutaneous biopsy of the renal mass before sunitinib treatment was performed in two patients. One patient was diagnosed after sunitinib treatment following nephrectomy. The primitive tumors shrank upon sunitinib therapy in four cases; however, although the caval thrombus was downstaged (from level II to I) in one patient, the level of caval thrombus did not change in five patients and increased in one patient (from level III to IV). We evaluated the histopathological effects in two patients. In one patient, the IVC tumor thrombus was mostly replaced with necrotic tissue, but its thrombus level was not downstaged. In the other patient,

the IVC tumor thrombus was downstaged, but tumor thrombus was not replaced with necrotic tissue and viable tumor cells remained. Presurgical treatment with sunitinib for renal cell carcinoma with IVC tumor thrombus appears to have limited effect on IVC tumor thrombus, in contrast to its effects on primitive tumor shrinkage. In the absence of evidence of presurgical benefits from prospective studies, this treatment may not be systematically advisable. *Anti-Cancer Drugs* 27:1038–1043 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Renal cell carcinoma (RCC) is the 11th most common malignancy in men and the 17th most common malignancy in women in Japan [1]. RCC has the ability to invade the renal vein and/or inferior vena cava (IVC) and venous tumor invasion has been reported in 10% of patients with RCC [2,3].

In this situation, a radical nephrectomy with concomitant IVC thrombectomy is performed, with surgery often requiring cardiac arrest with extracorporeal circulation for better surgical control. This procedure is associated with high mortality and morbidity, and complication rates increase with upward extension of tumor thrombus [4].

The emergence of molecular-targeted therapies has improved the prognosis of patients with metastatic RCC. From a surgical perspective, these advances offer the potential to shrink the tumor and minimize tumor thrombus, thus permitting easier surgical resection. In

addition, presurgical treatment is appealing because it may allow early treatment of occult micrometastatic disease, potentially improving the curative potential of surgical resection.

In the current literature, only a few case reports have described the effect of presurgical molecular-targeted therapies on tumor thrombus. The aim of our study was to evaluate the effect of presurgical treatment with sunitinib in decreasing the extent of IVC tumor thrombus on clinical results and histopathological therapeutic effects.

Patients and methods

We treated seven patients with RCC and tumor thrombus of the IVC presurgically with sunitinib in Osaka University Hospital between 2010 and 2014. The decision to perform presurgical treatment with sunitinib was made on an individual basis and was not prospectively specified.

The following clinical data were collected retrospectively from the medical records at Osaka University Hospital: age at diagnosis, sex, Eastern Cooperative Oncology

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Group Performance Status, and 2010 TNM stage [5]. We retrospectively evaluated primitive tumor size (cm), the level of tumor thrombus according to Novick's classification [6], its distance (cm) above the renal vein, and thrombus diameter (cm) at its widest segment. The objective clinical response for primitive tumor and overall disease was assessed according to RECIST [7] using computed tomography or MRI at baseline screening and after every cycle of sunitinib treatment. We planned to continue sunitinib treatment for up to four cycles until there was either disease progression or unacceptable toxicity. We believed that at least three cycles were needed as presurgical treatment. If we observed no therapeutically significant effects (as assessed by image evaluation) after all four cycles of sunitinib treatment for a given patient, we pursued an alternative treatment strategy for that patient. In addition to these clinical results, we assessed histopathological therapeutic effects after sunitinib treatment.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. There were six male patients and one female patient. The median age of the patients at diagnosis was 66 years (range: 57–75 years). All patients had symptomatic disease and the median Eastern Cooperative Oncology Group Performance Status was 2 (range: 1–2). Three of seven patients were diagnosed histologically. Percutaneous biopsy of the renal mass before sunitinib treatment was performed in two patients (patients 2 and 5) and showed that these renal masses were clear cell RCC. One patient (patient 1) was diagnosed with papillary RCC after sunitinib treatment following nephrectomy. The other cases (patients 3, 4, 6 and 7) were histologically uncharacterized.

The thrombus level was staged I in one patient, II in two patients, III in one patient, and IV in three patients. Two patients (patients 1 and 2) underwent radical nephrectomy and tumor thrombectomy after presurgical treatment with sunitinib. The median duration of sunitinib treatment was one cycle (range: 1–4 cycles). We ended sunitinib treatment for four patients after one cycle. Of these four patients, two patients (patients 1 and 3) experienced major adverse effects (serum lipase elevation and liver dysfunction), one patient (patient 5) died suddenly of a

brain hemorrhage, and one patient (patient 4) did not show a significant response. Three patients underwent sunitinib treatment for at least three cycles. Patient 2 underwent radical nephrectomy after three cycles of sunitinib treatment. Patients 6 and 7 did not show a significant response upon four cycles of sunitinib for IVC tumor thrombus, and thus we changed our presurgical treatment of these patients from sunitinib to axitinib.

Clinical results

The effects of presurgical sunitinib treatment are outlined in Tables 2 and 3. The primitive tumors shrank upon sunitinib therapy in four cases (patients 4–7); tumor thrombus distance above the renal vein was decreased, stable, and increased in three, two, and two patients, respectively. However, the caval thrombus was downstaged (from level II to I) in only one patient (patient 2). The level of caval thrombus did not change in five patients and increased in one patient (from level III to IV). Two patients underwent radical nephrectomy concomitant with IVC thrombectomy. One patient showed a decreased level of tumor thrombus and achieved the treatment objectives of presurgical sunitinib therapy, but the other patient did not experience these improvements as such. According to the RECIST criteria, the overall tumor response included one (14%) patient with partial response, five (72%) with stable disease, and one (14%) with disease progression.

Histopathological effects

We could examine the histology of the primitive tumor and tumor thrombus in three patients (patients 1, 2, and 5). Because papillary RCC generally tends to form necrotic tissue, making it difficult to assess the pathological therapeutic effects of presurgical treatment in these cases, we excluded patient 1 from this study. We evaluated the therapeutic effects in two patients (patients 2 and 5) diagnosed with clear cell carcinoma.

Patient 2 underwent radical nephrectomy concomitant with IVC thrombectomy. In this patient, preoperative computed tomography showed that IVC tumor thrombus level was downstaged (from level II to I). Pathological findings showed that the renal vein was full of viable tumor cells. However, the primitive renal tumor was almost completely replaced with necrotic tissue (Fig. 1).

Table 1 Patient characteristics

Patient numbers	Sex	Age (years)	ECOG PS	Side of tumor	cTNM	IVC tumor thrombus level	Cycles of presurgical treatment
1	Male	60	1	Right	T3bN2M0	II	1
2	Female	72	1	Right	T3bNOM1	II	3
3	Female	57	2	Right	T3bNOM1	I	1
4	Male	66	2	Right	T3bNOM0	III	1
5	Male	66	2	Right	T3cNOM0	IV	1
6	Male	72	2	Left	T3cNOM0	IV	4
7	Male	75	1	Right	T3cNOM1	IV	4

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IVC, inferior vena cava.

Table 2 Summary of the efficacy of preoperative treatment with sunitinib

	n (%)
Primitive tumor size	
Increase	0 (0)
Stable	3 (43)
Decrease	4 (57)
Thrombus size	
Increase	3 (43)
Stable	3 (43)
Decrease	1 (14)
Thrombus level	
Increase	1 (14)
Stable	5 (72)
Decrease	1 (14)

Patient 5 was diagnosed with clear cell RCC by percutaneous renal mass biopsy. We decided to treat the patient presurgically with sunitinib for the purpose of IVC tumor thrombus downsizing. After one cycle of sunitinib therapy, computed tomographic scan showed that the primitive tumor shrank, although the level of IVC tumor thrombus did not change in terms of size. Contrast enhancement level was reduced in primitive renal tumor and IVC thrombus, and it was suggested that this reduction was because of replacement of the tumor thrombus by necrotic tissue (Fig. 2). This patient died suddenly of a brain hemorrhage after one cycle treatment, and after his death, an autopsy was conducted, which indicated no evidence of brain metastasis. Histologically, the IVC tumor thrombus was mostly replaced with necrotic tissue, but histopathological analysis of the primitive tumor showed that viable tumor cells remained (Fig. 1).

These results are summarized in Table 4. These cases suggested that even if pretreatment with sunitinib has a remarkable histopathological effect on IVC tumor thrombus, its effects did not enable downstaging of IVC thrombus according to Novick's classification.

Discussion

The only potential cure in patients with locally advanced RCC, including RCC with a venous tumor thrombus, is complete resection. Invasion of RCC into the renal vein and/or IVC occurs in 4–15% of RCC cases. Radical nephrectomy with concomitant IVC thrombectomy is associated with high mortality (5–15%) and high

morbidity (35–70%) [8,9], and complication rates increase with upward extension of tumor thrombus [4].

The emergence of targeted molecular therapies has improved the prognosis of metastatic RCC patients by potentially downsizing primary tumors, but the effect of targeted molecular therapies on IVC tumor thrombus has not yet been fully explored. If targeted molecular therapies can effectively reduce tumor thrombus enough to warrant downstaging according to Novick's classification, surgical resection could be performed with much greater efficiency. To investigate this possibility, we performed presurgical treatment with sunitinib on IVC tumor thrombus for seven RCC patients.

However, the results of our study suggest that the effect of presurgical sunitinib on IVC tumor thrombus appears to be limited. Only one patient showed regression of tumor thrombus level (from level II to level I), which did not modify the surgical strategy or reduce the risk of the operation. In addition, one patient's tumor thrombus level increased (from level III to level IV). He could not undergo nephrectomy and is now being treated with a different targeted molecular therapy.

Reports from the international literature have yielded similar results. Cost *et al.* [10] observed a decrease of IVC tumor thrombus in height above the renal vein in 11 (44%) cases and a reduction in the primary masses in 12 (48%) cases. However, downstaging of the thrombus level was achieved in only three (25%) patients. The median decrease in height above the renal vein was 0.28 cm and downstaging in tumor thrombus was achieved in only three (25%) patients. Bigot *et al.* [11] showed similar results in 11 patients from several French academic centers. They observed a reduction in the primary masses in four (37%) cases. However, downstaging of the thrombus level was achieved in only one (9%) patient. They concluded that neoadjuvant molecular-targeted therapy appears to have limited effects on renal tumor thrombus. These results, including those of the present study, are summarized in Table 5.

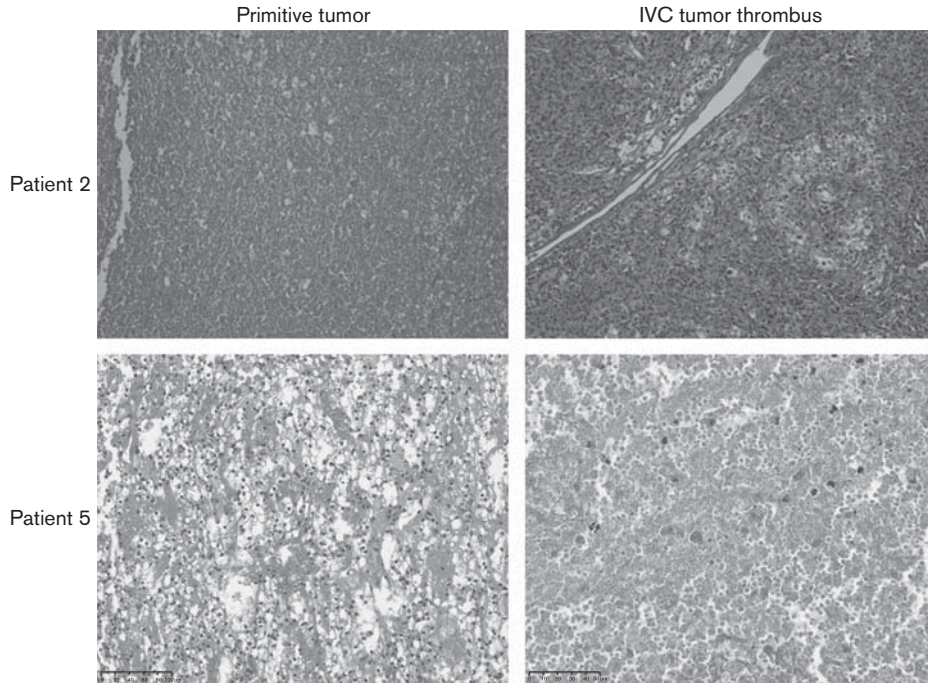
In the present study, we selected sunitinib as a pre-surgical treatment agent. Other studies from around the world have investigated other molecular-targeted agents

Table 3 Efficacy of preoperative treatment with sunitinib for seven cases

Patient numbers	Response on primitive tumor [cm (%)]	Response on tumor thrombus diameter [cm (%)]	Response on tumor thrombus distance above the renal vein [cm (%)]	Tumor thrombus level change	Overall tumor response according to the RECIST criteria	Surgery
1	0 (0)	+1.6 (+47.1)	+1.5 (+30.0)	II→II	PD	Yes
2	0 (0)	0 (0)	-2.5 (-55.6)	II→I	SD	Yes
3	0 (0)	0 (0)	0 (0)	I→I	SD	No
4	-1 (-12.5)	+0.4 (+12.5)	+4.1 (+63.1)	III→IV	SD	No
5	-0.7 (-10.4)	0 (0)	0 (0)	IV→IV	SD	No
6	-2.7 (-30.3)	-0.6 (-13.0)	-0.5 (-3.8)	IV→IV	PR	No
7	-0.8 (-16.0)	+1.8 (+20.8)	-1.0 (-9.5)	IV→IV	SD	No

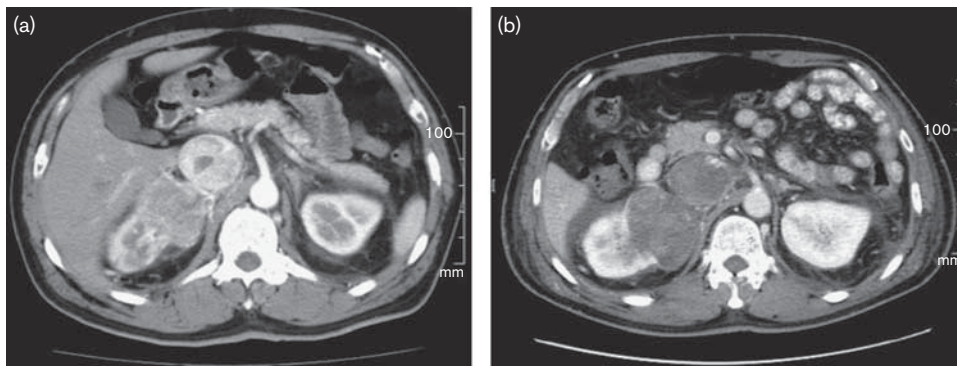
PD, progressive disease; PR, partial response; SD, stable disease.

Fig. 1



This figure shows the microscopic appearance of primitive tumor and IVC tumor thrombus after sunitinib therapy. The two photographs on the left are from primitive tumors and the two photographs on the right are from IVC tumor thrombus. IVC, inferior vena cava.

Fig. 2



Computed tomography comparing pretreatment imaging (a) with post-treatment imaging (b) showed partial necrotic changes in patient 5 without downsizing after treatment with sunitinib.

[12–16], such as sorafenib or temsirolimus; however, these case reports focused only on selected successful cases and present an incomplete view of the evidence. Cost *et al.* [10] evaluated pretreatment therapy using various drugs in 13 patients: nine patients received bevacizumab, three patients received temsirolimus, and one patient received sorafenib. They observed a decrease of IVC tumor thrombus in height above the renal vein in five (38%) cases. However, downstaging of the thrombus level was not achieved in any of the patients. Taken together, our

findings with sunitinib are similar to those of other studies that have used alternative molecular-targeted agents for pretreatment, in that these therapies all seem to show little efficacy in treating tumor thrombus.

The adequate length of presurgical molecular-targeted therapy is controversial. As in the studies of Cost *et al.* [10] and Bigot *et al.* [11], the median duration of therapy in this study was two cycles. These reports suggested that if tumor size is reduced after the first cycle, two

Table 4 Summary of histopathological therapeutic effects of sunitinib therapy

Patient numbers	Histology	Change in IVC tumor thrombus level before and following sunitinib therapy		Histopathological change in IVC tumor thrombus following sunitinib therapy		Histopathological change of primitive renal tumor following sunitinib therapy	
		II→I	IV→IV	Viable tumor cells remained	Tumor almost entirely replaced with necrotic tissue	Tumor almost entirely replaced with necrotic tissue	Viable tumor cells remained
2	Clear cell						
5	Clear cell						

IVC, inferior vena cava.

Table 5 Impact of preoperative treatment with sunitinib on tumor thrombus level

	Cost <i>et al.</i> [10] (n = 12) [n (%)]	Bigot <i>et al.</i> [11] (n = 11) [n (%)]	This study (n=7) [n (%)]
Primary tumor thrombus level			
I	0 (0)	0 (0)	1 (4.3)
II	8 (66.6)	8 (72.7)	2 (28.6)
III	2 (16.7)	3 (27.3)	1 (14.3)
IV	2 (16.7)	0 (0)	3 (42.8)
Effect on thrombus size			
Increase	2 (16.7)	2 (18.2)	3 (42.8)
Stable	3 (25.0)	6 (54.5)	3 (42.8)
Decrease	7 (58.3)	3 (27.2)	1 (14.3)
Effect on thrombus level			
Increase	0 (0)	1 (9.1)	1 (14.3)
Stable	9 (75)	9 (81.8)	5 (71.7)
Decrease	3 (25)	1 (9.1)	1 (14.3)

cycles of treatment may be sufficient to facilitate the surgical procedure. In the current study, we decided to set the upper limit of sunitinib treatment duration to four cycles because patients may benefit from alternative therapeutic agents that show greater efficacy. Actually, in two cases (patients 4 and 6), we switched the patients from sunitinib to axitinib and their caval thrombus shrank significantly. Thus, presurgical treatment with axitinib facilitated easier surgical resections in these cases.

In addition to these clinical evaluations, we assessed histopathological effects on three patients. There was no literature of histopathological changes on IVC tumor thrombus and primitive renal tumor by presurgical sunitinib treatment. Our results suggested that even if pre-treatment with sunitinib has a remarkable histopathological effect on IVC tumor thrombus, its effects did not enable downstaging of IVC thrombus according to Novick's classification.

The perioperative management of RCC patients with IVC tumor thrombus remains challenging, and there are currently no guidelines available to advise physicians in such difficult cases. One recent review article brought together experts from different specialties relevant to the management of these patients with the goal of creating clinical guidelines [17]. They recommend that all RCC patients with IVC tumor thrombus that do not have a contraindication to anticoagulation should receive low-molecular-weight heparin as the standard care. The hematological and oncological literature includes many articles that detail the data and make recommendations on the use of anticoagulation in patients with malignancy [18–24]. In fact, four patients received prophylaxis with warfarin in the present study.

Our data are biased by the retrospective acquisition and the small number of cases. This study included a small number of patients, but other literature reports have been likewise limited. Although our results should be validated in a prospective manner, our present study indicates that presurgical treatment with molecular-targeted drugs may not be effective for downstaging

the level of IVC thrombus, and in fact, may increase both the risk of bleeding episodes caused by anticoagulant therapy and the risk of embolism by thrombus itself during presurgical treatment. As such, presurgical treatment with sunitinib may not be advisable for RCC patients with IVC thrombus.

Conclusion

Presurgical treatment by sunitinib for RCC with IVC tumor thrombus appears to have limited effect on IVC tumor thrombus, in contrast to its effects on primitive tumor shrinkage. In the absence of evidence of presurgical benefits from prospective studies, this treatment may not be systematically advisable.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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