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Presurgical targeted molecular therapy for advanced renal cell carcinoma: Long-term clinical outcomes in a Japanese population

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Abstract

Purpose: This study is to investigate the efficacy and safety of presurgical targeted molecular therapy with tyrosine kinase inhibitors (TKIs) and mammalian targets of rapamycin inhibitors (mTORIs) for advanced renal cell carcinoma in a Japanese population.

Methods: We retrospectively identified patients with renal cell carcinoma treated with targeted molecules before tumor resection.

Results: Between July 2008 and February 2014, 11 patients were treated with targeted molecular therapy and subsequently underwent resection. Operations were performed by open laparotomy in all cases for locally advanced and metastatic disease, with the exception of one patient who had an inoperable tumor. The average reduction rates of primary tumor and metastases were −14.9% (range, −47~ +18%) and −35.7% (range, −100~ +40%), respectively. Cancer-related deaths tended to occur in patients who had weak reduction of primary tumor despite therapy. Two patients had minor perioperative complications, including wound healing delay and infection. Pathological analysis revealed clear cells in all cases.

Conclusions: Surgical resection of renal cell carcinoma after targeted therapy was feasible with low morbidity in most patients. Presurgical therapy might help identify patients with renal cell carcinoma who have a poor prognosis and might not achieve survival benefit from cytoreductive surgery.

Key words：Presurgical therapy, Renal cell carcinoma, Targeted molecules

INTRODUCTION

Localized RCC can be treated with partial or radical nephrectomy (removal of the kidney) [1], ablation [2] (destruction of the malignant tissue with heat or cold) or active surveillance [3] (monitoring of tumour growth with periodic radiographic studies). Despite nephrectomy with curative intent, ~30% of patients with RCC with localized disease eventually develop metastases [4-7], which require systemic therapies and is associated with high mortality. The estimated 5-year survival for patients with disease confined to the kidney (stages T1 and T2) is approximately 90% to 95%.4,5 However, once locally advanced or metastatic disease develops, the prognosis for long-term survival is poor, with 5-year survival ranging between 0% and 20% [8-10]. Tyrosine kinase inhibitors (TKIs) and mTORs pathways have been developed, but treatment response is varied and most patients eventually progress [11].

Since the introduction of targeted molecular agents, the treatment of metastatic renal cell carcinoma (mRCC) has dramatically changed [12-13]. In Japan, three kinds of tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, and axitinib) and two kinds of mammalian targets of rapamycin inhibitors (mTORIs; temsirolimus and everolimus) are currently available for use in routine clinical practice. In addition to their cytoreductive effects

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on primary tumors, distant metastases, and lymph node metastatic lesions, these agents also prolong progression-free and overall survival compared with control agents such as interferon-alpha or placebo [14-17]. However, a complete response is rare. Complete recovery requires combined modality therapy that includes surgical resection. Recent studies have demonstrated the efficacy of targeted molecular agents as presurgical therapy for mRCC [18-24]. In the present study, we analyzed the clinical results of presurgical therapy with targeted molecules in patients with advanced RCC.

MATERIALS AND METHODS

We retrospectively reviewed the records of patients with advanced RCC who underwent resection after targeted therapy between July 2008 and February 2014 in the Department of Urology Kindai University Faculty of Medicine. Patients were included regardless of the availability of tumor histology or prior treatment with systemic therapy. The indication for presurgical therapy in patients before primary or metastatic tumor removal was an unresectable tumor. All available clinicopathological data were reviewed to obtain information regarding patient demographics, clinical stage, therapy type/duration, surgical approach, perioperative complications, pathological findings, and outcomes. At the time of administration of the targeted molecular agents, patients were evaluated according to the Modified Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification (Table 1) [25]. Tumor response was evaluated by the treating urologist according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) [1]. Patients were followed-up every 1-3 months, generally with history taking, physical examination, routine blood tests, computed tomography, and chest radiography. Due to the retrospective nature of this study, the need for individual patient consent was waived by the ethics committee at Kindai University Faculty of Medicine.

Table 1 MSKCC* risk factors

KPS** <80%
<1 year from diagnosis to treatment
Haemoglobin concentration <lower limit of normal
Calcium concentration >upper limit of normal
Neutrophil count >upper limit of normal
Platelet count >upper limit of normal

*MSKCC: Memorial Sloan-Kettering Cancer Center

**KPS=Karnofsky performance status.

Risk factors were Eastern Cooperative Oncology Group performance status ≥2, low hemoglobin, and high calcium. For patients without prior treatment, additional risk factors were increased lactate dehydrogenase and time-to-use of sunitinib <1 year. Patients were classified as favorable, intermediate, or poor if 0, 1–2, or >2 risk factors were present, respectively.

RESULTS

A total of 11 patients were enrolled in this study. The clinical and perioperative data are shown in Table 2. The study population included 9 men and 2 women with a median age of 67 years (range, 40–77 years), and 8 (73%) patients had an Eastern Cooperative Oncology Group performance status of 0. Patient characteristics are shown in Table 3. The main molecular target agent was TKIs (n = 9), and the other 2 patients received mTORs. With the exception of one patient with local, advanced RCC (case 5 in Table 3), metastatic lesions were present in all patients. Preoperative pathological diagnoses were obtained in 3 patients, all of whom had clear cell RCC. Targeted agents were administered before all of the resections and were ceased a median of 14 days (range, 3–44 days) before the operation. Postoperative targeted molecular therapy was continued in all but 2 patients (cases 4 and 5, Table 3). The average duration of targeted therapy was 2.8 months (range, 0.4–9.8 months). Two patients classified as poor risk had short durations of targeted therapy (0.4 and 0.6 months). An open approach was used for all patients to eradicate locally advanced or metastatic disease. Two patients underwent both nephrectomy and metastasectomy, and one patient had an inoperable tumor. Two patients did not undergo preoperative imaging; for the remaining patients, the average reduction rates of primary tumors and metastases

were −14.9% (range, −47~ +18%) and −35.7% (range, −100~ +40%), respectively (Figure 1). A case with primary tumor progression also showed metastatic progression. The median follow-up duration was 38 months (range, 2-102 months).

Of the patients in the present study, a 67-year-old man with clinical stage T3cN0M0 disease (PS0, Hb 11.7 g/dL; case 3 in Table 3), who received sunitinib for 3.2 months before surgery survived for 75 months. Similarly, a 77-year-old man, with clinical stage T3bN0M0 (PS0, Hb 8.3 g/dL; case 5 in Table 3), who received sunitinib for 2.4 months before surgery survived for 38 months. Both patients were considered intermediate risk. These patients, who would have previously been considered difficult cases for immediate surgery. In terms of postoperative survival, although it is difficult to assess the efficiency of presurgical therapy by postoperative targeted molecular therapy, several of the patients in this study had a long post-operative survival period, suggesting that presurgical therapy is an effective option to select patients. However, one patient classified as poor risk (case 2 in Table 3) survived for 36 months post-operatively, suggesting that cytoreductive nephrectomy was more effective than presurgical therapy. Two patients (18%) experienced minor perioperative complications. One patient experienced minor wound complications in the postoperative recovery period, while another experienced a fever of unknown origin 2 weeks after resection which resolved promptly with intravenous antibiotic therapy.

The median estimated blood loss was 826 mL. The final pathological diagnosis in all cases except for the patient with an inoperable tumor was clear cell carcinoma.

Table 2 Clinical and perioperative data of patients who underwent resection after targeted therapy for renal cell carcinoma (RCC)

Variables	n=11
Median age (range)	67 (40-77)
Sex (%)	
M	9 (82)
F	2 (18)
Eastern Cooperative Oncology Group performance status (%)	
0	8 (73)
1	3 (27)
2	0
MSKCC* risk group (%)	
Intermediate	9 (82)
Poor	2 (18)
Targeted molecular therapy (%)	
Sunitinib	3 (27)
Sorafenib	3 (27)
Temsirolimus	2 (18)
Axitinib	2 (18)
Pazopanib	1 (9)
Surgical complications (%)	
Intraoperative	0
Postoperative	2 (18)
Pathological findings (%)	
Clear cell carcinoma	11 (100)
Postoperative targeted therapy/total (%)	9 (82)

Table 3 Characteristics of patients who underwent resection after targeted molecular therapy for renal cell carcinoma (RCC)

No.	Clinical stage	MSKCC risk	Metastasis	Targeted therapy	Administration Period(mo)	Tumor reduction rate (%)	Procedure	EBL (mL)	Postoperative perioed
1	T3aN0M1	intermediate	Lung + Brain	Sorafenib	0.8	10 Reduction	Nephrectomy	783	Dead (21 mo)
2	T1bN0M1	Poor	Lung	Sorafenib	0.6	NA	Nephrectomy	170	Dead (64 mo)
3	T3cN0M1	intermediate	Lung	Sunitinib (3 cycles)	3.2	10 Reduction	Nephrectomy Lymphadenec-tomy	913	Alive (75 mo*)
4	T1bN0M1	intermediate	Liver	Sunitinib (2 cycles)	2.4	47 Reduction	Nephrectomy Lobectomy of liver	1188	Alive (71 mo)
5	T3bN0M0	intermediate	None	Sunitinib (5 cycles)	2.4	22 Reduction	Nephrectomy	868	Alive (38 mo)
6	T3bN2M1	intermediate	Lung	Sunitinib (1 cycles) →Temsirolimus (8 cy-cles)	3.2	18 Increase	Inoperability	266	Dead (10 mo)
7	T1bN2M0	intermediate	None	Axitinib	5	15 Reduction	Nephrectomy	289	Dead (36 mo)
8	T3aN0M1	intermediate	Lung	Axitinib	1.2	10 Reduction	Nephrectomy	150	Alive (48 mo)
9	T3aN1M1	intermediate	Lung + adrenal	Temsirolimus (2 cycles) →Sorafenib	1.9	7 Reduction	Nephrectomy	3275	Dead (38 mo)
10	T3aN2M1	Poor	Adrenal	Temsirolimus (2 cycles)	0.4	NA	Nephrectomy	135	Dead (2 mo)
11	T1bN0M1	intermediate	Lung	Pazopanib (7 cycles)	9.8	30 Reduction	Nephrectomy	1725	Alive (102 mo)

EBL, estimated blood loss; NA, not assesed; mo, months

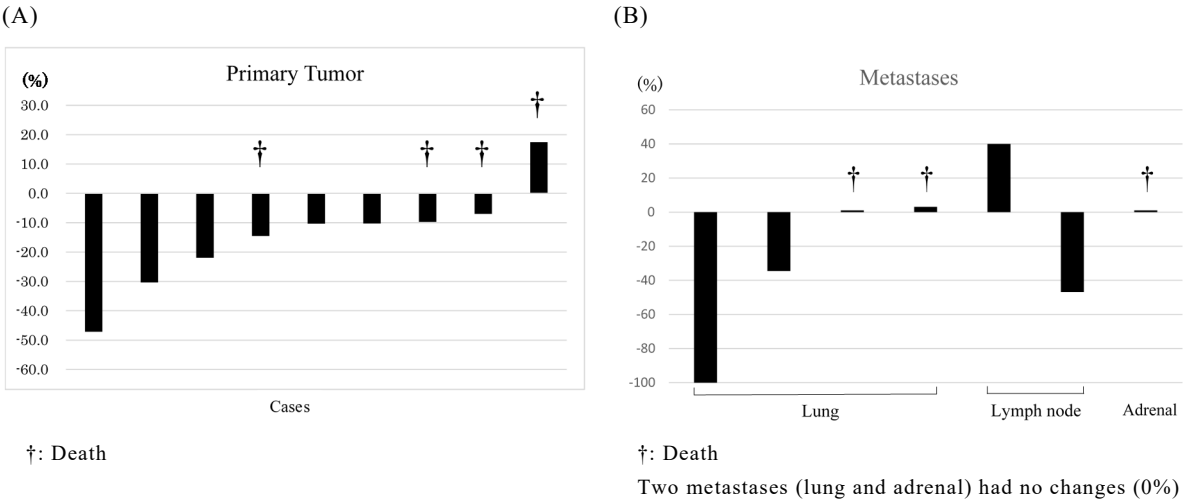

Figure 1 Waterfall plot of response to targeted molecular presurgical therapy by (A) primary tumors (evaluable n = 9) and (B) metastases (n = 7) in renal cell carcinoma

DISCUSSION

This study evaluated the efficacy and safety of presurgical targeted molecular therapy with TKIs (2 patients) and mTORIs (9 patients) in Japanese patients with advanced renal cell carcinoma. Both of the patients who received mTORIs died. Because guidelines regarding the use of molecular target agents as presurgical therapy are lacking, we determined the optimal agent for each patient on a case by case basis. Generally, TKIs is chosen to reduce tumor size [26], and it is for this reason that we chose this agent prior to surgery. Alternatively, mTORIs was chosen for patients with hypertension and renal dysfunction, although there are no current reports regarding the selection of mTORIs for presurgical therapy in the Japanese population [18]. It has been suggested that the inability to use TKIs as presurgical therapy in specific patients is a poor prognostic factor.

The mean tumor regression rate was 14.9% in the present study, similar to that in previous studies [18,22]. Reportedly, the smaller the tumor, the greater tumor reduction ratio that can be achieved with molecular target agents [27]; therefore, larger tumors, which are indicated for presurgical therapy as in the present study, may not have as great

a tumor reduction. Regarding the association between reduction ratio and prognosis, cancer-associated deaths occurred in patients with lower tumor reduction rates. Also, the lowest reduction ratios for both primary tumors and metastases were observed in cases treated withmTORIs. Including inoperable cases, cases receiving presurgical therapy that achieve low reduction rates might have rapidly progressing cancer for which cytoreductive surgery does not prolong survival; therefore, presurgical therapy might help to identify patients with RCC that have a poor prognosis. In our study, presurgical therapy was more effective for metastases than primary tumors, which is also similar to other reports [16]. Depending on the metastases, presurgical therapy might enable surgery for unresectable metastasis. However, it is unclear for which cases with unresectable metastases that surgery was possible following the presurgical therapy.

In the intermediate risk group, presurgical therapy was administered for an average of 3.3 months (range, 0.8–9.8 months), which was longer than that for the poor risk group. In addition to the short period of presurgical therapy in the poor risk group, a preoperative radiological evaluation was not conducted. Therefore, a prospective analysis that includes a sufficient period of presurgical therapy for those at poor risk should be conducted to confirm the results of the present study.

Disease progression of both the primary tumor and the metastasis was observed during presurgical therapy in one of the patients in this study. Thus, progression can occur in some cases during presurgical therapy, thus making the operation more difficult. In addition, the possibility of a delayed operation owing to potential adverse effects of presurgical therapy should be considered.

Importantly, no severe perioperative complications were noted in our patients, and the minor perioperative complications that were observed were associated with infection, suggesting that these complications might be caused by molecular target agent toxicity. Intraoperative blood loss volumes were acceptable, and increased blood loss associated with coagulopathy was not observed. However, it is difficult to evaluate the direct association between blood loss and molecular agent use because of the possible influence of a number of other factors, including the surgeon's ability and surgical difficulty. Conflicting results regarding complications have been previously reported, with one report describing an increase in both complications and severe complications with presurgical therapy, while other studies have not reported the same association [18,19,24]. Therefore, the effect of presurgical therapy on perioperative complications remains unclear. When perioperative complications do occur, postoperative hospital stay is prolonged, and the resumption of systemic treatment is delayed. Therefore, we believe it is important to prevent complications associated with presurgical therapy for advanced RCC.

There are several limitations to the current study. It is retrospective, and patient selection bias and unmeasured confounding remain a potential issue. It is also should be viewed with caution due to the small number of cases. Moreover, We have to pay a close attention for differrences among targeted molecular agents were used in current study.

The clinical benefits of and standard protocol for presurgical targeted therapy remain to be determined through a prospective analysis of more patients.

CONCLUSIONS

Presurgical therapy with targeted molecules was feasible in most patients with advanced RCC. In addition, presurgical therapy might help identify patients with advanced RCC who have a poor prognosis and are unlikely to experience a survival benefit from cytoreductive surgery. However, the clinical benefits of and standard protocol for presurgical targeted therapy remain to be determined through a prospective analysis of more patients.

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Conflict of interest

All authors have no conflict of interest to declare.