Original Article

Efficacy and safety of third- and fourth-line targeted therapy in Japanese patients with metastatic renal cell carcinoma: A retrospective analysis

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ABSTRACT

Introduction: There is limited data on the efficacy of sequential targeted therapy for metastatic renal cell carcinoma (mRCC) beyond the second line, especially for Asian patients. We evaluated the efficacy and side effects of targeted therapy beyond the second line.
Materials and Methods: We retrospectively reviewed 69 patients who were administered targeted therapy for mRCC at our institution between 2008 and 2016. Sunitinib, pazopanib, sorafenib, axitinib, everolimus, and temsirolimus were available in Japan in 2016, and treatment had been conducted with those six agents. Twenty-four patients underwent therapy beyond the second line. The progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. In addition, a survey on patients' attitudes toward cancer treatment was conducted. Twenty-five of the 69 patients responded to the question with their opinions on the continuation of treatment after standard therapy failure.
Results: The median PFS was 7.6 and 2.5 months for third- and fourth-line therapy. The median OS calculated from the initiation of third-line therapy was 14.2 months. The rates of serious toxicities with third- and fourth-line regimens were not markedly increased compared with first- and second-line therapies. Forty percent of patients hoped to continue treatment after exhausting standard care.
Conclusions: Our retrospective study indicates the efficacy and safety of third- and fourth-line targeted therapies. In addition to the efficacy, a patient can also influence treatment continuation.

BACKGROUND

Localized renal cell carcinoma is generally treated with surgery, including nephron-sparing surgery and radical nephrectomy. However, even if no metastases are noted in surgery-treated patients, 20%–40% of cases undergo relapse during the follow-up period[1,2] and targeted therapies are recommended as the initial treatment.[3] In addition, 25%–30% of newly diagnosed renal cell carcinoma cases present with metastases[4] and also require targeted therapy.

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In Japan, six targeting agents are available for metastatic renal cell carcinoma (mRCC), including four vascular endothelial growth factor receptor tyrosine kinase inhibitors and two mammalian targets of rapamycin (mTORs). While efficacy of those agents, which improves overall survival (OS) or progression-free survival (PFS), has been demonstrated, there are so few patients who achieve complete response[5] that most of them need further treatment in sequential manner.

With respect to sequential targeted therapies, everolimus and axitinib, which are administered as second-line therapy

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after failure of first-line targeted therapy, have been proven to improve the PFS in phase 3 trials.[6,7] However, although 13%–21%[8] of patients advance beyond second-line therapy, evidence supporting the efficacy of third- and fourth-line therapies is limited. Therefore, continuing treatment beyond the second line is decided based on physicians' preference and experience.

There have also been no studies focusing on the efficacies of third- or fourth-line targeted therapy mainly in Asian patients. The side effect profile of targeted therapy for Asian patients is reported different from that for Western patients,[9] so the efficacy and side effects of therapies beyond the second line for Asian patients remain unknown. We conducted a retrospective study to assess this clinical question.

In addition, because of the low amount of evidence supporting the efficacy of sequential therapy beyond the second line, physicians should emphasize patients' intentions when deciding to continue treatment. For this reason, we conducted a survey regarding patients' intention to continue targeted therapy in a sequential manner in 2014. We also reviewed the results of this survey in the present study.

MATERIALS AND METHODS

We retrospectively reviewed 69 patients who were administered targeted therapy for mRCC at our institution between 2008 and 2016. The present study was approved by the institutional review board of National Hospital Organization Kyushu Cancer Center.

A total of 24 patients underwent therapy beyond the second line. Although the number of approved targeted agents differed depending on the treatment timing, sunitinib, pazopanib, sorafenib, axitinib, everolimus, and temsirolimus were available in Japan in 2016, and treatment had been conducted with those six agents. All agents were given in a standard dose with standard dose reductions in case of toxicity.[10]

To assess the safety, we performed a number of clinical assessments every 4 weeks (including a physical examination, an assessment of the patient's vital signs, and analyses of the complete blood cell counts and serum chemistry). The response was evaluated by computed tomography every 8–12 weeks according to the response evaluation criteria in solid tumors, version 1.1, and toxicity was graded according to the common toxicity criteria for adverse events (CTCAE), version 4.0. Toxicities occurring with first- and second-line therapy were graded in the same manner as toxicities occurring with third- and fourth-line therapy. When intolerable toxicity or progression disease occurred, agents were changed or treatment was terminated which agent to administer was determined by each physician.

From 2014, whenever we changed the targeted agents and started a new therapy line, patients' attitudes concerning cancer treatment were routinely inquired about as a part of advanced care planning. One such question was as follows: "When it becomes difficult to continue standard cancer treatment because of inefficiency or adverse events, would you like to try another treatment that might be able to achieve a certain effect but may also cause severe side effects?" Five answer options were prepared for patients to choose from: "I have a strong desire to continue treatment," "I have only a little desire to continue treatment," "I do not want to continue treatment," "I have a strong desire not to continue treatment," and "I cannot decide." A total of 25 of the 69 patients responded to this question with their opinions on the continuation of treatment after standard therapy failure.

The Kaplan–Meier method was used to estimate the PFS with third- and fourth-line therapy and the OS after starting third-line therapy. They were also estimated in the subgroups of patients who required a change of treatment due to toxicity and patients who required a change of treatment due to disease progression. A log-rank test was used to compare the PFS and OS between the groups. $P < 0.05$ was considered to indicate statistical significance. All of the analyses were performed using the JMP® Pro software package (version 12.2.0; SAS Institute, Inc., Cary, NC, USA).

RESULTS

A total of 69 patients started targeted therapy between 2008 and 2016. Twenty-four of them (35%) underwent therapy beyond the second line, and 12 of them underwent therapy beyond the third line. Patients' characteristics are shown in Table 1. The Eastern Cooperative Oncology Group performance status of all patients was 0 or 1, and 6 (25%)

Table 1: Characteristics of patients

Characteristics	All (*n*=69)	Beyond second-line therapy (*n*=24)
Age at first targeted therapy (years), median (IQR)	67 (62-73)	66 (62-72)
Male sex, *n* (%)	50 (72)	19 (79)
MSKCC criteria, *n* (%)		
Favorable	19 (28)	6 (25)
Intermediate	37 (54)	15 (63)
Poor	12 (17)	3 (12)
Unknown	1 (1)	0
ECOG performance status, *n* (%)		
0	50 (72)	18 (75)
1	14 (20)	6 (25)
2	2 (3)	0
3, 4	3 (5)	0
Prior nephrectomy, *n* (%)	52 (75)	21 (88)
Metastases at diagnosis, *n* (%)	25 (36)	13 (54)
Histology, *n* (%)		
Clear cell	57 (83)	18 (75)
Nonclear cell	11 (16)	6 (25)
Unknown	1 (1)	0

IQR=Interquartile range, MSKCC=Memorial Sloan-Kettering Cancer Center, ECOG=Eastern Cooperative Oncology Group

patients with nonclear cell carcinoma were included in the study.

The sequence of treatment is shown in Table 2. Regarding third-line therapy or earlier, 13 (54%) patients underwent only tyrosine kinase inhibitor (TKI) therapy while 9 out of 12 patients (75%) who received therapy beyond the third-line received at least one round of mTOR therapy. The number of patients whose treatments were changed due to toxicities in the first-line to fourth-line treatments was as follows: first line, $n = 32$; second line, $n = 15$; third line, $n = 10$; and fourth line, $n = 3$. The details of the toxicities and CTCAE grades are shown in Table 3. The median PFS was 7.6 and 2.5 months for third- and fourth-line therapy. The median OS calculated from the initiation of third-line therapy was 14.2 months [Figure 1]. The PFS and OS did not differ according to the reason for the discontinuation of the prior therapy. In patients receiving third-line therapy, the PFS of patients who discontinued the prior therapy due to disease progression was 5.3 months while that of patients who discontinued treatment due to toxicities was 9.6 months ($P = 0.870$). In patients receiving fourth-line therapy, the PFS of patients who discontinued the prior therapy due to disease progression was 3.0 while that of patients who discontinued treatment due to toxicities was 2.5 months ($P = 0.665$). The median OS from the initiation

Table 2: Treatment sequence

Treatment line	Sequence	Patients (%)
First	TKI	67 (97)
	mTOR	2 (3)
Second	TKI-TKI	34 (85)
	TKI-mTOR	4 (10)
	mTOR-TKI	2 (5)
Third	TKI-TKI-TKI	13 (54)
	TKI-TKI-mTOR	7 (30)
	TKI-mTOR-TKI	2 (8)
	mTOR-TKI-TKI	2 (8)
Fourth	TKI-TKI-TKI-TKI	3 (25)
	TKI-TKI-TKI-mTOR	1 (8)
	TKI-TKI-mTOR-TKI	6 (50)
	TKI-mTOR-TKI-TKI	1 (8)
	mTOR-TKI-TKI-mTOR	1 (8)

TKI=Tyrosine kinase inhibitor, mTOR=Mammalian target of rapamycin inhibitor

Table 3: Number of patients changing agents due to toxicity and the details of the toxicities and Common Toxicity Criteria for Adverse Event grades

Toxicities	Grade	First line (n=32)	Second line (n=15)	Third line (n=10)	Fourth line (n=3)
Myelosuppression	2	3	1		
	3	3		1	
Hand-foot syndrome	3	2			
	2	2	2		
Exanthema (skin)	2	2		1	
	3	1			
Fatigue	2		1		
	3	1	2		
Pneumonitis	1			1	
	2		1	2	
	3	2			1
Cholecystitis	3	1			
Infection	3	1			1
Leukoencephalopathy	3	1			
	4	1			
Liver dysfunction	2	1			
	3	1			
Cardiac insufficiency	3	1			
Gastric ulcer (bleeding)	3	1			
Stroke	4	1			
Headache	2	1			
Acute kidney injury	2	1		1	
Edema face	2	1			
Muscle weakness lower limb	2	1			
Hypoglycemia	2	1			
Erythroderma	2		1		
	1	2			
Pleural effusion	2		1		
Edema trunk	2		1		
Nausea	2		1	1	
	3		1		
Diarrhea	2			1	
	3		1		
Colonic perforation	3		2		
Gastric hemorrhage	3			1	
Cognitive disturbance	2			1	
Hypertension	3				1

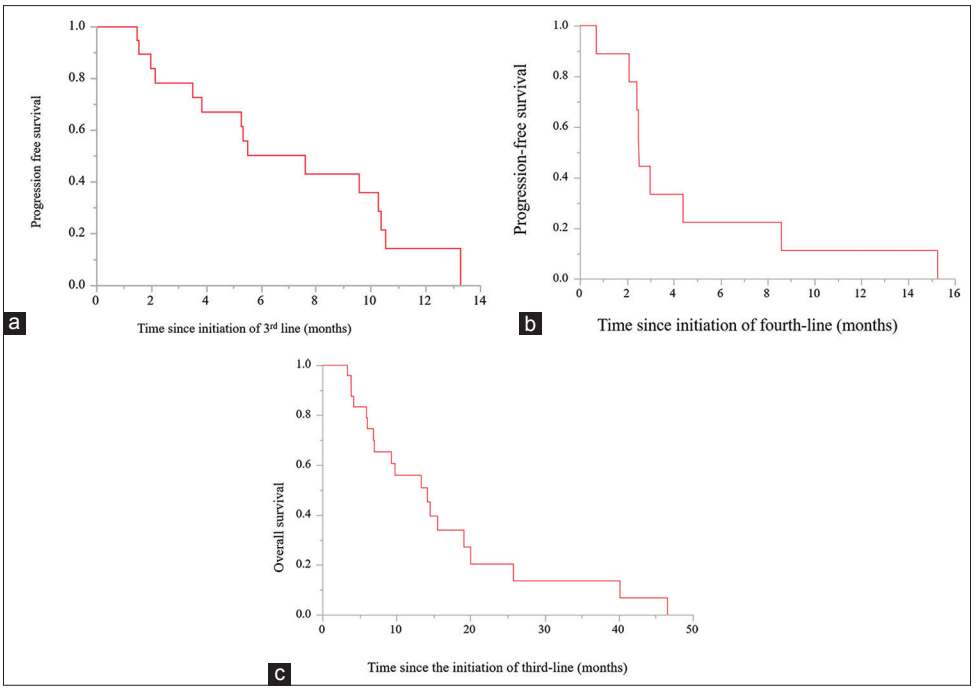

Figure 1: (a-c) The progression-free survival since initiation of third-line therapy. The progression-free survival since initiation of fourth-line therapy. The overall survival since the initiation of third-line therapy

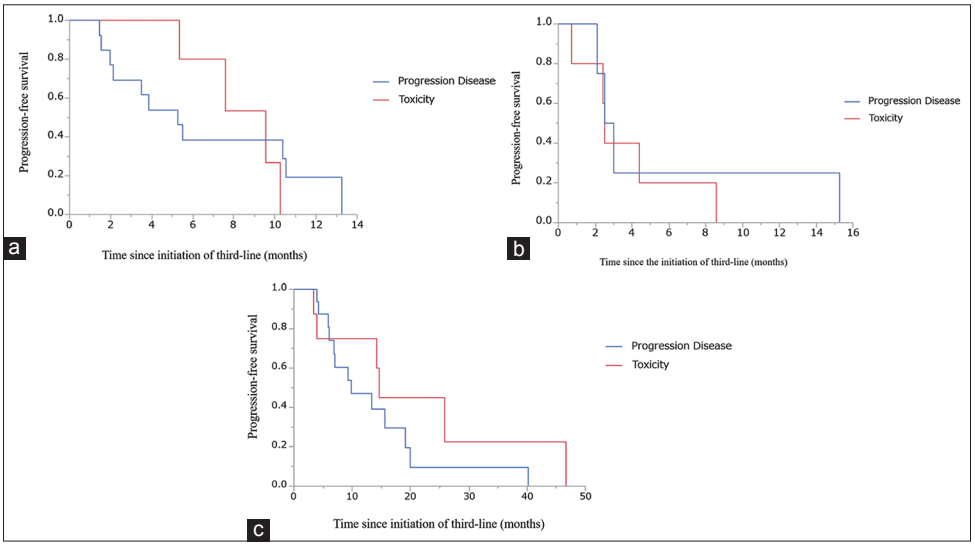

Figure 2: (a-c) The progression-free survival since initiation of third-line therapy according to cases of changing prior treatment: progression disease and toxicity. The progression-free survival since initiation of third-line therapy according to cases of changing prior treatment: progression disease and toxicity. The overall survival since the initiation of third-line therapy

of third-line therapy patients in patients who discontinued the prior therapy due to disease progression was 9.8 months while that of the patients who discontinued treatment due to toxicities was 14.5 months ($P = 0.271$) [Figure 2].

Grade 3 or 4 toxicities for each treatment line are shown in Table 4. The rates of serious toxicities with third- and fourth-line regimens were not markedly increased compared with first- and second-line therapies. Most of side effects shown in Table 4 occurred in patients treated with TKIs. Only two cases involved patients treated with mTOR inhibitors. One involved grade 3 myelosuppression in third-line therapy, and the other involved grade 3 myelosuppression in fourth-line therapy.

A total of 25 out of 69 patients explained their feelings with regard to continuing treatment when standard modalities were exhausted. The results are shown in Figure 3. Ten patients (40%) chose "I have a strong desire to continue treatment" or "I have only a little desire to continue treatment," and 9 patients (36%) chose "I do not want to continue treatment" or "I have a strong desire not to continue treatment."

Table 4: Toxicity profiles in each treatment line

Toxicities	First line (*n*=69), patients (%)	Second line (*n*=40), patients (%)	Third line (*n*=24), patients (%)	Fourth line (*n*=12), patients (%)
Myelosuppression	27 (39)	5 (13)	1 (4)	1 (8)
Hypertension	4 (6)	4 (10)	2 (8)	1 (8)
Hand-foot syndrome	4 (6)	1 (3)	0	0
Exanthema (skin)	2 (3)	0	0	0
Fatigue	1 (1)	1 (3)	1 (4)	0
Pneumonitis	3 (4)	0	0	1 (8)
Cholecystitis	3 (4)	0	2 (8)	0
Infection	2 (3)	0	0	1 (8)
Leukoencephalopathy	2 (3)	1 (3)	0	0
Liver dysfunction	1 (1)	0	1 (4)	0
Cardiac insufficiency	1 (1)	0	0	0
Gastric ulcer (bleeding)	1 (1)	0	0	0
Colonic perforation	0	2 (5)	0	0
Stroke	1 (1)	0	0	0
Nausea	0	1 (3)	0	0
Diarrhea	0	1 (3)	0	0
Hyperkalemia	0	1 (3)	0	0
Gastric hemorrhaging	0	0	1 (4)	0
Anorexia	0	0	1 (4)	0

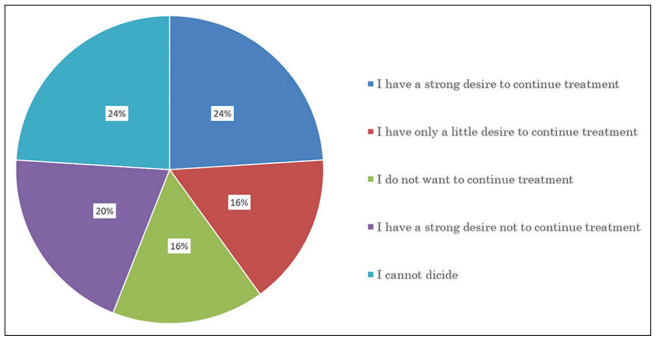

Figure 3: Response to the question, "When it becomes difficult to continue standard cancer treatment because of inefficiency or adverse events, would you like to try another treatment that might be able to achieve a certain effect but may also cause severe side effects?"

DISCUSSION

Although 13% to 21% of patients undergoing sequential targeted therapies for mRCC are reported to receive therapy beyond the third line,[8] only two prospective third-line trials have explored this matter.[11,12] This leaves physicians at a loss as to which agent to choose for third-line therapy. Furthermore, no prospective trials and few retrospective analyses have been published concerning fourth-line therapy.[10,13] For this reason, fourth-line therapy is necessarily empirically administered. Furthermore, since those studies were mainly conducted in the US and Europe, only a little information about third- or fourth-line targeted therapy for Asian patients is available at present.

Previous studies in the US and Europe have reported the PFS of third- and fourth-line targeted therapy to be 3.6–4.0 months and 3.2–5.8 months, respectively.[5-7] In our study, the PFS was 7.6 and 2.5 months for third- and fourth-line therapy, respectively. These values were comparable with those of previous studies.

Regarding adverse events, Ueda *et al*. reported that hypertension, dysphonia, hand–foot syndrome, hypothyroidism, and stomatitis occurred more frequently in Japanese patients receiving axitinib or sorafenib than in the overall population.[9] However, in our study, the rate of adverse events was similar to that in previous studies in Western patients,[12,13] and targeted therapy beyond the third line was considered tolerable for Asian patients.

In Japan, there is a universal health insurance system that covers all citizens, and standard treatments are supported by public resources. Targeted therapy for mRCC, including therapy beyond the second line, has also been approved, despite there being little evidence supporting its efficacy, and it can be administered without placing a large economic burden on patients. Therefore, few patients stop treatment for financial reasons, and most hope to continue treatment beyond second-line therapy as long as they can tolerate the treatment. In this study, 35% of patients, the highest among recent studies,[8] underwent therapy beyond the second line. This is partly because of the Japanese health insurance system, suggesting that the trend for hoping to continue treatment beyond second-line therapy will continue for many years to come. For this reason, we should continue to collect information concerning sequential targeted therapy, particularly for Asian patients.

Previous studies have shown that 81% of patients feel that "Fighting against disease until one's last moment is important for their good death"[14] and 24%–56% of cancer patients received chemotherapy until their last month of life.[15,16] In the present series, 40% of patients hoped to continue treatment after exhausting standard care. These feelings have likely contributed to the continuation of sequential therapy beyond the second line despite there being little evidence to support its efficacy. This is another

reason that more information about sequential therapy is necessary.

Several limitations associated with the present study warrant mention. This was a retrospective study and contained a relatively small sample size and heterogeneous group of patients. However, our data reflect the clinical practice and provide results of the treatment of mRCC in a group of Japanese patients at a single academic center. Despite these limitations, our findings suggest that targeted therapy beyond the second line provides a certain degree of effect in select patients without serious side effects. This is meaningful as no evidence has been provided supporting the efficacy of third- or fourth-line therapy in Asian patients.

Nivolumab has been approved in Japan since 2016 and is supported by public health insurance. Although the number of patients receiving Nivolumab is expected to increase, targeted therapy still plays an important role in mRCC treatment, and targeted agents have started to be administered in a postimmunotherapy setting. Targeted therapy may, therefore, show different outcomes in this setting in contrast to the findings of previous studies. More evidence must be gathered before any hard conclusions on efficacy can be drawn.

CONCLUSIONS

Our data indicate that third- and fourth-line targeted therapies are efficacious in metastatic RCC.

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