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Efficacy of Axitinib as Second-line Treatment in Locally Advanced and Metastatic Renal Cell Carcinoma

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Abstract. *Aim: To investigate prognostic factors for patients with advanced renal cell carcinoma (RCC) treated with axitinib as second-line therapy. Patients and Methods: This study included 35 patients with RCC who received axitinib as second-line therapy after the failure of first-line tyrosine kinases inhibitor from November 2012 to March 2017. Results: In univariate analyses, the following factors were associated with poor prognosis: bone and extrapulmonary metastasis for progression-free survival; and prior nephrectomy, Memorial Sloan Kettering Cancer Center risk classification, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification of poor, extrapulmonary metastasis and early tumor response for overall survival. Multivariate analyses identified the following factors as independent poor prognostic effects: extrapulmonary metastasis for progression-free survival, and no prior nephrectomy, IMDC risk classification of poor and extrapulmonary metastasis for overall survival. Conclusion: Axitinib as second-line treatment is effective for patients with pulmonary metastasis alone of RCC, but not for those with extrapulmonary metastasis.*

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and is the fourth most common urogenital malignancy in Japan (1, 2). For the last several years, the strategy for locally advanced and metastatic RCC has been changing to administration of molecular-targeted therapies, such as inhibitors of tyrosine kinases (TKIs) and mammalian target of rapamycin, instead of immunotherapy as the first-line therapy (3-5). These therapeutic agents have prolonged the survival of patients with RCC (6, 7). However, the disease of the majority of patients with RCC will eventually fail to respond to first-line therapy as a result of progression or intolerable adverse effects (AEs) (8).

Axitinib, a second-generation targeted drug, is a potent and highly selective inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase 1, 2, and 3. The AXIS trial was the first randomized phase III study to compare two active VEGF-targeted agents, axitinib and sorafenib, for second-line therapy of advanced RCC (9). Compared with sorafenib, axitinib significantly improved progression-free survival (PFS) in the overall trial population, as well as in the subgroups of patients previously treated with sunitinib or cytokines.

In Japan, axitinib was approved in 2012 and has been widely accepted as an efficacious second-line treatment for patients with locally advanced and metastatic RCC. Previously, Miyake *et al*. demonstrated that the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification (10) and C-reactive protein (CRP) are prognostic factors in patients with metastatic RCC receiving axitinib as second-line therapy (11). However, previous reports included many patients who received cytokines as first-line treatment, and almost no reports have discussed prognostic predictors in patients who received second-line axitinib after the failure of first-line TKI therapy.

In the present study, we aimed to investigate the prognostic factors for patients with locally advanced and metastatic RCC treated with axitinib as second-line therapy after the failure of first-line TKI.

Materials and Methods

Patients. Data for all patients with locally advanced and metastatic RCC who received axitinib as second-line therapy after the failure of first-line TKI at the Kurume University Hospital from November 2012 to March 2017 were analyzed. All patients who received at least one dose of axitinib were eligible. The clinical information of these patients was obtained from the medical records and was retrospectively reviewed and analyzed. This study was approved by the Ethics Review Committee at Kurume University School of Medicine (16227).

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Key Words: Renal cell carcinoma, axitinib, second-line therapy.

Therapy. Axitinib was given according to standard recommendations (9) with a starting dose of 5 mg twice daily (10 mg/day). Whenever possible, dose titration was performed according to the standard dosing schedule. When patients experienced an intolerable AE, dose reduction was performed based on the same recommendations. Severity of AEs was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (12).

PFS was defined as the time from the start of axitinib to the first documentation of progression or death from any cause. Overall survival (OS) was defined as the time from the start of axitinib therapy to death from any cause or last contact.

Radiological evaluations were performed for all patients by computed tomography (CT). Tumor response was evaluated as best response according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (13). Early tumor response on the first-follow up CT was evaluated at 4-12 weeks after the introduction of axitinib and a 10% decrease in diameter of the tumor was used as the cut-off value based on a previous report (14).

Statistical analysis. PFS and OS were determined using the Kaplan–Meier method, and analyzed using the log-rank test. To identify the prognostic factors associated with PFS and OS, Cox proportional hazards regression was used. Univariate and multivariate analyses were performed for independent prognostic factors for PFS and OS. The relationships between groups were compared using chi-squared test, Fisher's exact test or Student's *t*-test. All statistical analyses were performed using JMP version 13 (SAS Institute Inc., Cary, NC, USA) and a value of $p<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Patient characteristics are summarized in Table I. The median patient age was 66 years (range=40-78 years). The majority of patients were male (74.3%). More than one-half of patients were in the intermediate-risk group, for both MSKCC and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification (15) (74.3% and 74.3%, respectively). Axitinib was introduced as second-line therapy after the failure of first-line TKI. The most common first-line therapy was sunitinib, administered to 68.6% of patients. The median PFS on first-line therapy in the whole patient cohort was 7.7 months [95% confidence interval (CI)=0.5-56.0 months].

Objective response rate. Complete response was not obtained as best response to axitinib. Partial response and stable disease were achieved in eight (22.9%) and 18 (51.4%) patients, respectively. However, the remaining nine (25.7%) patients were judged to have progressive disease. Therefore, the objective response rate and the clinical benefit rate in this study were 22.9% and 74.3%, respectively.

Outcomes after treatment with axitinib. PFS and OS after introducing treatment with axitinib were assessed. As shown in Figure 1, the median PFS and OS were 5.8 and 29.5 months, respectively. To identify the prognostic factors associated with PFS and OS, univariate and multivariate analyses were performed using the Cox proportional hazards model (Tables II and III). Univariate analyses identified the following factors as being significantly associated with a poor prognosis, with two-fold hazard ratios or more: bone metastasis ($p=0.0287$) and extrapulmonary metastasis ($p=0.0005$) for PFS; and prior nephrectomy ($p=0.0229$), MSKCC risk classification ($p=0.0076$), IMDC risk classification of poor ($p=0.0011$), extrapulmonary metastasis ($p=0.0336$) and early tumor response ($p=0.0221$) for OS. Multivariate analyses of these significant prognosticators were performed, and the following factors demonstrated independent prognostic effects: extrapulmonary metastasis ($p=0.0037$) for PFS, and prior nephrectomy ($p=0.0449$), IMDC risk classification of poor ($p=0.0217$) and extrapulmonary metastasis ($p=0.0020$) for OS.

Table I. *Patient characteristics*.

Characteristic	All patients (n=35)
Age, years	
Median (range)	66 (40-78)
Gender, n (%)	
Male	26 (74.3%)
Female	9 (25.7%)
Prior nephrectomy, n (%)	
Yes	26 (74.3%)
No	9 (25.7%)
MSKCC risk classification, n (%)	
Favorable	4(11.4%)
Intermediate	26 (74.3%)
Poor	5 (14.3%)
IMDC risk classification, n (%)	
Favorable	3 (8.6%)
Intermediate	26 (74.3%)
Poor	6 (17.1%)
Metastatic sites, n (%)	
Lung	21 (60%)
Bone	11 (31.4%)
Liver	4 (11.4%)
Number of organs with metastasis, n (%)	
1	18 (51.4%)
2	8 (22.9%)
≥3	9 (25.7%)
Histology of primary tumor, n (%)	
CCRCC	22 (62.9%)
Non-CCRCC	5 (14.3%)
Unknown	8 (22.9%)
First-line treatment, n (%)	
Sunitinib	24 (68.6%)
Sorafenib	6 (17.1%)
Pazopanib	5 (14.3%)
PFS on first-line treatment, months	
Median (range)	7.7 (0.5-56.0)

MSKCC: Memorial Sloan Kettering Cancer Center; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; CCRCC: clear cell renal cell carcinoma; PFS: progression-free survival.

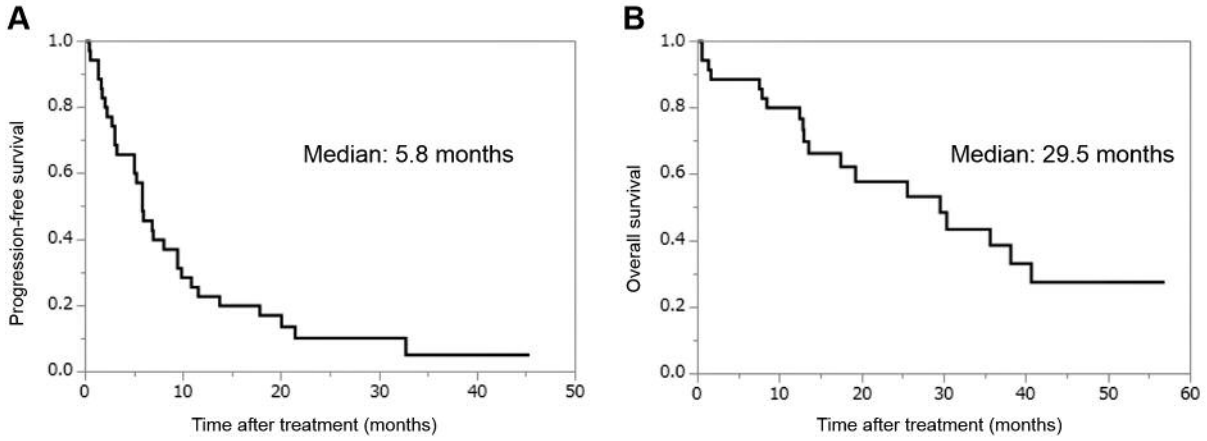

Figure 1. *Progression-free survival (A) and overall survival (B) in patients with advanced renal cell carcinoma treated with axitinib as second-line therapy.*

Table II. *Univariate and multivariate analyses of progression-free survival in patients with advanced renal cell carcinoma treated with axitinib as second-line therapy (n=35).*

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*p*-VaIue	HR (95% CI)	*p*-VaIue
Age				
<66 Years	1			
≥66 Years	0.990 (0.493-2.030)	0.9780		
Gender				
Male	1			
Female	1.571 (0.684-3.313)	0.2716		
Prior nephrectomy				
Yes	1			
No	1.861 (0.798-4.024)	0.1435		
MSKCC risk classification				
Favorable or intermediate	1			
Poor	1.080 (0.361-2.634)	0.8780		
IMDC risk classification				
Favorable or intermediate	1			
Poor	1.480 (0.544-3.439)	0.4139		
CRP				
<1.0 mg/dl	1			
≥1.0 mg/dl	1.822 (0.882-3.750)	0.1038		
Metastatic site				
Pulmonary alone	1		1	
Extrapulmonary	5.391 (1.989-18.952)	0.0005	4.693 (1.610-17.113)	0.0037
Bone metastasis				
No	1		1	
Yes	2.424 (1.102-5.083)	0.0287	1.437 (0.631-3.197)	0.3793
Number of organs with metastasis				
1	1			
≥2	1.935 (0.918-4.216)	0.0828		
PFS on first-line TKI				
<6 Months	1			
≥6 Months	1.476 (0.726-3.068)	0.2826		
Early tumor response				
≥10% shrinkage	1			
Progression or 10% shrinkage	2.163 (0.979-5.457)	0.0569		

HR: Hazard ratio; CI: confidence interval; MSKCC: Memorial Sloan Kettering Cancer Center, IMDC: International Metastatic Renal Cell Carcinoma Database Consortium, CRP: C-reactive protein, PFS: progression-free survival, TKI: tyrosine kinase inhibitor, PR: partial response, SD: stable disease, PD: progressive disease.

Table III. *Univariate and multivariate analyses of overall survival in patients with advanced renal cell carcinoma treated with axitinib as second-line therapy (n=35).*

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*p*-VaIue	HR (95% CI)	*p*-VaIue
Age				
<66 Years	1			
≥66 Years	1.065 (0.438-2.692)	0.8910		
Gender				
Male	1			
Female	1.585 (0.553-4.047)	0.3694		
Prior nephrectomy				
Yes	1		1	
No	3.409 (1.197-9.338)	0.0229	3.988 (1.033-15.545)	0.0449
MSKCC risk classification				
Favorable or intermediate	1		1	
Poor	5.392 (1.638-15.842)	0.0076	1.175 (0.236-5.497)	0.8375
IMDC risk classification				
Favorable or intermediate	1		1	
Poor	7.266 (2.342-21.368)	0.0011	6.561 (1.325-33.635)	0.0217
CRP				
<1.0 mg/dI	1			
≥1.0 mg/dI	1.931 (0.770-4.922)	0.1587		
Metastatic site				
Pulmonary alone	1		1	
Extrapulmonary	3.938 (1.099-25.117)	0.0336	12.849 (2.272-131.245)	0.0020
Bone metastasis				
No	1			
Yes	2.301 (0.835-5.906)	0.1031		
Number of organs with metastasis				
1	1			
≥2	2.422 (0.889-7.662)	0.0848		
PFS on first-line TKI				
<6 Months	1			
≥6 Months	0.837 (0.335-2.122)	0.7020		
Early tumor response				
≥10% shrinkage	1		1	
Progression or 10% shrinkage	4.229 (1.209-26.699)	0.0221	4.360 (0.817-80.520)	0.0920

HR: Hazard ratio; CI: confidence intervaI; MSKCC: Memorial Sloan Kettering Cancer Center, IMDC: International Metastatic Renal Cell Carcinoma Database Consortium, CRP: C-reactive protein, PFS: progression-free survival, TKI: tyrosine kinase inhibitor, PR: partial response, SD: stable disease, PD: progressive disease.

AE profile of axitinib. Most AEs were grade 1 or 2 (Table IV). Fatigue and hypertension were the most common AEs. Common AEs corresponding to grade 3 or higher were hypertension (11.4%), proteinuria (11.4%), and diarrhea (8.6%). However, there was no case of treatment-related death in this study.

Subsequent lines after treatment with axitinib. Of the 35 patients, three (8.6%) remained under treatment with axitinib, while the remaining 32 (91.4%) were unable to continue axitinib as a result of either disease progression (in 27, 77.1%) or intolerable AEs (in five, 14.3%). Of the 32 patients who stopped receiving axitinib, nine (28.1%), five (15.6%), four (12.5%), two (6.3%), and one (3.1%) were treated with everolimus, nivolumab, pazopanib, sorafenib, and sunitinib, respectively, as third-line therapy. Meanwhile, the remaining 11 (34.4%) received best supportive care as a result of disease progression.

Discussion

Axitinib has been recognized as a standard second-line treatment in patients with locally advanced and metastatic RCC and first-line treatment failure (11, 16, 17). However, there are few reports on the correlation between the treatment effect of second-line axitinib and prognostic predictors. Recently, treatment options have diversified since nivolumab was approved as second-line treatment for patients with first-

Table IV. *Treatment-related adverse effects in patients with advanced renal cell carcinoma treated with axitinib as second-line therapy (n=35).*

Adverse effect	All grades, n (%)	Grade ≥3, n (%)
Fatigue	18 (51.4%)	1 (2.9%)
Hypertension	16 (45.7%)	4 (11.4%)
Anemia	14 (40.0%)	2 (5.8%)
Diarrhea	13 (37.1%)	3 (8.6%)
Decreased appetite	9 (25.7%)	0 (0.0%)
Hypothyroidism	7 (20.0%)	0 (0.0%)
Proteinuria	6 (17.1%)	4 (11.4%)
Hand–foot syndrome	5 (14.3%)	1 (2.9%)
Thrombocytopenia	5 (14.3%)	1 (2.9%)
Increased creatinine	4 (11.4%)	1 (2.9%)
Hematuria	2 (5.7%)	0 (0.0%)
Hoarseness	2 (5.7%)	0 (0.0%)
Cerebral hemorrhage	1 (2.9%)	0 (0.0%)
Heart failure	1 (2.9%)	0 (0.0%)
Oral mucositis	1 (2.9%)	0 (0.0%)

line TKI failure (18). The present study examined the treatment effect of second-line axitinib treatment and prognostic predictors in patients with first-line TKI failure.

The objective response rate in our study, 22.9%, was slightly lower than those shown by previous reports (9, 19). This could be because many previous studies included patients treated with cytokine therapy as first-line treatment.

Miyake *et al*. reported that MSKCC risk classification and pretreatment CRP levels were the independent predictors of PFS in second-line axitinib therapy (11). In our study, there was no significant correlation between MSKCC risk classification or pretreatment CRP level and PFS of patients treated with axitinib. This can be partly accounted for by the fact that these reported studies had included patients who received cytokine therapy as first-line treatment, without being limited to patients with TKI failure. Previous reports have demonstrated that early tumor response to molecular targeted agents was involved in the prolongation of PFS or OS in the treatment of metastatic RCC (14, 20). Miyake *et al*. showed that early tumor shrinkage under treatment with a second-line molecular targeted therapy could serve as a useful parameter with an independent impact on OS in patients with metastatic RCC (21). In their reports, some molecular targeted agents, including axitinib as second-line therapy, were administrated to patients with metastatic RCC. In our study, the patients with ≥10% early tumor shrinkage tended to have a longer PFS with second-line axitinib compared with the patients with progression or less than 10% shrinkage. However, there was no significant difference between the two groups. A recent report demonstrated that longer response duration to first-line TKI was associated with longer PFS with second-line molecular targeted therapy (22). Li *et al*. showed that patients who responded to first-line sunitinib achieved fair disease control using second-line axitinib (23). However, Miyazaki *et al*. (24) also reported that the clinical response to second-line TKI therapy is not dependent on that to first-line TKI therapy in patients with metastatic RCC (24). In our study, no significant correlation was observed between the first-line treatment duration and PFS with second-line axitinib. In the sub-analysis of CheckMate 025 (25), nivolumab showed a higher treatment effect compared to everolimus in patients with bone or liver metastasis of RCC. Although this study was a retrospective single-arm study to explore the treatment outcome of axitinib and cannot simply be compared with nivolumab, as the treatment effect of second-line axitinib in patients with extrapulmonary metastasis was limited in our results, clinicians need to consider available treatment options including nivolumab. In our evaluation of OS, prior nephrectomy, IMDC risk classification of poor, and extrapulmonary metastasis were determined to be independent predictors conferring poorer prognosis, which suggests the effect of response to third-line treatment.

In this study, grade 3 or higher AE, namely hypertension, proteinuria, and diarrhea, were observed in approximately 10% of patients. These did not differ much from prior reports and none of the events was serious (11, 26).

Our study has several weaknesses, including its retrospective design and the limited number of patients from a single institution. Prospective investigation of clinical and molecular features in a large number of patients with locally advanced and metastatic RCC is required.

In conclusion, our results suggest that axitinib as second-line treatment is effective for patients with pulmonary metastasis alone of RCC. However, the role of axitinib as second-line treatment for patients with extrapulmonary metastasis must be explored by further investigations.

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