The Inverse Association between the Baseline Renal Function and Overall Survival in Patients with Metastatic Renal Cell Carcinoma Treated with Molecular-Targeted Agents

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Key Words

Renal cell carcinoma • Baseline renal function • Overall survival • Molecular-targeted therapy

Abstract

Background: The objective of this study was to investigate the prognostic significance of the baseline renal function in metastatic renal cell carcinoma (mRCC) patients treated with molecular-targeted agents. **Patients and Methods:** This study included 408 consecutive mRCC patients receiving molecular-targeted therapy, consisting of 124 patients in group A and 284 patients in group B who had baseline estimated glomerular filtration rates ≥ 60 ml/min/1.73 m² and < 60 ml/min/1.73 m², respectively. **Results:** Compared with group A, group B was significantly less likely to have poor prognostic factors, such as a high proportion of patients without nephrectomy. The median overall survivals (OSs) after the initiation of targeted therapy in groups A and B were 21.4 and 35.8 months, respectively, and there was a significant difference in the OS between the 2 groups. However, multivariate analysis showed a lack of independent impact of the baseline renal function on the OS. Furthermore, when patients without a nephrectomy were excluded, no significant difference was noted in the OS between the 2 groups. **Conclusion:** These findings suggested that there was no adverse impact of an unfavorable baseline renal function on

the efficacy of targeted agents against mRCC. Thus, molecular-targeted therapy should not be avoided in mRCC patients with an impaired baseline renal function.

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Introduction

Renal cell carcinoma (RCC) is the most common malignancy in the adult kidney, and annual estimates of patients newly diagnosed with RCC have been steadily increasing. Although RCC is characterized by a high incidence of metastatic spread to distant organs, due to a phenotype highly resistant to conventional chemotherapeutic agents [1], immunotherapy using cytokines was previously the only therapeutic option for patients with metastatic RCC (mRCC). It had limited efficacy with an objective response rate $< 20\%$, resulting in a poor prognosis of mRCC patients with a median overall survival (OS) of approximately 1 year [2]. In recent years, however, a variety of novel molecular-targeted agents have been developed based on intensive investigation of the molecular mechanisms mediating the progression of RCC. The introduction of these novel agents into clinical practice has

revolutionized the therapeutic strategy for patients with mRCC and contributed to a marked improvement of the prognosis of these patients [3]. However, major signaling pathways targeted by such novel agents are also active in normal organs, and thus the inactivation of these signaling pathways by molecular-targeted agents is usually accompanied by several types of adverse events (AE) [4].

A number of studies presented the profiles of AEs associated with the treatment of mRCC patients with molecular-targeted agents [4, 5]. Of these, renal toxicity is regarded as one of the most frequently observed AEs in mRCC patients, irrespective of the type of targeted agent introduced [6]. Furthermore, mRCC patients are likely to have risk factors for the impairment of the renal function due to several of their characteristics, such as aging, comorbidities, and a high prevalence of a prior nephrectomy [7]. Collectively, these findings suggest that it is important to assess whether the efficacy of molecular-targeted agents against mRCC is compromised in the context of renal dysfunction. However, there are limited data with respect to the impact of the renal function on the prognostic outcomes of mRCC patients who received molecular-targeted therapy [8–13]. Therefore, in this study we retrospectively assessed the data from a total of 408 consecutive patients who were diagnosed with mRCC and subsequently treated with molecular-targeted agents in a routine clinical setting, focusing on the prognosis of this cohort according to the baseline renal function.

Patients and Methods

A total of 513 Japanese patients with mRCC were treated with molecular-targeted agents between April 2008 and March 2015 at our institutions. From these 513 patients, this study excluded 105, consisting of 45 on chronic hemodialysis and 16 treated with pazopanib in addition to 44 without sufficient data on their renal function, due to the special strategy of targeted therapy in patients on chronic hemodialysis as well as the very small proportion of patients receiving pazopanib. As a result, the remaining 408, who were treated with sunitinib, sorafenib, axitinib, everolimus, or temsirolimus, were included in this study. Of these 408, 53, who did not receive a radical nephrectomy, underwent needle biopsies of either the primary or metastatic tumor to examine the histological subtype. Thus, all of the included patients were pathologically diagnosed with primary RCC. Informed consent was obtained from each patient prior to participation in this study, and the study design was approved by the Research Ethics Committee of our institutions.

In this series, immunotherapy using interferon- α and/or interleukin-2 was the only systemic therapy allowed prior to the introduction of molecular-targeted therapy against mRCC. Targeted agents were administered according to the following schedules: sunitinib, 50 mg orally, once daily in repeated 6-week cycles con-

sisting of 4 weeks on, followed by 2 weeks off. Sorafenib, 400 mg orally, twice daily. Axitinib, 5 mg orally, twice daily. Everolimus, 10 mg orally, once daily. Temsirolimus, 25 mg intravenously, once weekly. The treatment with targeted agents was continued until disease progression or intolerable AEs occurred. As a rule, dose modification of each agent was conducted according to AEs as follows: for Grade 2 AEs that were poorly tolerated, dose reduction was considered, while treatment was withheld in cases with Grade 3 or 4 AEs and restarted at a reduced dose after recovery to Grade 2 or lower.

As baseline assessments, clinicopathological examinations and the performance status were assessed based on the seventh edition of the UICC TNM classification system and Karnofsky performance status scale, respectively. The risk classification was conducted using both the Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification systems [14, 15]. Prior to the introduction of molecular-targeted agents, all patients were generally examined by computed tomography (CT) of the brain, chest, and abdomen, and a radionuclide bone scan. As a rule, tumor measurements were generally done by CT before and every 12 weeks after the initiation of treatment with targeted agents. Responses and AEs were evaluated by the treating physician based on the Response Evaluation Criteria in Solid Tumors 1.0 and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, respectively. In addition, the baseline estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology formula [16] prior to the initiation of treatment with a molecular-targeted agent.

All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA), and a value of p value < 0.05 was considered significant. Differences between the 2 groups were compared using the unpaired t -test and chi-square test. The OS rates were calculated by using the Kaplan–Meier method, and differences were determined by the log-rank test. The prognostic significance of certain factors was assessed by using the Cox proportional hazards regression model.

Results

Based on the baseline eGFR value prior to the introduction of molecular-targeted agents, the 408 patients with mRCC included in this study were classified into 124 patients in group A and 284 patients in group B who had a baseline eGFR ≥ 60 ml/min/1.73 m² and < 60 ml/min/1.73 m², respectively. The characteristics of these 408 patients are summarized according to each group in table 1. Patients in group B were significantly older and were more likely to have received a previous nephrectomy than those in group A, but were significantly less likely to have features associated with a poor prognosis, including an unfavorable risk classified by the MSKCC or IMDC system, elevated C-reactive protein (CRP) level, and high incidence of lymph node, bone, or liver metastasis compared with those in group A.

Table 1. Patient characteristics according to baseline renal function

	eGFR $\geq$ 60 mL/min/1.73 m ² (n = 124)	eGFR < 60 mL/min/1.73 m ² (n = 284)	p
Mean age, years (range)	64.2 (37–82)	71.4 (39–88)	< 0.001
Gender, %			0.71
Male	98 (79.0)	229 (80.6)	
Female	26 (21.0)	55 (19.4)	
Prior nephrectomy, n (%)			< 0.001
Yes	95 (76.6)	260 (91.5)	
No	29 (23.4)	24 (8.5)	
Prior immunotherapy, n (%)			0.078
Yes	42 (33.9)	72 (25.4)	
No	82 (66.1)	212 (74.6)	
MSKCC classification, n (%)			< 0.001
Favorable	13 (10.5)	40 (14.1)	
Intermediate	53 (42.7)	220 (77.4)	
Poor	58 (46.8)	24 (8.5)	
IMDC classification, n (%)			< 0.001
Favorable	13 (10.5)	41 (14.4)	
Intermediate	61 (49.2)	190 (66.9)	
Poor	50 (40.3)	53 (18.7)	
CRP, n (%)			0.0051
< 1.0 mg/dL	63 (50.8)	186 (65.5)	
$\geq$ 1.0 mg/dL	61 (49.2)	98 (34.5)	
Metastatic organ, n (%)			
Lung	76 (61.9)	190 (66.9)	0.27
Lymph node	42 (33.9)	58 (20.4)	0.0037
Bone	48 (38.7)	49 (17.3)	< 0.001
Liver	23 (18.5)	29 (10.2)	0.020
Brain	8 (6.5)	17 (6.0)	0.86
Histological subtype, n (%)			0.14
Clear cell carcinoma	105 (84.7)	255 (89.8)	
Others	19 (15.3)	29 (10.2)	
Sarcomatoid feature, n (%)			0.30
Yes	106 (85.5)	253 (89.1)	
No	18 (14.5)	31 (10.9)

Fig. 1. OS of patients with mRCC who were treated with molecular-targeted agents according to the baseline renal function evaluated by the eGFR.

As shown in figure 1, the median OSs after the initiation of targeted therapy in groups A and B were 21.4 and 35.8 months, respectively, and there was a significant difference in the OS between these 2 groups. We then assessed the impacts of several parameters, including the baseline eGFR value, on OS in the 408 mRCC patients included in this study by using the Cox proportional hazards regression model (table 2). Univariate analysis identified a prior nephrectomy, prior immunotherapy, MSKCC risk classification, IMDC risk classification, CRP level, lymph node metastasis, bone metastasis, liver metastasis, the sarcomatoid feature, and the baseline eGFR value. Of these 10 factors, only the CRP level, lymph node metastasis, and liver metastasis, but not the baseline eGFR value, were independently associated with OS on multivariate analysis.

Table 2. Univariate and multivariate analyses of associations between various parameters with OS

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age (years) (< 65 vs. ≥ 65)	0.91 (0.52–1.45)	0.57	–	–
Gender (male vs. female)	1.24 (0.79–2.49)	0.23	–	–
Prior nephrectomy (yes vs. no)	1.98 (1.34–8.25)	0.0012	1.81 (0.82–3.19)	0.23
Prior immunotherapy (yes vs. no)	1.97 (1.45–7.89)	0.0013	1.27 (0.89–2.96)	0.16
MSKCC classification (poor vs. others)	3.04 (1.35–5.73)	< 0.001	1.09 (0.59–2.39)	0.88
IMDC classification (poor vs. others)	3.62 (1.92–4.98)	< 0.001	2.01 (0.92–2.74)	0.12
CRP (mg/dL) (< 1.0 vs. ≥ 1.0)	0.35 (1.37–4.40)	< 0.001	0.39 (1.18–4.83)	0.032
Lung metastasis (yes vs. no)	0.85 (0.52–1.53)	0.68	–	–
Lymph node metastasis (yes vs. no)	3.40 (1.86–4.66)	< 0.001	2.49 (1.19–4.72)	0.0084
Bone metastasis (yes vs. no)	1.78 (1.12–3.23)	0.0014	1.98 (0.89–3.22)	0.77
Liver metastasis (yes vs. no)	2.04 (1.19–5.34)	0.022	2.66 (1.32–4.26)	0.0012
Brain metastasis (yes vs. no)	1.23 (0.44–2.80)	0.40	–	–
Histological subtype (CCC vs. others)	0.95 (1.15–3.04)	0.73	–	–
Sarcomatoid feature (yes vs. no)	2.20 (1.36–4.76)	< 0.001	1.49 (0.88–3.27)	0.30
eGFR (mL/min/1.73 m ²) (< 60 vs. ≥ 60)	0.53 (1.27–4.18)	0.0046	0.76 (0.84–3.02)	0.26

CI = Confidence interval; CCC = clear cell carcinoma.

Fig. 2. OS of patients with mRCC who underwent a nephrectomy and were subsequently treated with molecular-targeted agents according to the baseline renal function evaluated by the eGFR.

Of the several factors examined in this study, whether or not prior radical nephrectomy was performed could be regarded as the strongest factor directly influencing the baseline renal function. Therefore, we excluded 53 patients who had not undergone a radical nephrectomy, and compared the OS between the remaining 91 in group A and 257 in group B. As shown in figure 2, there was no significant difference in the OS between these 2 groups.

Discussion

Despite the wide prevalence of molecular-targeted therapy for mRCC, it is currently well recognized that various types of AEs, including those specific to targeted agents, occur during treatment with molecular-targeted agents, which may significantly undermine their benefits [4, 5]. Thus, it is important to precisely analyze the characteristics of major AEs associated with the use of these agents against mRCC. Several studies have reported a high incidence of chronic kidney disease in patients with solid tumors, including those with RCC [17, 18], and a significant proportion of patients with mRCC have received nephrectomy prior to the initiation of systemic treatment using targeted agents [7]. Although the metabolism of all molecular-targeted agents against RCC, except for that of bevacizumab, is mainly hepatic, and only 5–15% of these agents are excreted in the urine, the deterioration of the renal function is assumed to occur with all of them [4]. Furthermore, despite recent reports showing the pharmacokinetics of some targeted agents in patients with renal dysfunction were similar to those in patients with a normal renal function [19, 20], the majority of clinical trials evaluating the efficacy and safety of targeted agents against mRCC excluded patients with an insufficient renal function [4]. Collectively, these findings indicate that due to the high proportion of mRCC patients with an unfavorable baseline renal function who are scheduled to receive molecular-targeted therapy, it is

important to assess whether or not the effective administration of targeted agents is possible in the context of an impaired renal function in routine clinical practice.

In this series, based on the baseline eGFR value, 408 patients were classified into 124 with an eGFR ≥ 60 ml/min/1.73 m² and 284 with an eGFR < 60 ml/min/1.73 m², who are generally considered to have chronic kidney disease. In this series, 284 patients with an eGFR < 60 ml/min/1.73 m² were shown to be significantly less likely to have features associated with a poor prognosis than the 124 patients with that an eGFR ≥ 60 ml/min/1.73 m². However, conflicting findings on the association between the baseline renal function and prognostic parameters were reported in previous studies. Poprach et al. [13] analyzed the data from 790 patients with mRCC who were treated with sunitinib, and found no significant differences in several factors, except for hemoglobin, among 534 with a GFR ≥ 60 ml/min, 234 with a GFR between 30 and 60 ml/min, and 22 with a GFR < 30 ml/min. However, Macfarlane et al. [9] conducted a retrospective study including 529 mRCC patients who received vascular endothelial growth factor-targeted therapy, and showed that the 267 with an eGFR ≥ 60 ml/min/1.73 m² were more likely to be positive for poor prognostic features, such as a low performance status, short diagnosis to treatment interval, anemia, hypercalcemia, neutrophilia, and thrombocytosis, than the 262 patients with an eGFR < 60 ml/min/1.73 m². It is difficult to clearly explain the conflicting findings among these studies. However, the different selection bias in each study may partially have affected these outcomes. For example, in the present series, targeted therapy might have been more likely to be introduced in favorable risk rather than poor risk patients with renal dysfunction, since Japanese mRCC patients, even those with a normal renal function, were reported to be less tolerant of targeted agents than a Western population [21].

It is of interest to assess the impact of the baseline renal function on the survival of mRCC patients treated with molecular-targeted agents. In this series, the OS of 284 patients with an eGFR < 60 ml/min/1.73 m² was significantly more favorable than that of 124 patients with an eGFR ≥ 60 ml/min/1.73 m². Limited data on the relation between the renal function and prognosis in mRCC patients who received molecular-targeted therapy are available. For example, Macfarlane et al. [9] reported findings similar to those of this study. That is, the OS (median 19.2 months) in mRCC patients with a **GFR** ≥ 60 ml/min/1.73 m² was inferior to that (median 27.5 months) in those with a **GFR** < 60 ml/min/1.73 m². How-

ever, there have been some studies reporting no significant impact of the baseline renal function on the prognosis of mRCC patients treated with targeted agents [8, 13]. Thus, to more precisely investigate the prognostic impact of the baseline renal function in mRCC patients receiving targeted therapy, the significance of several prognostic factors in addition to the baseline renal function as predictors of OS were evaluated by using the Cox proportional hazards regression model. Despite being identified as a significant predictor of OS by univariate analysis, the baseline renal function appeared to lack an independent association with OS on multivariate analysis. Macfarlane et al. [9] also showed that when adjusted for poor risk factors, the baseline renal function did not have an impact on the time to treatment failure or OS. Collectively, these findings suggest that although it remains controversial whether or not the survival of mRCC patients receiving targeted therapy would be affected by the baseline renal function, it may not have an independent prognostic impact, irrespective of other potential prognostic indicators.

A previous history of a nephrectomy may be the most dominant factor directly affecting the baseline renal function prior to the introduction of targeted agents. Thus, another point of interest is assessment of the relation between the baseline renal function and prognosis in only mRCC patients who underwent a nephrectomy and subsequently received targeted therapy. In this series, after excluding patients who had not undergone a nephrectomy, no significant difference in OS was noted between patients with an eGFR ≥ 60 ml/min/1.73 m² and those with an eGFR < 60 ml/min/1.73 m². Therefore, some other factors could also be involved in the different OS according to the baseline renal function. However, considering the poor risk features in mRCC patients without a nephrectomy, a previous history of a nephrectomy may have an important impact on the inverse association between the baseline renal function and prognosis in the patients included in this study. In addition, different features between the 124 patients with an eGFR ≥ 60 ml/min/1.73 m² and the 284 patients with an eGFR < 60 ml/min/1.73 m² presented in table 1 could also be explained, at least in part, by the characteristics associated with poor prognosis in mRCC patients without a nephrectomy.

There are several limitations of this study. First, although the present study obtained data from a comparatively large number of mRCC patients, this was performed as a retrospective study, and thus the findings generated by this study need to be prospectively confirmed. Second, 60 ml/min/1.73 m² is not a very sensitive

cutoff point of eGFR for renal impairment in the cohort of this study. Thus, if possible, it would be interesting to use a more appropriate cutoff value, such as 30 ml/min/1.73 m². However, only 59 (14.5%) of the 408 included patients had an eGFR < 30 ml/min/1.73 m², and therefore it may not have been appropriate to use 30 ml/min/1.73 m² as a cutoff point in this series. Third, it is optimal to use creatinine clearance rather than eGFR in order to precisely evaluate the renal function. However, it was impossible to determine the value of creatinine clearance from all patients included in this study. Fourth, because of the timing of the approval of targeted agents in Japan, a significant proportion of patients were not treated based on the currently established strategy of the sequential use of targeted agents against mRCC. Finally, this study included patients with heterogeneous characteristics. That is, no restrictions were made concerning several issues, such as the histological subtype, previous history of treatment with immunotherapy and a nephrectomy, and types of targeted agents administered.

In conclusion, we assessed the impact of the baseline renal function on the prognosis of a total of 408 consecu-

tive mRCC patients who were treated with molecular-targeted agents. On dividing the 408 patients into 124 with baseline an eGFR $\geq$ 60 ml/min/1.73 m² and 284 with an eGFR < 60 ml/min/1.73 m², patients with an unfavorable baseline renal function were shown to be significantly less likely to have features associated with a poor prognosis than those with a favorable baseline renal function, and OS in patients with an unfavorable baseline renal function was significantly superior to that in those with a favorable baseline renal function. However, the baseline renal function appeared to lack independent significance as a predictor of OS on multivariate analysis, and, in fact, when patients without a previous history of a nephrectomy were excluded, there was no significant difference in OS between patients with an unfavorable baseline renal function and those with a favorable one. Collectively, these findings suggest that an unfavorable baseline renal function prior to the introduction of targeted therapy may not have an AE on the efficacy of targeted agents against mRCC, and therefore molecular-targeted therapy should not be avoided in mRCC patients with an impaired baseline renal function.

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