Targ Oncol (2016) 11:329–335
DOI 10.1007/s11523-015-0395-4

ORIGINAL RESEARCH ARTICLE

Changes in Renal Function of Patients with Metastatic Renal Cell Carcinoma During Treatment with Molecular-Targeted Agents

Hideaki Miyake[1] · **Mototsugu Muramaki**[1] · **Satoshi Imai**[1] · **Ken-ichi Harada**[1] · **Masato Fujisawa**[1]

Published online: 27 October 2015

Abstract
Background Impairment of renal function is a serious issue that should be considered in patients undergoing treatment with molecular-targeted agents for metastatic renal cell carcinoma (mRCC).
Aims The objective of this study was to assess the impact of molecular-targeted therapy on changes in renal function among patients with mRCC.
Patients and Methods The study included 408 mRCC patients treated with sunitinib, sorafenib, axitinib, everolimus and/or temsirolimus. Among these, 185, 128 and 95 received molecular-targeted agents as first-line (group 1), second-line (group 2) and third-line (group 3) therapy, respectively.
Results No significant differences between the estimated glomerular filtration rate (eGFR) at baseline and that at the end of molecular-targeted therapy were noted among the three groups of patients. In addition, there were no significant differences between eGFR prior to the introduction of molecular-targeted therapy and that at the end of therapy across agents and lines of targeted therapy, with the exception of patients treated with axitinib and everolimus in second-line and third-line therapy, respectively. In group 1, a reduction in eGFR of >10 % from baseline was independently associated with performance status, hypertension and treatment duration, while in groups 2 and 3, only treatment duration was independently related to a reduction in eGFR of >10 %.
Conclusions It appears that renal function in patients with mRCC is not markedly impaired by molecular-targeted therapies, irrespective of the specific agents introduced; however, it may be necessary to pay special attention to deterioration in renal function when molecular-targeted therapy is continued for longer periods.

Key Points

Among patients with metastatic renal cell carcinoma treated with molecular-targeted agents, there were no significant differences in changes between renal function at baseline and that recorded after first-, second- or third-line therapy.

Treatment duration was shown to be independently associated with impaired renal function in patients with metastatic renal cell carcinoma, regardless of the line of treatment with molecular-targeted agents.

1 Introduction

In recent years, the introduction of molecular-targeted agents has resulted in a paradigm shift in therapeutic strategies for metastatic renal cell carcinoma (mRCC), which has led to a marked improvement in prognosis among patients with mRCC compared with that in the era of cytokine therapy [1]. This novel drug was developed based on findings from the intensive investigation of molecular mechanisms mediating the growth and progression of RCC [2]. However, major signaling pathways targeted by these agents are also active in normal organs; therefore, the inactivation of these signaling pathways by molecular-targeted agents is usually accompanied by several types of adverse events (AEs) [3].

To date, a number of studies have reported AE profiles associated with the use of molecular-targeted agents for

✉ Hideaki Miyake
hideakimiyake@hotmail.com

[1] Division of Urology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

patients with mRCC [3, 4]. Of these, impairment of renal function is one of the most serious issues to consider during treatment with this type of agent, as baseline renal function among mRCC patients receiving molecular-targeted therapy is generally poor because of aging, comorbidities and a high prevalence of prior nephrectomy in this cohort, and the kidney is an organ in which most of the signaling pathways targeted by these agents have been shown to have active functions [5, 6]. However, there have been limited data regarding the impact of molecular-targeted agents on renal function in these patients, particularly those assessed in routine clinical practice, as enrollment in clinical trials has generally been limited to patients with adequate renal function [7].

To this end, we retrospectively assessed changes in renal function among a total of 408 Japanese patients who were diagnosed with mRCC and were subsequently treated with molecular-targeted agents in a routine clinical setting, and investigated parameters affecting deterioration in renal function during targeted therapy in these patients.

2 Patients and Methods

2.1 Patients

Between April 2008 and March 2015, a total of 513 Japanese patients with mRCC were treated with molecular-targeted agents. Of these 513 patients, 105 were excluded, as follows: 45 who were on hemodialysis, 44 without sufficient data on renal function, and 16 treated with pazopanib, due to an inadequate number of patients for statistical analysis. Therefore, the remaining 408, who were treated with sunitinib, sorafenib, axitinib, everolimus and/or temsirolimus, were included in the study. Among these, 53 who did not receive radical nephrectomy underwent needle biopsy of either the primary or metastatic tumor to determine the histological subtype, and thus all included patients were pathologically diagnosed with primary RCC. In this series, informed consent was obtained from each patient prior to study participation, and the study design was approved by the research ethics committees of our institutions.

2.2 Treatment with Molecular-Targeted Agents

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. Targeted agents were administered according to the following schedules: sunitinib, 50 mg orally, once daily in repeated 6-week cycles consisting 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; and temsirolimus, 25 mg intravenously, once weekly. The administration of targeted agents was continued until disease progression or intolerable AEs developed. 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.

2.3 Evaluation

Baseline assessment of patients included an evaluation of clinicopathological features, risk classification and performance status (PS) based on the UICC [Union for International Cancer Control] TNM classification system, Memorial Sloan Kettering Cancer Center (MSKCC) risk classification system [8] and Karnofsky Performance Status (KPS) scale, respectively, and body mass index was defined as the ratio of weight in kilograms divided by the square of height in meters. Prior to the introduction of molecular-targeted agents, all patients generally underwent examinations including computed tomography (CT) of the brain, chest and abdomen, and radionuclide bone scan. Tumor measurements were typically performed by CT before and every 12 weeks after the initiation of treatment with targeted agents. Patients with blood pressure >140/90 mmHg or who were receiving antihypertensive agents were regarded as positive for hypertension, while patients receiving hypoglycemic agents and/or insulin injection were regarded as having diabetes mellitus. Treatment response and AEs were evaluated by the treating physician based on the Response Evaluation Criteria in Solid Tumors 1.0 and the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, respectively. In addition, at each clinic visit, the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [9], and the change in renal function in each patient was defined as the difference between the eGFR value just prior to the initiation of treatment with a molecular-targeted agent and the final measurement after treatment with this type of agent in each line of targeted therapy.

2.4 Statistical Analysis

All statistical analyses were performed using StatView 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA), and a value of $p<0.05$ was considered significant. Differences between groups in changes in renal function were examined using the unpaired t test. Forward stepwise logistic regression analysis was used to determine the association between several parameters and impaired renal function.

3 Results

Of the 408 patients with mRCC included in this study, 185, 128 and 95 were treated with molecular-targeted

agents during first-, second- and third-line therapy, respectively, and were classified accordingly into groups 1, 2 and 3. The characteristics of these 408 patients are summarized by group in Table 1.

Table 1 Patient characteristics according to lines of molecular-targeted therapy received

Variable	Classification[a]			
	Group 1 (n=185)	Group 2 (n=128)	Group 3 (n=95)	Overall (n=408)
Age (years) (%)				
≥70	84 (45.4)	62 (48.4)	49 (51.6)	195 (47.8)
<70	101 (54.6)	66 (51.6)	46 (48.4)	213 (52.2)
Gender (%)				
Male	141 (76.2)	102 (79.7)	84 (88.4)	327 (80.1)
Female	44 (23.8)	26 (20.3)	11 (11.6)	81 (19.9)
Prior nephrectomy (%)				
Yes	153 (82.7)	113 (88.3)	89 (93.7)	355 (87.0)
No	32 (17.3)	15 (11.7)	6 (6.3)	53 (13.0)
Prior immunotherapy (%)				
Yes	58 (31.4)	36 (28.1)	20 (21.1)	114 (27.9)
No	127 (68.6)	92 (71.9)	75 (78.9)	114 (27.9)
Karnofsky Performance Status at baseline (%)				
≥80	154 (83.2)	111 (86.7)	86 (90.5)	351 (86.0)
<80	31 (16.8)	17 (13.3)	9 (9.5)	57 (14.0)
Median body mass index at baseline (kg/m^2)	21.2	21.8	21.4	21.4
Hypertension at baseline (%)				
Yes	91 (49.2)	50 (39.1)	58 (61.1)	199 (48.8)
No	94 (50.8)	78 (60.9)	37 (38.9)	209 (51.2)
Diabetes mellitus at baseline (%)				
Yes	30 (16.2)	21 (16.4)	17 (17.9)	68 (16.7)
No	155 (83.8)	107 (83.6)	78 (82.1)	340 (83.3)
MSKCC risk classification at baseline (%)				
Favorable	20 (10.8)	17 (13.3)	16 (16.9)	53 (13.0)
Poor	119 (64.3)	85 (66.4)	69 (72.6)	273 (66.9)
Intermediate	46 (24.9)	26 (20.3)	10 (10.5)	82 (20.1)
Histological subtype (%)				
Clear cell carcinoma	165 (89.2)	116 (90.6)	87 (91.6)	368 (90.2)
Others	20 (10.8)	12 (9.4)	8 (8.4)	40 (9.8)
eGFR at baseline [mL/min/1.73 m^2] (%)				
≥60	36 (19.5)	38 (29.7)	15 (15.8)	89 (21.8)
30–59	122 (65.9)	74 (57.8)	64 (67.4)	260 (63.7)
<30	27 (14.6)	16 (12.5)	16 (16.8)	59 (14.5)
Median treatment duration after start of initial molecular-targeted therapy (months)	20.2	33.4	41.7	24.5
Agents introduced throughout all lines of therapy (%)				
Sunitinib	96 (51.9)	106 (82.8)	94 (98.9)	296 (72.5)
Axitinib	57 (30.8)	42 (32.8)	36 (37.9)	135 (33.1)
Sorafenib	7 (3.8)	55 (43.0)	73 (76.8)	135 (33.1)
Temsirolimus	0 (0)	27 (21.1)	57 (60.0)	84 (20.6)
Everolimus	25 (13.5)	26 (20.3)	25 (26.3)	76 (18.6)

MSKCC Memorial Sloan Kettering Cancer Center, *eGFR* estimated glomerular filtration rate

[a] Groups 1, 2 and 3 received first-, second- and third-line targeted therapy, respectively

The differences between eGFR at baseline and at the end of molecular-targeted therapy in groups 1, 2 and 3 were −0.1± 16.9, −2.2±14.7 and −3.9±13.9 mL/min/1.73 m^2, respectively; however, there were no significant differences in the reduction in eGFR during treatment among these three groups. Table 2 shows changes in renal function according to the molecular-targeted agents used in each line of therapy. No significant differences between eGFR prior to the introduction of molecular-targeted therapy and at the end of therapy were noted among the five agents used in this study in any lines of targeted therapy, except for axitinib and everolimus in second-line and third-line therapy, showing significant impairment of renal function in patients treated with everolimus compared with those treated with axitinib.

We then assessed the impact of several parameters on changes in renal function in each group using forward stepwise logistic regression analyses. As shown in Table 3, univariate analysis identified age, PS, hypertension and treatment duration as significant predictors of a reduction in eGFR >10 % from baseline in group 1, of which PS, hypertension and treatment duration were shown to be independently associated with a reduction in eGFR >10 %, while only treatment duration was significantly related to a reduction in eGFR >10 % across all lines of targeted therapy in groups 2 and 3, based on both univariate and multivariate analyses.

4 Discussion

The advent of novel agents targeting vascular endothelial growth factor and mammalian target of rapamycin pathways have revolutionized therapeutic strategies for patients with mRCC [2], and a marked improvement in patient prognosis has been observed [1]. However, treatment with molecular-targeted agents is now recognized as causing a wide variety of AEs, including those specific to these agents, which may significantly undermine their benefits [3, 4]. Accordingly, it is important to precisely characterize major AEs associated with the use of targeted agents, which could represent an obstacle to maintaining an optimal dosing schedule, and thus hinder effective treatment. We retrospectively assessed data from a total of 408 Japanese patients who were diagnosed with mRCC and subsequently received molecular-targeted therapy, with a focus on deterioration of renal function, one of the most common AEs observed during such treatment [5, 6], in order to identify parameters associated with impaired renal function during treatment with targeted agents.

Several recent studies have reported a high prevalence of chronic kidney disease in patients with solid tumors, including those with RCC [5, 10]; thus, when the systemic administration of anticancer drugs is necessary, it is important to carefully evaluate their impact on renal function. This is particularly true in patients with mRCC who are scheduled to receive molecular-targeted therapies, considering that unfavorable baseline renal function is common in such patients due to the high proportion who undergo nephrectomy prior to the introduction of these agents. In fact, although only 9 (2.2 %) of the 408 patients included in this study were definitively diagnosed with renal disease showing progressive loss of renal function at baseline, 319 (78.2 %) patients had eGFR <60 mL/min/1.73 m^2. Moreover, except for that of bevacizumab, the metabolism of all molecular-targeted agents against RCC is mainly hepatic, and only 5–15 % of these agents is excreted in the urine; however, renal impairment is assumed to occur with all of these agents [11]. In this series as well, progressive impairment of renal function was clearly observed with an increase in the number of lines of targeted therapy. However, the degree of decrease in eGFR value in the cohort of this study seems to be narrow, and thus lacks clinical significance. Collectively, these findings suggest that molecular-targeted therapy could be safely introduced and continued sequentially in a majority of mRCC patients from the perspective of renal function.

It is of interest to determine whether the degree of renal impairment differs among molecular-targeted agents administered to patients with mRCC. In this series, there were no

Table 2 Changes in estimated glomerular filtration rate during treatment with molecular-targeted agents according to each line of therapy

Agent	First-line[a] (n[b]) [Treatment duration[c]]	Second-line[a] (n[b]) [Treatment duration[c]]	Third-line[a] (n[b]) [Treatment duration[c]]
Sunitinib	−0.1±16.2 (238) [18.3]	−3.1±5.6 (43) [15.1]	−1.1±6.2 (15) [6.1]
Sorafenib	−0.2±10.4 (126) [17.7]	−0.3±17.2 (4) [10.8]	−1.2±13.9 (5) [3.7]
Axitinib	0.1±3.5 (7) [18.8]	−0.4±13.8* (105) [16.6]	−0.2±4.3** (23) [11.4]
Everolimus	- (0) [0]	−5.3±10.9 (47) [13.3]	−3.9±8.0 (37) [7.7]
Temsirolimus	−0.1±5.7 (37) [17.5]	−2.3±10.8 (24) [14.7]	−1.7±9.4 (15) [11.2]

*p=0.033, **p=0.046 vs. everolimus

[a] Values are expressed as mean ± standard deviation (mL/min/1.73 m^2)

[b] Number of patients who were treated with each agent by each line of therapy

[c] Values are expressed as median (months)

Table 3 Univariate and multivariate analyses of several factors predicting decrease in estimated glomerular filtration rate (eGFR) >10 % from baseline during treatment with molecular-targeted agents according to line of therapy received

Variables	Classification[a]											
	Group 1				Group 2				Group 3			
	Univariate analysis Odds ratio	*p* value	Multivariate analysis Odds ratio	*p* value	Univariate analysis Odds ratio	*p* value	Multivariate analysis Odds ratio	*p* value	Univariate analysis Odds ratio	*p* value	Multivariate analysis Odds ratio	*p* value
Age at baseline	2.59	0.0092	2.03	0.41	1.03	0.89	1.14	0.85	1.04	0.69	1.13	0.72
Gender	2.44	0.24	1.19	0.70	1.69	0.55	1.29	0.70	1.94	0.21	1.78	0.33
Prior nephrectomy	1.45	0.54	1.30	0.61	1.55	0.59	1.40	0.67	1.53	0.45	1.54	0.57
Prior immunotherapy	1.55	0.47	1.22	0.55	1.49	0.62	1.45	0.62	1.59	0.41	1.55	0.52
Karnofsky Performance Status at baseline[b]	3.77	0.017	5.03	0.013	1.98	0.35	1.19	0.81	1.38	0.55	1.62	0.39
Body mass index at baseline	1.38	0.58	1.63	0.29	1.09	0.91	1.09	0.89	1.69	0.37	1.73	0.37
Hypertension at baseline	7.93	0.0012	4.11	0.0092	1.20	0.65	2.07	0.20	2.02	0.15	2.22	0.30
MSKCC risk classification at baseline[c]	1.12	0.92	1.39	0.53	2.05	0.33	1.69	0.52	1.25	0.53	2.07	0.67
Histological subtype[d]	1.06	0.90	1.48	0.47	1.70	0.51	1.66	0.58	1.80	0.26	1.27	0.33
Diabetes mellitus at baseline	1.27	0.71	1.15	0.77	1.36	0.64	1.48	0.61	1.36	0.57	2.49	0.69
eGFR at baseline	1.19	0.82	1.08	0.93	1.95	0.37	1.27	0.74	2.75	0.11	2.07	0.17
Median treatment duration[e]	4.86	0.014	3.07	0.024	4.25	0.029	2.88	0.039	4.59	0.036	5.22	0.0082
Introduction of mTOR inhibitor[f]	1.49	0.52	1.30	0.57	1.72	0.44	1.57	0.59	1.88	0.24	1.75	0.35

MSKCC Memorial Sloan Kettering Cancer Center, *mTOR* mammalian target of rapamycin, *eGFR* estimated glomerular filtration rate

[a] Groups 1, 2 and 3 received first-, second- and third-line targeted therapy, respectively

[b] <80 vs. ≥80

[c] Favorable or intermediate vs. poor

[d] Clear cell carcinoma vs. other

[e] After starting initial molecular-targeted therapy

[f] Everolimus or temsirolimus

significant differences in changes in renal function among the five targeted agents used during first-line therapy, whereas reduced renal function in patients receiving everolimus was significantly greater than in those receiving axitinib during second- and third-line treatments, despite the lack of significant differences among any of the other agents during the second and third lines of therapy. Although the utility of both axitinib and everolimus as sequential agents following failure of an initially introduced drug have been demonstrated in pivotal clinical trials [12, 13], given the absence of reliable trials directly comparing the efficacy of these two agents, it remains controversial which agent should be given priority when introducing them in a sequential setting. However, based on our findings, it might be preferable to use axitinib rather than everolimus after failure of first- or second-line therapy, at least in mRCC patients with insufficient renal function.

Another point of interest is the identification of factors associated with changes in renal function during treatment with molecular-targeted agents. To our knowledge, however, the available information on this issue remains limited [5–7]. For example, Launay-Vacher et al. reported that all 73 patients with RCC who received antiangiogenic therapy showed a decline in renal function over time, and patients with hypertension exhibited a greater decrease in GFR than those without hypertension [7]. In the present study, the duration of treatment with molecular-targeted agents was identified as an independent predictor of decreased renal function throughout all groups, regardless of whether they received first-, second- or third-line of treatment with targeted agents, while PS and hypertension were also shown to be independently associated with impairment of renal function in patients receiving only first-line targeted therapy. Considering these findings, special attention should be paid to the negative impact of targeted agents on renal function in mRCC patients who receive treatment for extended periods of time. Certain demographic risk factors such as unfavorable PS and hypertension that are likely correlated with renal function deterioration after the initial introduction of this type of agent should be taken into account as well.

Here we should note several limitations of this study. First, although data were assessed from a comparatively large number of patients with mRCC, this was performed as a retrospective study, and our findings will thus need to be prospectively confirmed. Second, the study included patients with heterogeneous features; that is, no restrictions were made with respect to histological subtype or previous history of treatment with immunotherapy and nephrectomy. Third, due to the timing of the approval of molecular-targeted agents in Japan, a significant proportion of patients were not treated based on the current recommended strategy of sequential targeted therapy against mRCC; therefore, more than ten different sequential treatment patterns were applied, making it difficult to assess the impact of treatment order on changes in renal function. Fourth, the suitability of eGFR >10 % as a cut-off point for renal impairment induced by molecular-targeted agents must be investigated in further studies. Finally, renal function may be significantly affected by dose intensity of targeted agents, irrespective of cumulative dose of total agents or the dose of a single agent in each line. However, the precise calculation of dose intensity for all agents for each patient would be extremely difficult due to the retrospective nature of this study conducted based on a routine clinical setting.

5 Conclusions

The findings presented in this study suggest that renal function in the majority of patients with mRCC is not significantly impaired by molecular-targeted therapies, irrespective of the administered agents; however, if the duration of treatment using these agents is extended, the negative impact of this therapy on renal function should be considered.

Compliance with Ethical Standards

Funding None.

Conflict of Interest Hideaki Miyake, Mototsugu Muramaki, Satoshi Imai, Ken-ichi Harada and Masato Fujisawa declare no conflict of interest.

References

1. Escudier B, Albiges L, Sonpavde G (2013) Optimal management of metastatic renal cell carcinoma: current status. Drugs 73:427–438
2. Figlin R, Sternberg C, Wood CG (2012) Novel agents and approaches for advanced renal cell carcinoma. J Urol 188:707–715
3. Alasker A, Meskawi M, Sun M et al (2013) A contemporary update on rates and management of toxicities of targeted therapies for metastatic renal cell carcinoma. Cancer Treat Rev 39:388–401
4. Cohen RB, Oudard S (2012) Antiangiogenic therapy for advanced renal cell carcinoma: management of treatment-related toxicities. Invest New Drugs 30:2066–2079
5. Launay-Vacher V, Aapro M, De Castro G Jr et al (2015) Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN). Ann Oncol 26:1677–1684
6. Kelly RJ, Billemont B, Rixe O (2009) Renal toxicity of targeted therapies. Target Oncol 4:121–133
7. Launay-Vacher V, Ayllon J, Janus N et al (2011) Evolution of renal function in patients treated with antiangiogenics after nephrectomy for renal cell carcinoma. Urol Oncol 29:492–494
8. Motzer RJ, Bacik J, Murphy BA et al (2002) Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 20:289–296

9. Levey AS, Stevens LA, Schmid CH et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
10. Huang WC, Levey AS, Serio AM et al (2006) Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol 7:735–740
11. Alasker A, Meskawi M, Sun M et al (2013) A contemporary update on rates and management of toxicities of targeted therapies for metastatic renal cell carcinoma. Cancer Treat Rev 39:388–401
12. Rini BI, Escudier B, Tomczak P et al (2012) Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase III trial. Lancet 378:1931–1939
13. Motzer RJ, Escudier B, Oudard S et al (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 372: 449–456