Evaluation of renal function change during first-line tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma

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Abstract

Background: The change in renal function induced by first-line tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma remains unclear.

Methods: One hundred and thirty-four patients were evaluated. Sunitinib (SU) and sorafenib (SO) were administered to 91 (67.9%) and 43 (32.1%) patients, respectively. The change in estimated glomerular filtration rate (ΔeGFR) was calculated as [(eGFR at each time point – pre-treatment eGFR)/pre-treatment eGFR] × 100. ΔeGFR was compared between SU- and SO-users using a mixed-effects model for repeated measures data with two or greater. Additionally, predictors for ΔeGFR ≤ −10% at 6 months after therapy initiation were evaluated using multivariate logistic regression analysis.

Results: Throughout the 24 months after therapy initiation, ΔeGFR was negatively greater in SU users, compared with that in SO users (P < 0.0001). In SU users, renal dysfunction was observed regardless of pre-treatment chronic kidney disease (CKD) status, whereas the magnitude of renal dysfunction was milder in SO users. In SO users without pre-treatment CKD, renal function did not significantly deteriorate. Moreover, ΔeGFR ≤ −10% was more frequently observed in SU users after 3 months (P = 0.0121) and 6 months (P = 0.0009). Finally, SU usage was an independent predictor for ΔeGFR ≤ −10% at 6 months (odds ratio 8.87, P = 0.0053), along with pre-treatment hypertension (odds ratio 4.69, P = 0.0072).

Conclusions: Deterioration of renal function was stronger with SU than SO. During SU therapy, renal function should be monitored and pre-treatment kidney function should be taken into consideration for therapy selection.

Key words: renal function, renal cell carcinoma, sunitinib, sorafenib, tyrosine kinase inhibitor

Introduction

The treatment for metastatic renal cell carcinoma (mRCC) is dominated by molecular-targeted therapies. Presently, oncologists today have a number of options to offer their patients. With the use of these agents, the survival of patients can be extended. Vascular endothelial growth factor (VEGF), one of the main angiogenic growth factors, is a major therapeutic target for mRCC treatment along with its downstream pathways and receptors. Sunitinib (SU)
and sorafenib (SO) are orally administered inhibitors of tyrosine kinases, including VEGF receptor (VEGFR) and platelet-derived growth factor receptor. These receptor tyrosine kinases play a role in the pathogenesis of clear-cell carcinoma, the predominant type of renal cell carcinoma, through the involvement of the von Hippel-Lindau gene (1–4). These novel drugs have contributed to an improvement in prognosis for patients with mRCC compared with previous treatments with cytokines (1, 5).

VEGF inhibition causes a reduction in the free VEGF levels, which may lead to endothelial dysfunction and glomerular epithelial cell (podocyte) dysregulation, and ultimately resulting in clinical adverse events, including renal dysfunction (6–9). However, the kinetics of renal function during VEGFR-tyrosine kinase inhibitor (TKI) therapy in real-world conditions remains unclear. Therefore, we investigated the changes in renal function induced by first-line TKI therapy, focusing on SU and SO, for mRCC.

Patients and methods
Between January 2007 and June 2016, 242 patients received first-line SU (n = 123) and SO (n = 119) therapy for mRCC at our department. Several patients were excluded because they had received prior treatments with cytokines (n = 35), underwent hemodialysis or kidney transplant (n = 32), or the administration period was too short (n = 15). From the remaining 160 patients, 26 patients with missing detailed data were also excluded. Finally, 134 patients (SU: n = 91 and SO: n = 43) were included in this analysis (Fig. 1).

All study procedures were approved by the Institutional Review Board of Tokyo Women’s Medical University (ID: 4297), and were in accordance with the Declaration of Helsinki.

Study design
The aim of this study was to evaluate the changes in renal function during first-line SU and SO therapy, and to identify predictive factors for the deterioration of renal function. The change in estimated glomerular filtration rate (ΔeGFR) was calculated as [eGFR at each time point – pre-treatment eGFR]/pre-treatment eGFR × 100. ΔeGFR was compared between patients that received SU and SO in the 134 included patients. Of these 134 patients, 38 patients were without pre-treatment CKD, and 96 patients received pre-treatment CKD. Moreover, ΔeGFR ≤ −10% was compared between patients who received SU and SO at various time points, respectively (3, 6, 9 and 12 months after therapy initiation). Finally, we investigated the predictive factors for ΔeGFR ≤ −10% at 6 months after therapy initiation.

Renal function
Renal function was assessed using eGFR, which was calculated using the Modification of Diet in Renal Disease equation that was recently modified for Japanese patients and is regulated by The Japanese Society of Nephrology (10):

\[\text{eGFR} = 194 \times \text{serum creatinine}^{0.1094} \times \text{age}^{0.287} \times 0.739(\text{if female}),\]

where eGFR is measured in ml/min/1.73 m², serum creatinine is in mg/dl, and age in years.

Protocol for sunitinib and sorafenib therapy
Our protocol for SU and SO therapy has been described previously (11–13).

For the SU regimen, we treated our patients with mRCC using a 4-week-on/2-week-off or a 2-week-on/1-week-off schedule. SU therapy was initiated at a dose of 50 mg/d, and was modified according to the following three patient factors: (I) age >65 y, (II) serum creatinine levels >2 mg/dl and (III) body weight <50 kg. If one of these three factors was noted, the initial dose was reduced to 37.5 mg. If two factors were noted, the initial dose was reduced to 25 mg. The minimum initial dose was 25 mg, even if all three factors were noted. The dose was subsequently increased by 12.5 mg based on the patient’s tolerance; however, the dose never exceeded 50 mg. In the SO regimen, 200 mg of SO was orally administered twice daily and was increased up to 800 mg within 2–4 weeks in an effort to reduce adverse event development typically associated with a continuous dosing schedule. In these regimens, the drugs were administered until disease progression was observed, or intolerable adverse events developed.

Relative dose intensity
For SU, relative dose intensity (RDI) was determined after 6 months (i.e. four cycles of SU) as the ratio of the cumulative dose received during the cycle to 1400 mg. For SO, RDI was defined as dose intensity divided by the dose prescribed for the duration of the study therapy (800 mg x the number of days the patient received treatment).

Patient survival
To evaluate oncologic outcomes according to first-line therapy, progression-free survival (PFS) and overall survival (OS) after therapy initiation were analyzed. PFS and OS were defined as the time from therapy initiation to the date of progression, and the date to death from any cause, respectively.

Statistical analysis
Continuous variables were analyzed using the Mann–Whitney U-test, and categorical variables were analyzed using the χ² test. ΔeGFR during therapy was compared between SU and SO users using a mixed-effects model for repeated measures data for two or greater. Multivariate logistic regression analysis was used to identify predictors for the deterioration of renal function. Patient survival was calculated using the Kaplan–Meier method and compared using the log-rank test. Risk was expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA), and P values <0.05 were considered statistically significant.
Results

Patient background
Table 1 shows the patients’ characteristics. Older age (P = 0.0436) and poorer risk (P = 0.0399) according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria were observed in patients that received SU compared with those that received SO. There were no differences in other factors including sex, prior nephrectomy status, pathology, pre-treatment eGFR level, CKD status, urine protein status, diabetes mellitus or hypertension status, and duration of treatment or follow-up period (all P > 0.05).

Change in renal function with sunitinib vs. sorafenib
Figure 2 shows the comparison of ΔeGFR between SU and SO users over the 24 months after therapy initiation in all 134 patients. The mean ΔeGFR was negatively greater in SU users, compared with that in SO users (P < 0.0001). Similar findings were observed in the patients without pre-treatment CKD (P < 0.0001, Fig. 3) and those with pre-treatment CKD (P = 0.0009, Fig. 4). According to the CKD stage, there was no significant difference in ΔeGFR between SU and SO users in the CKD 3a subgroup (n = 47, P = 0.100), as shown in Supplementary Fig. 1, whereas ΔeGFR was negatively greater in SU users, compared with SO users in the CKD 3b subgroup (n = 39, P = 0.0202), as shown in Supplementary Fig. 2.

Predictors for deterioration of renal function
Table 2 shows the multiple logistic regression analysis for independent predictors for ΔeGFR ≤ −10% at 6 months after therapy initiation in a cohort of 92 patients who received therapy for 6 months. Overall, 36 patients (39.1%) had ΔeGFR ≤ −10%. Multivariate analysis revealed that first-line SU therapy (ORs 14.0, P = 0.0016) and pre-treatment hypertension (ORs 4.65, P = 0.0073) were independent predictors after adjusting for other factors including age, sex, RDI at 6 months, baseline serum eGFR level and pre-treatment diabetes mellitus status.

Patient survival with sunitinib vs. sorafenib
During the follow-up period, disease progression (i.e. PFS) and death from any cause (i.e. OS) were observed in 96 (71.6%) and 78 (58.2%) patients, respectively (Table 1). Figure 6 shows that there

Table 1. Patient background

| Variable                        | Sunitinib (N = 91) | Sorafenib (N = 43) | P     |
|---------------------------------|--------------------|--------------------|-------|
| Sex                             |                    |                    | 0.417 |
| Male (ref. female)              | 66 (72.5%)         | 34 (79.1%)         |       |
| Age, years                      | 65.0 (60.0–71.0)   | 68.0 (63.0–74.0)   | 0.0436|
| Prior nephrectomy               |                    |                    | 0.903 |
| With (ref. without)             | 79 (86.8%)         | 37 (86.1%)         |       |
| Pathology                       |                    |                    | 0.746 |
| CCC                             | 68 (74.7%)         | 31 (72.1%)         |       |
| Non-CCC                         | 23 (25.3%)         | 12 (27.9%)         |       |
| CCC with spindle                | 7 (7.69%)          | 1 (2.33%)          |       |
| Papillary renal cell carcinoma type 2 | 7 (7.69%) | 4 (9.30%) |       |
| Others                          | 4 (4.40%)          | 1 (2.33%)          |       |
| Unknown                         | 5 (5.49%)          | 6 (14.0%)          |       |
| MSKCC                           |                    |                    | 0.0399|
| Favorable                       | 15 (16.5%)         | 6 (14.0%)          |       |
| Intermediate                    | 60 (65.9%)         | 36 (83.7%)         |       |
| Poor                            | 16 (17.6%)         | 1 (2.33%)          |       |
| eGFR at treatment initiation, ml/min/1.73 m² | 49.4 (37.9–61.3) | 51.7 (41.6–66.7) | 0.0758|
| CKD at treatment initiation     |                    |                    | 0.741 |
| With                            | 66 (72.5%)         | 30 (69.8%)         |       |
| Grade 3/4/S                     | 59 (64.8%) /6 (6.39%) /1 (1.10%) | 27 (62.8%)/2 (4.65%)/1 (2.33%) | 0.437 |
| Without                         | 23 (27.5%)         | 13 (30.2%)         |       |
| Urine protein at treatment initiation | 26 (28.6%) | 9 (20.9%) |       |
| With (ref. without)             |                    |                    | 0.347 |
| Diabetes mellitus               | 14 (15.4%)         | 8 (18.6%)          |       |
| With (ref. without)             |                    |                    | 0.639 |
| Hypertension                    | 36 (39.6%)         | 18 (41.9%)         | 0.800 |
| With (ref. without)             | 9,17 (5.16–18.8)   | 7.69 (3.91–18.6)   | 0.678 |
| Duration of treatment, months   | 63 (69.2%)         | 33 (76.7%)         | 0.368 |
| Disease progression             | 54 (59.3%)         | 24 (55.8%)         | 0.699 |
| Death from any cause            |                    |                    |       |
| Duration of follow-up, months   | 19.7 (9.76–31.5)   | 15.5 (10.9–31.4)   | 0.834 |

Data are presented as frequency (percentage) or median (interquartile range), unless otherwise noted.

CCC; clear-cell carcinoma; MSKCC; Memorial Sloan Kettering Cancer Center; eGFR; estimated glomerular filtration rate; CKD; chronic kidney disease.
was no significant difference in PFS nor OS between patients who received SU and SO (median PFS: 10.6 vs. 11.6 months, \(P = 0.478\); OS: 24.4 vs. 22.8 months, \(P = 0.938\)). Additionally, similar findings were observed in the 92 patients who received therapy for 6 months (PFS: 14.7 vs. 15.7 months, \(P = 0.231\); OS: 33.7 vs. 37.6 months, \(P = 0.449\)) (Supplement Fig. 3).

**Discussion**

SU and SO have similar mechanisms of anti-carcinogenesis via VEGFR-TKI, and the pharmacokinetics and pharmacodynamics are also quite similar. Nevertheless, the present study revealed that SU had a larger negative impact on renal function, compared with SO during first-line TKI therapy for mRCC. Moreover, the deterioration patterns were different between these two therapies; SU caused a deterioration of renal function soon after therapy initiation and the deterioration occurred regardless of pre-treatment renal function (Figs 2–4). Meanwhile, SO did not have a negative effect on renal function for approximately the first 9 months after therapy initiation, and thereafter, renal dysfunction developed, especially in patients with pre-treatment CKD (Figs 2 and 4). In addition, renal function was not deteriorated by SO in patients without pre-treatment CKD (Fig. 3). Finally, multivariate analysis showed that SU usage was an independent predictor for renal dysfunction during first-line therapy for mRCC. To the best of our knowledge, this is the first study to demonstrate that SU has a larger negative impact on sequential renal function than SO.

**Figure 2.** \(\Delta eGFR\) by sunitinib and sorafenib therapy in 134 patients. Mean \(\Delta eGFR\) was negatively greater in sunitinib users compared with that in sorafenib users throughout the study (\(P < 0.0001\)). Error bars indicate standard deviation. \(P\) value was obtained using a mixed model test of trend profile. \(\Delta eGFR\), change in estimated glomerular filtration rate.

**Figure 3.** \(\Delta eGFR\) by sunitinib and sorafenib therapy in 38 patients without pre-treatment chronic kidney disease. Mean \(\Delta eGFR\) was negatively greater in sunitinib users compared with that in sorafenib users throughout the study (\(P < 0.0001\)).
SU-induced renal dysfunction has been reported in previous studies. Motzer et al. reported that 66/375 (17.6%) patients experienced all-grade creatinine increase during SU therapy for mRCC (14), and Zhu et al. reported in a meta-analysis that the incidence of all-grade creatinine increase was 65.6% in patients that received SU therapy (1). We have previously reported that SU therapy was associated with decreased eGFR; the median relative change in eGFR from baseline to the nadir was -21% (9). Meanwhile, Miyake et al. reported no change in renal function during first-line targeted therapy (15). The differences in findings might be caused by different study designs, as several types of agents were analyzed together. Unlike SU, studies evaluating SO's impact on renal function are limited. SO is considered a safer targeted agent for tolerability (16–18). In this context, we found that the toxicity of SO on renal function was milder, compared with that of SU, especially in patients without CKD (Fig. 3).

Interestingly, among patients with pre-treatment CKD, the magnitude of ΔeGFR difference between the two drugs was higher in the CKD 3b subgroup compared with the CKD 3a subgroup that was caused by severer deterioration of renal function from SU therapy in the CKD 3b subgroup (Supplementary Figs 1 and 2). Thus, even though impairment of renal function was observed during SU therapy regardless of pre-treatment CKD status, patients with severe renal insufficiency might need to be more carefully monitored during SU therapy.

Moreover, the magnitude of ΔeGFR induced by SU was higher in patients without pre-treatment CKD compared with those with CKD 3a (Fig. 3 and Supplementary Fig. 1). This finding was consistent with a previous study by Khan et al. who suggested that a stronger decline of creatinine clearance was observed in patients with de novo renal insufficiency (i.e. without baseline CKD) compared with those with baseline renal insufficiency during SU or SO therapy (19).

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**Figure 4.** ΔeGFR by sunitinib and sorafenib therapy in 96 patients with pre-treatment chronic kidney disease. Mean ΔeGFR was negatively greater in sunitinib users compared with that in sorafenib users throughout the study (P = 0.0009).

**Figure 5.** Renal function deterioration with sunitinib vs. sorafenib therapy. The number of patients with ΔeGFR ≤ -10% was significantly higher in sunitinib users compared with that in sorafenib users at 3 and 6 months after therapy initiation (3m: 32.5% vs. 10.8%, P = 0.0121; 6m: 50.0% vs. 13.8%, P = 0.0009). The number of sunitinib users evaluated after 3, 6, 9 and 12 months was 27, 31, 24 and 25, respectively, and the number of sorafenib users was 13, 19, 18 and 16, respectively. NS, not significant.

**Table 2.** Multivariate logistic regression analysis for the predictors of ΔeGFR ≤ -10% at 6 months after first-line therapy in a cohort of 92 patients who received first-line therapy for 6 months

| Variable                      | Multivariate ORs (95% CI) | P     |
|-------------------------------|--------------------------|-------|
| *Age*                         | 0.98 (0.92–1.04)         | 0.480 |
| *Sex*                         | 1.19 (0.34–4.17)         | 0.788 |
| *Therapy*                     |                          | 0.0016|
| Sunitinib (ref. sorafenib)    | 14.0 (2.72–72.5)         |       |
| *RDI during 6 months*         | 0.98 (0.94–1.02)         | 0.317 |
| *Baseline serum eGFR level*   | 1.03 (0.99–1.06)         | 0.150 |
| *Diabetes mellitus*           |                          | 0.0712|
| With (ref. without)           | 4.00 (0.89–18.1)         | 0.0073|
| *Hypertension*                |                          |       |
| With (ref. without)           | 4.65 (1.51–14.3)         |       |

*Continuous variable.

ORs, odds ratio; CI, confidence interval; RDI, relative dose intensity; eGFR, estimated glomerular filtration rate.
Fukuda et al. reported that patients treated for a long time tended to have greater eGFR deterioration (9). In another study, there was a significant association between the deterioration of renal function and treatment duration (15). Thus, as the analysis targeting renal function could be affected by treatment duration, we evaluated the value of renal dysfunction at a fixed time-point (i.e., at 6 months after therapy initiation). Moreover, since we believed that not only duration but also intensity of therapy could influence renal function, RDI was incorporated into the multivariate analysis (Table 2). Consequently, SU usage was an independent factor after exclusion of possible bias induced by these confounders.

Although renal function has been suggested as an ‘on-target’ adverse event induced by TKI in several studies, the evidence remains unclear (9,20). Previously, we reported that renal dysfunction induced by SU had an association with better prognosis (9). Another study indicated that presence of proteinuria, and not renal insufficiency, was correlated with poorer PFS (20). In this context, our analysis did not show that oncologic outcome was associated with differences of deterioration of renal function between SU and SO (Fig. 6 and Supplement Fig. 3).

It is difficult to adequately explain the different findings for these two VEGFR-TKI drugs. The loss of VEGF function through pharmacologic inhibition is associated with damage to glomerular endothelial cells and podocytes. Additionally, anti-VEGF treatment leads to vasoconstriction via decreased nitrogen monoxide and prostaglandin I2 production, resulting in decreased blood flow in the glomeruli (7,21). SU and SO target a number of kinases, such as VEGFRs or platelet-derived growth factor receptors; they are not selective. Although these two drugs have similar pharmacokinetics/pharmacodynamics characteristics, including mechanism of action, metabolism and elimination (22), SU inhibits a wider range of tyrosine kinases (23,24). Thus, SU might have a potentially stronger influence on the deterioration of renal function; however, this is merely speculation.

Our study is limited by its retrospective design and a small number of patients. Patients with poor performance status or other patient-related backgrounds could influence the physician’s treatment plan; thus, unmeasured or immeasurable confounders might have affected our findings. Therefore, our findings should be confirmed in a larger prospective randomized controlled trial. Additionally, as shown in Table 1, patients that received SO were older, and had a trend towards better baseline renal function, which may have affected the results. Though possible confounders were adjusted through multivariate analyses, patient background should be matched in further studies.

In conclusion, SU and SO can deteriorate renal function during first-line therapy for mRCC; however, the magnitude of deterioration was higher in SU users. Renal dysfunction was observed, regardless of pre-treatment renal function in SU users, whereas renal function was not significantly deteriorated by SO, especially in patients without pre-treatment CKD. Consequently, renal function should be monitored during SU therapy, as well as in patients with pre-treatment CKD during SO therapy. We believe that these findings will be helpful for decisions on treatment strategies for first-line VEGFR-TKI therapy for mRCC.

Supplementary data
Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest statement
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