Efficacy and safety of sunitinib alternate day regimen in patients with metastatic renal cell carcinoma in Japan: Comparison with standard 4/2 schedule

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Abstract
Aim: Sunitinib is a standard agent for metastatic renal cell carcinoma (mRCC). The standard schedule, 4 weeks-on followed by 2 weeks-off (4/2 schedule), often does not maintain an adequate dosage because of the severe adverse events (AEs). We compared the efficacy and safety of an alternative every other day (q.a.d.) dosing with that of the 4/2 schedule in mRCC patients.

Methods: Of the 55 Japanese patients, 32 and 23 were administered 4/2 (standard group) and q.a.d. schedules (50 or 37.5 mg, every other day; experimental groups), respectively. The AEs, anticancer effects, and trough plasma concentrations of sunitinib were compared between them.

Results: The most common AE in the standard group was thrombocytopenia (43.2%), but it was observed in only two patients in the experimental group (8.7%). Although leukopenia and hand-foot syndrome were both detected in six patients (18.8%) in the standard group, no patients had these AEs in the experimental group. The incidence of dose interruption in the experimental group (21.7%) was significantly lower than that in the standard group was (59.4%, P = 0.005). Time to progression (TTP) and overall survival (OS) of the experimental group were better than those of the standard group (P < 0.001 and P = 0.002, respectively). Mean plasma levels in the experimental group (64.83 ng/mL) were significantly lower than those in the standard group (135.82 ng/mL, P < 0.001) were.

Conclusion: Sunitinib administered q.a.d. was safe and effective for mRCC patients. We speculate that the persistent optimal drug plasma concentrations contributed to these effects.

KEYWORDS
alternative sunitinib regimen, plasma concentration, prognosis, renal cell carcinoma, safety

1 | INTRODUCTION

Renal cell carcinoma (RCC) is a common urological cancer and approximately 30% of patients present with metastatic disease. Unfortunately, conventional treatment strategies often have limitations in prolonging survival and minimizing adverse events (AEs) in patients with metastatic RCC (mRCC). In recent years, immune checkpoint inhibitors have been reported to be effective in patients with mRCC, and there is a consensus that they are the epochal therapeutic strategy for patients with mRCC.¹ However, immune-checkpoint inhibitors are currently extremely expensive and produce severe AEs. Therefore, we believe that efforts should be focused on improving the anticancer effects and decreasing the AEs of conventional therapies including molecularly target therapy, in patients with mRCC.

Sunitinib malate is an oral tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor.² It is approved for mRCC treatment because of its high level of activity, reflected in high response rates and improvements in survival.³ In various guidelines, sunitinib is still the standard first-line therapy for patients with mRCC.⁴,⁵ The standard...
dosing schedule for sunitinib is 4 weeks-on and 2 weeks-off (4/2 schedule) to enable patients to recover from bone marrow suppression and drug toxicities. However, clinically, maintaining the targeted sunitinib dosing is difficult with the high prevalence of serious AEs that can lead to dose reductions or interruptions. As a result, these patients are not exposed to the full anticancer effects of sunitinib. Therefore, various clinical trials of alternative sunitinib treatment regimens have been conducted.

There is a consensus that the plasma concentration of an anticancer agent is the determinant of its efficacy and safety in patients with cancer. Specifically, an optimal plasma concentration maximizes the anticancer effects and minimizes the AEs. For sunitinib, the target plasma concentration range is 50–100 ng/mL. However, based on its half-life of 50–75 h, pharmacokinetic studies of sunitinib have indicated that the plasma concentration in patients on the standard regimen (i.e., 4/2 schedule) is above the upper levels of the target range during the on-time and below the lower levels during the off-time. Therefore, we devised a new alternative sunitinib treatment regimen to maintain the optimal plasma concentration by administering sunitinib every other day. In this study, we compared the anticancer effects and safety between the 4/2 schedule and our new regimen in Japanese patients with mRCC. In addition, plasma sunitinib concentrations were measured in patients on both regimens.

## 2 METHODS

We retrospectively investigated 55 Japanese patients with mRCC who were treated with sunitinib between April 2009 and December 2015 at Nagasaki University Hospital. The performance status of all patients was over 2. All patients received the treatment under the care of three urologists (K. Ohba, Y. Miyata, and Y. Mochizuki). RCC was histologically confirmed using surgically resected renal tumors or biopsy specimens. Metastasis was evaluated using whole-body computed tomography (CT) and bone scintigraphy before treatment commenced. The patients were then stratified according to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification. All patients had been treated with sunitinib, and 14 had also received it as a second-line therapy. In our study population, 13 patients were treated with sorafenib as first-line therapy because of the approval period of the Japanese medical system. In contrast, if an intolerable AE was observed in patients treated with the initial starting dose of sunitinib (50 or 37.5 mg/day), it was decreased to 37.5 mg/day or replaced with another agent. Swimmer plots of the detailed course of such treatments are shown in Figure 1. Finally, the ranges of sunitinib treatment periods as first-line and second-line were 3–29 and 4–24 months, respectively.

We previously treated mRCC with the standard 4/2 dosing regimen. However, from June 2011, 23 patients were started on sunitinib 50 or 37.5 mg, every other day (q.a.d., experimental group). The remaining 32 patients remained on the 4/2 schedule (standard group). Thus, our study design was not a randomized clinical trial.

Measurable tumors were assessed every 3 months and at the end of the treatment. The best tumor response was determined according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The clinical benefit rate was defined as CR + PR + SD. Time to progression (TTP), AE frequency, best response and overall survival (OS) were assessed in all 55 patients. Patients provided written informed consent to participate in all aspects of the study. The study protocol was approved by the Human Ethics Review Committee of Nagasaki University Hospital (Nagasaki, Japan), and was conducted according to the Declaration of Helsinki.

AEs were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0, and the worst grade of AE was also determined. The sunitinib dose was temporarily reduced or suspended based on AEs and the health status of each patient, as required.

The plasma levels of sunitinib were calculated as trough concentrations (ng/mL), and they were assayed two or three times using high-performance liquid chromatography (HPLC) according to a previous report. Blood samples were collected at steady state just before drug administration in both groups (at 24 hours after last dose with standard group and 48 hours after last dose with experimental group) at
3 months after starting sunitinib treatment, and then the plasma concentrations were immediately measured. In this study, we excluded patients with a short duration of treatment (<3 months) to obtain accurate sunitinib trough concentrations.

The patient characteristics and frequency of AEs were compared using the Student's t-test or Mann–Whitney U tests. Continuous variables are expressed as the means ± standard deviation (SD) or medians. The TTP and OS were determined using Kaplan–Meier curves, and statistical significance was analyzed using the log-rank test. Values with P < 0.05 were considered statistically significant, and all the data were statistically analyzed using the PASW statistics 18.

3 | RESULTS

As shown in Table 1, there was no significant difference in all clinicopathological features between the experimental and standard groups. Specifically, age, sex and MSKCC risk at the beginning of sunitinib treatment were similar between the two groups. In addition, the frequency of patients treated with sunitinib as a second-line therapy was similar between the groups. The median (range) follow-up period was 24.6 (5.3–95.0) months.

The means ± SDs of trough plasma concentrations of sunitinib were determined in 156 and 82 samples from the experimental and control groups, respectively. Concentrations in the experimental group were significantly lower than those in the control group were (64.83 ± 21.91 vs 135.82 ± 48.78 ng/mL, P < 0.001; Figure 2).

The information on grade ≥3 treatment-related AEs is shown in Table 2. In the control group, the most common AE was thrombocytopenia (n = 14, 43.2%). In contrast, thrombocytopenia was observed in only two patients (8.7%) in the experimental group. Similarly, although leukopenia and hand-foot syndrome were also common AEs (both n = 6; 18.8%) in the control group, there were no patients with these AEs in the experimental group. Thus, the frequencies of grade ≥3 treatment-related AEs in the experimental group were clearly lower than those in the control group were (Table 2). In contrast, renal dysfunction and heart failure were observed only in the experimental group, albeit at a low frequency. Finally, the incidence of regimen interruption due to severe AE was significantly lower (P = 0.005) in the experimental group (n = 5, 21.7%) than it was in the control group (n = 19, 59.4%).

On the contrary, among 24 patients with grade ≥3 treatment-related AEs, 5 (20.8%), 8 (33.3%) and 11 (45.8%) patients showed plasma sunitinib concentrations of <100, 100–200 and <200 ng/mL, respectively. Patients recovered from all severe AEs including renal dysfunction and heart failure following sunitinib withdrawal.

| TABLE 1 | Patients’ characteristics according to treatment regimen |
|----------|--------------------------------------------------------|
|          | Standard, n = 32                                      | Experimental, n = 23 |  P-value |
| **Beginning of sunitinib** |
| Age; years, mean ± SD | 57.6 ± 15.6 | 59.9 ± 10.9 | 0.831 |
| Sex; male, n (%) | 28 (87.5) | 19 (82.6) | 0.707 |
| MSKCC risk, n (%) | 0.963 |
| Favorable | 7 (21.9) | 5 (21.7) | |
| Intermediate | 20 (62.5) | 15 (65.2) | |
| Poor | 5 (15.6) | 3 (13.1) | |
| **Histological, n (%)** | 0.446 |
| Clear cell | 28 (81.3) | 21 (91.3) | |
| Non-clear cell | 6 (18.7) | 6 (18.7) | |
| **As second-line, n (%)** | 0.756 |
| Yes | 8 (25.0) | 6 (26.1) | |
| **At diagnosis** |
| Pathological T stage, n (%) | 0.372 |
| T1 | 7 (21.9) | 6 (26.1) | |
| T2 | 4 (12.5) | 0 (0.0) | |
| T3 | 20 (62.5) | 16 (69.6) | |
| T4 | 1 (3.1) | 1 (4.3) | |
| Lymph node metastasis, n (%) | 0.376 |
| N0 | 26 (81.3) | 16 (69.6) | |
| N1 | 4 (12.5) | 7 (30.4) | |
| N2 | 2 (6.3) | 0 (0.0) | |
| Distant metastasis, n (%) | 0.271 |
| M0 | 15 (46.9) | 7 (30.4) | |
| M1 | 17 (53.1) | 16 (69.6) | |
FIGURE 2  Trough concentrations of sunitinib in standard and experimental groups. Mean levels in the experimental group were significantly lower ($P < 0.001$) than those in the standard group were. In contrast to that of the experimental group, the trough concentrations of most patients in the standard group were over the upper limit of the optimal serum concentration (dashed line).

### TABLE 2  Frequencies of ≥grade 3 adverse events

|                      | Standard | Experimental |
|----------------------|----------|--------------|
| Thrombocytopenia, n (%) | 14/43.8  | 2/8.7        |
| Leukopenia           | 6/18.8   | 0/0.0        |
| Hand-foot syndrome   | 6/18.8   | 0/0.0        |
| Appetite loss        | 4/12.5   | 0/0.0        |
| Diarrhea             | 2/6.3    | 2/8.7        |
| Vomiting             | 2/6.3    | 0/0.0        |
| Fatigue              | 2/6.3    | 0/0.0        |
| Proteinuria          | 1/3.1    | 1/4.3        |
| Taste disorder       | 1/3.1    | 0/0.0        |
| Fever up             | 1/3.1    | 0/0.0        |
| Gastric ulcer        | 1/3.1    | 0/0.0        |
| Renal dysfunction    | 0/0.0    | 2/8.7        |
| Heart failure        | 0/0.0    | 1/4.3        |

FIGURE 3  Kaplan–Meier survival curves of (A) time to progression and (B) cause-specific survival in patients with metastatic renal cell carcinoma. For both parameters, the outcomes in the experimental group were significantly better than those in the standard group were not statistically significant ($P = 0.117$). On the contrary, the duration of Sd in the experimental group (median/range = 20.1/5.5–54.4 month) was significantly higher ($P < 0.001$) than that in the standard group (6.7/1.7–80.5). If tumor progression was detected, another agent (axitinib, everolimus or pazopanib) was used as the next-line therapy. In our study population, no patient had a short duration of treatment (<3 months) due to tumor progression including death.

The median TTP in the experimental group was significantly higher than that in the control group was (27.6 months vs 7.4 months, $P < 0.001$), and the Kaplan–Meier survival curves also supported these findings (Figure 3A). Similarly, analysis of the OS showed that the experimental group had a better prognosis than the control group did ($P = 0.002$, Figure 3B).

The best responses for patients in the experimental and control groups are shown in Table 3. In this study, no patient had a CR, regardless of treatment. In the control group, 12 and 10 patients were determined to have PR and Sd, respectively. In the experimental group, PR and Sd were obtained in 10 patients each. Thus, the clinical benefit rate in the experimental group (20/23 = 87.0%) was higher than that in the standard group (22/32 = 68.8%), although the difference was
DISCUSSION

Our results demonstrate that administering sunitinib q.a.d. is safer than administering it using the standard 4/2 regimen in patients with mRCC. These results were expected because the plasma concentrations in the experimental group were lower than those in the standard group. When we measured plasma concentrations to verify our expectation, the mean trough plasma concentration of sunitinib in the experimental group was less than half that of the standard group. Regarding the optimal plasma concentration of sunitinib, previous pharmacokinetic studies showed it to be between 50 and 100 ng/mL. In fact, there is a report that the frequency of grade ≥3 toxicities in patients with RCC with ≥100 ng/mL sunitinib was greater than that in patients with <100 ng/mL, and other investigations have corroborated this finding. In our study, we noticed that the plasma concentration of the standard group (135.82 ± 48.78 ng/mL) exceeded the optimal concentration. Therefore, in our study population, the optimal concentration of sunitinib could be obtained in the experimental group (administered the q.a.d. regimen). Renal dysfunction and heart failure were observed in the experimental group. These occurred in very few patients, and they may have had preexisting disease conditions or their presence in the experimental group may have been due to random chance, rather than drug treatment. Future studies would clarify the reasons.

One of the most interesting study results is that the prognosis of the experimental group was significantly better than that of the standard group. The mean duration of the TPP in the standard group (7.4 months) was similar to that in previous studies (4.3–19 months). Specifically, the TPP in our experimental group was longer than that in the standard regimen, regardless of the study population. We speculate that the anticancer effects of sunitinib depend on its concentration in tumor tissues. However, unfortunately, it is very difficult to measure the tissue concentrations of sunitinib. The area under the curve (AUC) of sunitinib concentrations is significantly associated with TTP and OS, and AUC is closely correlated with trough concentrations. Based on these facts, the trough concentrations appear to be associated with the efficiency of sunitinib treatment. However, it is important to note that there is no evidence to support that sunitinib concentrations above the optimal therapeutic range further increase anticancer effects. The advantage of sunitinib concentrations above the optimal plasma level may be minimal in patients with mRCC. As mentioned above, high concentrations of sunitinib (over 100 ng/mL) are associated with the severity and frequency of AEs. As a result, high serum concentrations worsen tolerance and shorten treatment periods. Our results showed that the treatment periods in the experimental group were longer than those in the standard group. We speculate that this was one reason the survival period of the experimental group was significantly better than that of the standard group.

In addition to improving tolerance, we also scrutinized the differences in drug administration. In brief, our experimental method did not have a prolonged off-treatment period. Many studies of alternative sunitinib regimens have been reported, and these regimens improve the tolerance of patients with RCC. For example, a regimen comprising 2-weeks-on and 1-week-off was tolerated more than the standard regimen was. However, this report also showed that although PFS in the alternative regimen was longer than that in the standard regimen (18.4 months vs 9.1 months, respectively), the difference was not statistically significant (P = 0.13). In addition, the randomized phase II RESTORE trial of sunitinib revealed that the 2-weeks-on and 1-week-off regimen was less toxic than the standard regimen, whereas the TTP was similar between them (12.1 months vs 10.1 months, respectively). Thus, an off-treatment period is useful for increasing tolerance but does not improve the prognosis of patients with RCC. However, the off-treatment period in our experimental regimen was only one day. We speculate that maintaining the optimal range of trough sunitinib concentrations may be important for favorable outcomes. However, recently, the pharmacokinetics and pharmacodynamics of sunitinib in the alternative 2-weeks-on and 1-week-off regimen in mRCC was reported, and pharmacological data are important in the discussion of strategies for improving anticancer effects and adverse events. We also think that the pharmacological data collection contributed useful information to the discussion in this manuscript.

The major limitation of our study is the relatively small number of patients and the retrospective design. In addition, the difference in the approved drug for renal cell carcinoma in Japan was a factor; for example, bevacizumab has not been approved. Furthermore, the difference on timing of blood sample collection should be noted. However, our study is the first analysis of the efficacy and safety of administering sunitinib q.a.d. We believe that our results are important for discussing treatment strategies in patients with mRCC. Furthermore, the indicators of survival period in our experimental group were much longer than those of the standard group and other alternative sunitinib regimens described in previous reports. On the contrary, pharmacogenomic determinants of TKIs are race-dependent. The relationships between pharmacogenomics determinants and sunitinib-induced toxicities in the Asian population have been previously reported. We would like to emphasize the importance of further studies in other races and larger study populations to provide solid evidence of the anticancer effects and safety of our experimental regimen. In addition, the relationship between the plasma concentration of sunitinib and patient outcome should be clarified in more detailed studies with a larger study population. Currently, various interesting clinical trials of alternative sunitinib treatment regimens such as intermittent therapy have been reported. We believe that more detailed information on this subject is currently required to improve the outcome of patients with mRCC.

In conclusion, our results showed that the experimental regimen of q.a.d. administration could simultaneously improve survival and tolerability. The low risk of treatment interruption and serious adverse events, which allowed treatment to continue for longer periods and maintain the better physical conditions, likely explains these improvements. The absence of a prolonged off-treatment period that allows the persistence of plasma sunitinib concentrations is also a suggested reason. We believe that this alternative regimen of sunitinib administration q.a.d. is worth further consideration as a useful treatment strategy in patients with mRCC.
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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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