Cancer Chemotherapy and Pharmacology (2019) 84:987–992
https://doi.org/10.1007/s00280-019-03935-x

ORIGINAL ARTICLE

Optimal dose of sunitinib for long-term treatment in Japanese patients with renal cell carcinoma

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Received: 6 August 2019 / Accepted: 21 August 2019 / Published online: 3 September 2019

Abstract

Background/aim Sunitinib is used for the treatment of metastatic renal cell carcinoma (mRCC). Asian patients, including Japanese, tend not to tolerate long-term sunitinib therapy of 50 mg p.o. once daily for 4 weeks, followed by 2 week off treatment due to severe adverse events at this dosage level. The aim of this retrospective study was to investigate the optimal dose of sunitinib for long-term continuation in Asian patients with mRCC.

Patients and methods The study cases were 50 patients with mRCC who were treated with sunitinib between June 2008 and December 2017. Risk analysis for "unacceptable" adverse events (depending on the physician, ranging from grade 2 to ≥ grade 3) leading to discontinuation of sunitinib was determined by time-dependent Cox proportional hazard regression analysis.

Results A total of 54 unacceptable adverse events leading to discontinuation occurred. Multivariable analysis indicated that a sunitinib dose of ≤ 37.5 mg/day significantly reduced the risk of discontinuation due to adverse events in comparison with 50 mg/day [hazard ratio (HR) 0.08, 95% confidence interval (CI) 0.03–0.21, $p < 0.001$). The progression-free survival (PFS) with a sunitinib dose ≤ 37.5 mg/day was longer than that associated with a dose of 50 mg/day, albeit not to a statistically significant degree (120 days for ≤ 37.5 mg/day vs 41 days for 50 mg/day, HR 0.39, 95% CI 0.10–1.44, $p = 0.157$).

Conclusion Our findings suggest that the optimal dose of sunitinib for Asian, including Japanese, patients with mRCC is ≤ 37.5 mg/day.

Keywords Sunitinib · Metastatic renal cell carcinoma · Adverse events · Asian patients

Introduction

Sunitinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, is used for the treatment of metastatic renal cell carcinoma (mRCC) [1–4]. Sunitinib has a robust therapeutic effect and is considered first-line treatment for mRCC in therapeutic guidelines [1–4]. The approved administration method of sunitinib in Japan was patterned after that in the EU and USA: administered at a starting dose of 50 mg p.o. q.d. for 4 weeks, followed by 2 week off treatment.

The suggested dose has a therapeutic effect in Asian patients, including Japanese, similar to the effect in Caucasian patients, but with more severe adverse events [5–7]. A postmarketing surveillance study revealed that adverse events ≥ grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [8] occurred in 70% of Japanese patients and tended to occur within 4 weeks of first administration [9]. Thus, it is speculated that many Asian patients cannot continue the standard sunitinib therapy dose due to these severe adverse effects. The possibility of treatment interruption and/or dose reduction raises

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concern about reduced therapeutic effect. In one study, progression-free survival (PFS) was prolonged in Asian patients receiving treatment for more than two courses or > 60% relative dose intensity (≥ 30 mg/day) [10]. Therefore, to allow continuation of treatment, it is important to decrease the adverse event rate while preserving the therapeutic effect in patients receiving sunitinib.

There have been other reports on adjusting the daily dose of sunitinib to maintain the therapeutic effective while decreasing adverse event frequency in Asian patients [11, 12]. Nagata et al. showed in results of pharmacokinetic–pharmacodynamic analysis that the initial daily dose of sunitinib could be reduced to 37.5 mg/day or 25 mg/day to avoid severe thrombocytopenia in most Japanese RCC patients [11]. However, it is important to note that the sample size of this study was very small (n = 6). Teo et al. also reported in Asian patients with mRCC that an attenuated sunitinib dosing regimen of 37.5 mg/day in repeated cycles of 4 weeks on/2 weeks off provided sufficient drug exposure with a lower incidence of toxicity. However, this dose was not compared with a dosing regimen of 50 mg/day [12]. Therefore, the optimal daily dose of sunitinib in Asian patients with mRCC has yet to be established.

The aim of this retrospective study was to investigate the optimal dose of sunitinib for long-term continuation in Japanese patients with mRCC.

Patients and methods

Patients and data collection

A total of 51 cases of mRCC received sunitinib in Gifu University Hospital during the period between June 2008 and December 2017. Among them, one patient who initially received sunitinib in another hospital was excluded, and the remaining 50 cases were enrolled. Data were extracted from the electronic medical records obtained from the central database in our hospital and retrospectively analyzed.

The present study was conducted according to the guidelines for human studies of the ethics committee of Gifu University Graduate School of Medicine and the Government of Japan, and was approved by the university's institutional review board (Approval No. 2018–187). In view of the retrospective nature of the study, informed consent from the subjects was not mandated.

Sunitinib treatment

Patients were treated with oral sunitinib, in which the initial dose (12.5, 25, 37.5, or 50 mg/day) was determined individually by each attending physician based on the patient's age, body weight, laboratory data, and performance status (PS). Treatment cycles were scheduled to last 6 weeks (4 weeks on/2 weeks off) or 3 weeks (2 weeks on/1 week off). Discontinuation or dose reduction of sunitinib was instituted in patients who suffered from "unacceptable" adverse events (depending on the physician, ranging from grade 2 to ≥ grade 3). Therapy was resumed in the subsequent treatment cycle after recovery from the adverse events, with the dose of sunitinib reduced based on individual safety and tolerability.

Assessment of adverse events

Adverse events included hematological toxicities, such as neutropenia, anemia, and thrombocytopenia, and non-hematological toxicities such as increased alanine aminotransferase, increased serum creatinine, infection, diarrhea, fatigue, and hand–foot syndrome.

Efficacy of chemotherapy

Progression-free survival (PFS) was defined as the time from the start of sunitinib treatment to objective tumor progression or death due to any cause, whichever occurred first.

Statistical analysis

Data were analyzed using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan) and R software version 3.5.1 (www.r-project.org). The two-sided p values less than 0.05 were considered significant. Baseline characteristics were described using mean and standard deviation for continuous variables and frequency and percentage for categorical variables.

The dose of sunitinib (mg/day) was treated as a "time-dependent" exposure variable, and the incidence of unacceptable adverse events leading to discontinuation was treated as a primary outcome. Patients were examined over the interval from the initiation or resumption of therapy to the incidence of severe adverse events or completion of therapy. For primary analysis, a time-dependent Cox proportional hazards regression model was used to evaluate the effect of dose on adverse events leading to discontinuation with adjustment for time-fixed covariates. The time-fixed covariates were only restricted to three variables, age, sex, and weight to avoid overfitting. Second, a time-dependent Cox proportional hazards regression was also used to assess the effect of sunitinib dose adjusted by weight per day (mg/kg/day) in those severe adverse events with adjustment for age and sex. To allow for non-linear relationships, modelling of the dose with adjustment by weight per day (mg/kg/day) was done using restricted cubic splines in the manner of Mizuno et al. [13].

To assess the PFS with starting doses of sunitinib of ≤ 37.5 or 50 mg/day, the Simon and Makuch's modified Kaplan–Meier curves was used [14].

Results

Patient demographics

Patient demographics are shown in Table 1. The initial dosage of sunitinib was as follows: 50.0 mg/day in 28 (56.0%) patients, 37.5 mg/day in 16 (32.0%) patients, 25.0 mg/day in 5 (10.0%) patients, and 12.5 mg/day in 1 (2.0%) patient. The most common metastatic sites were lung ($n=34$) followed by bone ($n=14$), lymph nodes ($n=10$), liver/pancreas ($n=7$), and brain ($n=4$). Thirty-eight (76.0%) patients were receiving sunitinib as first-line chemotherapy for mRCC, while the others had been previously treated as follows: interferon-alfa ($n=10$, 20.0%), sorafenib ($n=1$, 2.0%), and gemcitabine and carboplatin ($n=1$, 2.0%).

Incidence of unacceptable adverse events leading to discontinuation

A total of 54 unacceptable adverse events leading to discontinuation of sunitinib occurred (Table 2). The most common adverse event was thrombocytopenia ($n=27$, 50.0%), followed by neutropenia ($n=7$, 13.0%), liver dysfunction ($n=5$, 9.3%), renal dysfunction ($n=4$, 7.4%), infection ($n=3$, 5.6%), diarrhea ($n=3$, 5.6%), and hand–foot syndrome ($n=2$, 3.7%).

Table 1 Patient demographics

Number of patients, *n* (male/female)	50 (38/12)
Age, median (range)	66 (21–84)
Body weight, kg	60.8 ± 11.0
Serum albumin, g/dL	3.9 ± 0.6
Aspartate transaminase, U/L	23.4 ± 16.6
Alanine aminotransferase, U/L	27.7 ± 26.2
Serum creatinine, mg/dL	1.10 ± 0.41
White blood cells, /mm^3	6776 ± 3067
Hemoglobin, g/dL	12.3 ± 2.3
Platelets, 10^4/mm^3	25.3 ± 10.7
Initial dose, *n* (%)	
50.0 mg/day	28 (56.0)
37.5 mg/day	16 (32.0)
25.0 mg/day	5 (10.0)
12.5 mg/day	1 (2.0)
Sites of metastases, *n*	
Lung	34
Bone	14
Lymph nodes	10
Liver/pancreas	7
Brain	4
Previous treatment, *n* (%)	
None	38 (76.0)
Interferon-alfa	10 (20.0)
Sorafenib	1 (2.0)
Gemcitabine + Carboplatin	1 (2.0)

Each value represents the mean ± SD, unless otherwise indicated

Table 2 Type of unacceptable adverse event leading to discontinuation

Adverse events	*n*	(%)
Decreased platelet count	27	50.0
Decreased neutrophil count	7	13.0
Increased alanine aminotransferase	5	9.3
Increased serum creatinine	4	7.4
Infection	3	5.6
Diarrhea	3	5.6
Hand–foot syndrome	2	3.7
Others	3	5.6

Risk analysis for adverse events leading to discontinuation

In time-dependent Cox proportional hazards multivariable regression analysis, a sunitinib dose of ≤ 37.5 mg/day significantly reduced the risk of unacceptable adverse events leading to discontinuation of sunitinib in comparison with that of 50 mg/day [hazard ratio (HR) 0.08, 95% confidence interval (CI) 0.03–0.21, $p<0.001$] (Table 3). This analysis also indicated that sunitinib dose per body weight per day (mg/kg/day) was a significant risk factor for unacceptable adverse events leading to discontinuation (HR 1.99, 95% CI 1.19–3.31, $p=0.008$) (Table 3). Figure 1 shows that there was a nonlinear relationship between sunitinib dose per body weight per day and the predicted probability of severe adverse events.

Comparison of progression-free survival between sunitinib dose of 50 mg/day and ≤ 37.5 mg/day

The median PFS in all eligible patients and patients receiving sunitinib as first-line therapy and second- or third-line

Table 3 Time-dependent Cox proportional hazard analysis for unacceptable adverse events leading to discontinuation of sunitinib

Factors	HR (95% CI)	*p* value
(a) Sunitnib dose ≤ 37.5 mg/day	0.08 (0.03–0.21)	< 0.001
(b) Sunitinib dose adjusted by weight, mg/kg/day	1.99 (1.19–3.31)	0.008

Multivariable analyses for (a) and (b) were performed adjusted for (a) age, sex, and weight and (b) age and sex, respectively

HR hazard ratio adjusted for covariates

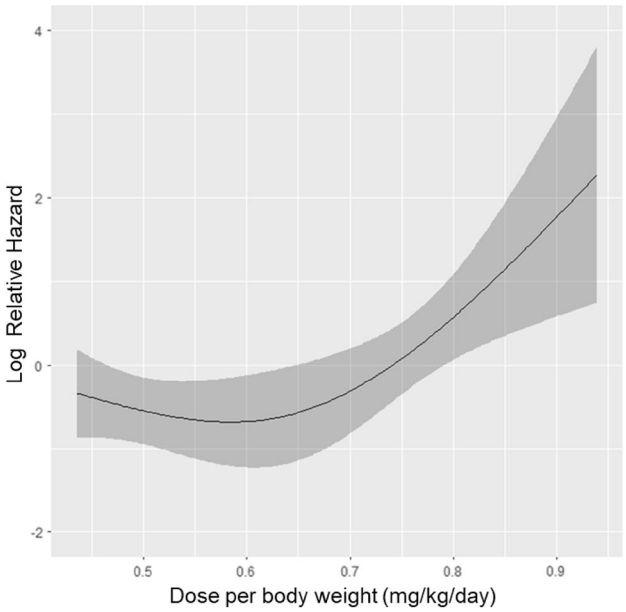

Fig. 1 Logarithmic hazard ratio of sunitinib dose adjusted by weight for unacceptable adverse events leading to discontinuation in mRCC patients receiving sunitinib. The curve represents the median, and gray area represents the 95% CI

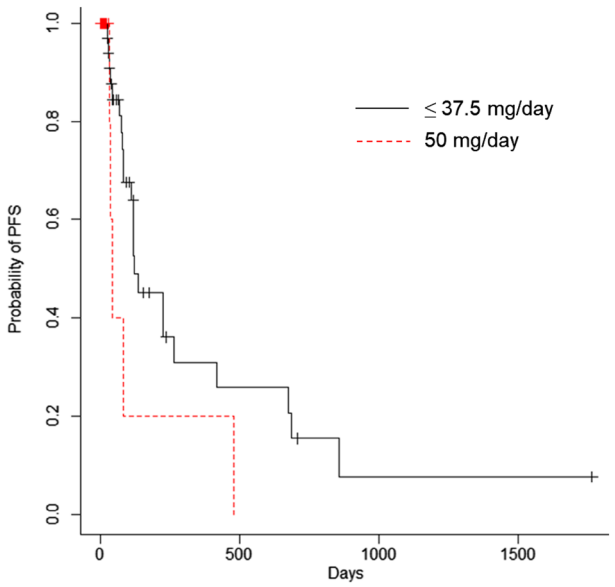

Fig. 2 Simon and Makuch's modified Kaplan–Meier curves for the comparison of PFS in mRCC patients who received sunitinib. One curve (solid line) represents patients receiving sunitinib at ≤ 37.5 mg/day, and the other curve (dashed line) represents patients receiving sunitinib at 50 mg/day

therapy was 141 days ($n=50$), 224 days ($n=38$, first-line therapy) and 133 days ($n=11$, second- or third-line therapy), respectively. As shown in Fig. 2, PFS in sunitinib dose of ≤ 37.5 mg/day was higher than in sunitinib dose of 50 mg/day, though not to a statistically significant degree (HR 0.39, 95% CI 1.01–1.44, $p=0.157$), and median duration of PFS was 120 days (95% CI 110–674) for sunitinib dose of ≤ 37.5 mg/day and 41 days [95% CI 35–not available (NA)] for sunitinib dose of 50 mg/day.

Discussion

The present results show that a sunitinib dose of ≤ 37.5 mg/day significantly reduced the risk of adverse events leading to discontinuation of sunitinib compared with a dose of 50 mg/day. Moreover, the PFS in sunitinib dose of ≤ 37.5 mg/day was longer than in those of 50 mg/day, though not to a statistically significant degree. These findings support the other groups' findings that a sunitinib dose of ≤ 37.5 mg/day is suitable in Asian, including Japanese, patients with mRCC.

Several investigators reported the relationship between the incidence of severe adverse events and sunitinib dose or blood concentrations of sunitinib in Asian patients with RCC [11, 15, 16]. Noda et al. reported in a retrospective observational study of 21 Japanese patients with RCC that patients ($n=8$) with ≥ 100 ng/mL total trough concentrations of sunitinib had a greater incidence of grade ≥ 3 toxicities compared with patients ($n=13$) with total trough concentrations of < 100 ng/mL (75.0% vs 23.1%) [15]. Nagata et al. conducted a pharmacokinetic–pharmacodynamic analysis of sunitinib-induced thrombocytopenia in 6 Japanese RCC patients and reported that the total trough concentration of sunitinib to prevent severe thrombocytopenia should be < 100 ng/mL. They also showed in their simulation results that the initial daily dose of sunitinib could be reduced to 37.5 mg/day or 25 mg/day in most Japanese patients [11]. Finally, Takasaki et al. demonstrated in 20 Japanese patients with mRCC that all patients with total sunitinib concentrations > 75 ng/mL had to discontinue or reduce the dose of sunitinib because of adverse events. Notably, all patients receiving sunitinib at a dose of 50 mg/day required dose reduction due to adverse events within 6 weeks [16]. These finding agreed with our results, in which a sunitinib dose > 37.5 mg/day was a significant risk factor for severe adverse events. Moreover, we revealed in this study that a dose of ≤ 37.5 mg/day significantly reduced the risk of severe adverse events in comparison with 50 mg/day by the time-dependent Cox proportional hazards multivariable regression analysis with adjustment for sex, age, and weight.

On the other hand, dose reduction of sunitinib may pose a risk for reduction in antitumor effects on renal cell carcinoma. In the present study, the median PFS in all patients and patients receiving sunitinib as first-line therapy or second- and third-line therapy were 4.7 months (141 days),

7.4 months (224 days), and 4.1 months (133 days), respectively. Miyake reported in 110 patients treated with sunitinib as first-line therapy for mRCC that the median PFS following the treatment with sunitinib was 7.8 months [2]. In addition, the median PFS following treatment with sunitinib as second-line therapy had a wide range from 2.5–8.0 months [17–19]. Thus, our finding of the median PFS was similar to the findings of previous reports.

We documented the duration of PFS for sunitinib at ≤ 37.5 or 50 mg/day by Simon and Makuch's modified Kaplan–Meier curves, which were used to account for time-dependent exposure. The PFS for a sunitinib dose of ≤ 37.5 mg/day was not statistically significantly different than that for a sunitinib dose of 50 mg/day and median duration of PFS was 120 days (95% CI 110–674) for a sunitinib dose of ≤ 37.5 mg/day and 41 days (95% CI 35–NA) for a sunitinib dose of 50 mg/day ($p = 0.153$). Mendel et al. reported in target modulation studies in vivo that a total sunitinib concentration of ≥ 50 ng/mL is necessary to inhibit phosphorylation of VEGF and PDGF receptors [1]. However, a recent study by Takasaki et al. demonstrated in Japanese patients with mRCC that the time to treatment failure (TTF) and PFS were better in patients with total sunitinib concentrations < 50 ng/mL than in those with concentrations ≥ 50 ng/mL [16]. Thus, this study group concluded that the effective range of total sunitinib concentration in Japanese mRCC patients was < 50–100 ng/mL and recommended that it is important to use sunitinib at the correct dosage in the first line as long as possible to maintain stable disease while preventing severe adverse events. Notably, the initial dose of sunitinib in all patients without discontinuation or dose reduction of sunitinib at 6 weeks after starting sunitinib was ≤ 37.5 mg/day [16], and these results are consistent with our results. Therefore, we agree that a sunitinib starting dose of ≤ 37.5 mg/day, and not 50 mg/day, is suitable in Japanese patients with mRCC.

There were several limitations in the present study. Several studies have reported on variations in sunitinib concentrations among patients caused by genetic polymorphisms [20–23]. We, however, could not rule out the effect of differences in genetic polymorphisms in the present analysis. In addition, this was a retrospective study; therefore, potentially relevant confounding factors may have been excluded. Second, although the sample size in this study was larger than the similar previous report [11], it was still small and data were obtained from a single institution. Finally, there were no sunitinib concentration measurements, and the relationship between blood sunitinib concentration and severe adverse events or PFS was not fully assessed.

Conclusion

A sunitinib dose of ≤ 37.5 mg/day significantly reduced the risk of unacceptable adverse event leading to discontinuation of sunitinib comparison with a dose of 50 mg/day, without affecting PFS in mRCC patients of Asian ancestry.

Acknowledgements We thank Libby Cone, MD, MA, from DMC Corp. (www.dmed.co.jp <http://www.dmed.co.jp/>) for editing a draft of this manuscript.

Funding This study did not receive funding from any funding source.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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