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Running title

Sunitinib concentration and clinical outcome treated with a 2-week-on and 1-week-off schedule

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Conflicts of Interest

All authors have no conflicts of interest to disclose.

Abstract

What is known and objective

Sunitinib is used as a first-line therapy for metastatic renal cell carcinoma. The primary aim of this study was to determine the optimal total sunitinib (sunitinib plus *N*-desethyl sunitinib) trough concentration for the alternative dosing schedule: 2-week-on and 1-week-off schedule (2/1 schedule).

Methods

Patients with metastatic renal cell carcinoma treated with the 2/1 schedule of sunitinib, whose total sunitinib concentrations were available, were recruited for this study. Out of 19 patients, 17 whose sunitinib dosage was not changed until the measurement of drug concentration were eligible for the analysis of the relationship between total sunitinib concentration and clinical outcome. Individual pharmacokinetic parameters in 19 patients were estimated *via* the Bayesian analysis.

Results

The onset of severe (grade ≥ 3) adverse effects among 17 patients during 3 weeks as a first course of sunitinib therapy was observed in 7 (41.2%) patients. The median total sunitinib concentration in patients with severe adverse effects was significantly higher compared with that in patients without severe adverse effects [median: 119 (113–131) *vs*. 87.8 (77.4–102) ng/mL, $p = 0.01$]. According to the receiver operating characteristic analysis of the onset of severe adverse effects, the cutoff value of the total sunitinib concentration was 108 ng/mL. Patients with a total sunitinib concentration lower than 108 ng/mL had a longer time to first dose reduction or withdrawal due to adverse effects compared with those with a total sunitinib concentration of 108 ng/mL or higher ($p = 0.03$). The probability without treatment

failure was not significantly different between the two concentration groups. In addition, the estimated sunitinib apparent oral clearance (CL/F) was significantly lower in the severe adverse effects group. Our simulation demonstrated that 0.67-time dose is needed for patients with approximately 90.0 ng/mL of sunitinib concentration on day 7 to maintain the concentration at the same level as the patients with higher CL/F.

What is new and conclusion

Maintaining the total sunitinib trough concentrations of less than 108 ng/mL is safe to avoid the onset of serious adverse effects without increasing the treatment failure in patients with metastatic renal cell carcinoma treated with the 2/1 schedule of sunitinib.

Keywords

sunitinib: alternative dosing schedule: metastatic renal cell carcinoma: therapeutic drug monitoring: Bayesian analysis

1. WHAT IS KNOWN AND OBJECTIVE

The prognosis for metastatic renal cell carcinoma has significantly improved after the advent of novel therapeutic agents, such as anti-angiogenic[1,2] and immunotherapy agents.[3,4] Sunitinib, an anti-angiogenic drug, is a first-line therapy for patients with metastatic renal cell carcinoma.[5] However, sunitinib frequently induces severe toxicities, such as fatigue, hypertension, palmar-plantar erythrodysesthesia syndrome, thrombocytopenia, anorexia, and diarrhea.[2] The traditional dosing schedule for sunitinib is 50 mg daily for 4 weeks, followed by 2 weeks off (4/2 schedule).[6] However, a recent meta-analysis demonstrated that the alternative dosing schedule, 2-week-on and 1-week-off schedule (2/1 schedule), is more effective [improved progression-free survival (PFS)] than the 4/2 schedule for the treatment of metastatic renal cell carcinoma.[7] Moreover, the 2/1 schedule is associated with less sunitinib-related severe toxicity and better tolerability among patients with metastatic renal cell carcinoma.[7,8]

Sunitinib is primarily metabolized by cytochrome P450 (CYP) 3A4 to its major pharmacologically active metabolite, *N*-desethyl sunitinib, which is further metabolized to inactive compounds by the same enzyme.[9,10] An *in vivo* study reported that a total sunitinib (sunitinib plus *N*-desethyl sunitinib) concentration ≥50 ng/mL is required to achieve an antitumor effect.[11] In a phase I study, all responders had a total sunitinib trough concentration >50 ng/mL.[6] Previous meta-analysis indicated that increased exposure to sunitinib is associated with improved clinical outcomes [time to tumor progression, overall survival (OS), and objective response].[12] On the other hand, adverse effects of sunitinib were also reported to occur more frequently according to

total sunitinib concentrations increase.[12-14] For example, a previous clinical study conducted in Japan reported that patients with a total sunitinib concentration ≥100 ng/mL had a significantly greater incidence of Grade 3 or higher toxicities compared with those having concentrations <100 ng/mL in the 4/2 schedule.[14] The thresholds of sunitinib concentration for safety and efficacy have been established based on data in the 4/2 schedule.[15] The practical guideline for therapeutic drug monitoring (TDM) of sunitinib has been published,[16] and it is feasible to perform sunitinib TDM as routine care. However, no report has demonstrated the optimal total sunitinib trough concentration with the 2/1 schedule of sunitinib.

In this study, the primary aim was to determine the optimal total sunitinib trough concentration in the 2/1 schedule. Moreover, we considered a practical TDM procedure for sunitinib by applying a pharmacokinetic model-based analysis.

2. METHODS

2-1. Patients

This study was a single-center, retrospective, observational study. Patients with metastatic renal cell carcinoma were recruited between August 2018 and January 2020 at Kobe University Hospital. The patient eligibility criteria were as follows: i) patients with histologically diagnosed renal cell carcinoma treated with the 2/1 schedule of sunitinib; ii) patients whose total sunitinib concentrations were available on days 9–15 following sunitinib therapy; iii) patients for whom information on medical treatment and prognosis could be obtained from the medical records; and iv) patients aged 18 years or older. The patient exclusion criteria were as follows: i) patients who requested

not to participate in this study and ii) patients undergoing dialysis. Data including age, gender, body weight, histology, laboratory data, performance status, and prescription history were collected from the electronic medical records. Patients whose sunitinib dose was not changed until the measurement of drug concentration were eligible for the analysis of the relationship between total sunitinib concentration and clinical outcome.

2-2. Ethics

This study was designed and implemented in accordance with the Declaration of Helsinki and its amendments. The present study was approved by the ethics committee of Kobe University Hospital (No.180324). Information about this study was disclosed on the website, and research subjects were given the opportunity to refuse enrollment in the study.

2-3. Evaluation of safety and efficacy

Sunitinib dose reduction or discontinuation was a decision made by the attending physician based on adverse effects or disease progression. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Adverse effects were evaluated on days 1–21 as a first course, during hospitalization, and severe adverse effects were defined as grade 3 or higher by the CTCAE. Time to treatment failure (TTF) was defined as the period from initiation to discontinuation of sunitinib treatment for any reasons. PFS was defined as the time

from the start of sunitinib treatment to the objective findings of disease progression or death. OS was defined from the date of sunitinib initiation until the date of death by all-cause. Tumor response was evaluated *via* first computed tomography (CT) scan after sunitinib therapy using the Response Evaluation Criteria in Solid Tumors version 1.1.

2-4. Measurement and simulation of drug concentrations

All patients of this study took sunitinib after breakfast (around 8:00 AM) and were drawn the blood samples from 5:30 to 6:00 AM. Because sunitinib reaches a steady state within 9 days after the therapy, we measured sunitinib and *N*-desethyl sunitinib concentrations on days 9–15 after the initiation of sunitinib therapy, and evaluated total sunitinib (sunitinib plus *N*-desethyl sunitinib) concentration as a routine care according as the practical guideline.[16] Both plasma trough sunitinib and *N*-desethyl sunitinib concentrations were measured at an external analysis center (MASIS Inc., Aomori, Japan) *via* liquid chromatography–tandem mass spectrometry (LC–MS/MS).[17] Intra- and inter-day precision and accuracy were <10%. Lower limits of quantification for both sunitinib and *N*-desethyl sunitinib were 1.0 ng/mL. The calibration curves showed linearity, with a correlation coefficient of 0.999.

All 19 patients were included in the analysis of the model-based pharmacokinetics. Bayesian prediction and simulation of drug concentrations were performed using the MwPharm++ software (Mediware, Prague, Czech Republic). Population pharmacokinetic parameters were entered on the appropriate sections of MwPharm++. The population pharmacokinetic parameters for sunitinib were established based on a previous report,[18] and the mean values were as follows: apparent

volume of distribution (Vd/F), 1680 L; apparent oral clearance (CL/F), 26.2 L/h; absorption rate constant (Ka), 0.418 h^{-1}; and lag time, 1.6 h. The individual CL/F was estimated by the Bayesian method using the one-point trough concentration following the sunitinib therapy. The simulations were conducted in cases without any dose change and with dose adjustment based on sunitinib concentration.

2-5. Statistical analysis

All statistical analyses were conducted using SPSS (SPSS® Statistics 26.0; IBM Japan, Tokyo, Japan). Data are expressed as the number of patients or the median with an interquartile range. Fisher's exact test was employed to compare the distribution of categorical data, whereas the Mann–Whitney *U* test was employed to compare the medians of continuous values between groups. Receiver operating characteristic (ROC) curves were utilized to determine the optimal cutoff values of the total sunitinib concentration and sunitinib CL/F. The cutoff values had maximum values in the Youden index (sensitivity + specificity − 1). Time-to-event analyses were conducted using the Kaplan–Meier method and compared using the log-rank test. *P* values less than 0.05 were considered statistically significant.

3. RESULTS

3-1. Patient characteristics

A total of 19 patients were recruited from August 2018 to January 2020. Out of 19 patients, 2 had their sunitinib dosage changed prior to the measurement of drug concentration. Table 1 presents the clinical characteristics of the 17 patients who were eligible for analysis of the relationship between total sunitinib concentration and clinical outcome. None of the patients had advanced renal or liver dysfunction and concomitantly used potent CYP3A4 inhibitors. The median total sunitinib concentration was 102 (77.7–118) ng/mL, and there was no patient with a total sunitinib concentration <50 ng/mL in this study. The median sunitinib and *N*-desethyl sunitinib concentrations were 76.8 (65.3–103) and 14.2 (11.6–25.5) ng/mL, respectively. The onset of severe adverse effects was observed in 7 (41.2%) patients (Table 2). All of the severe adverse effects reported in this study were of grade 3.

3-2. Association of severe adverse effects and total sunitinib concentration

The median total sunitinib concentration in the patients with severe adverse effects was significantly higher compared with that in patients without severe adverse effects [Fig. 1A; median: 119 (113–131) *vs*. 87.8 (77.4–102) ng/mL, $p = 0.01$]. The median *N*-desethyl sunitinib concentration was not significantly different between groups with and without severe adverse effects (Fig. S1, $p = 0.42$). According to a ROC analysis on the onset of severe adverse effects, the cutoff value of the total sunitinib concentration was 108 ng/mL [Fig. 1B; sensitivity 0.86, specificity 0.90, area under the curve (AUC)-ROC 0.87, $p = 0.01$]. Table 2 presents the relationship between the total sunitinib concentration and the severe adverse effects. Almost all severe adverse effects were observed in patients with a total sunitinib concentration of 108 ng/mL or higher.

3-3. Association of time-to-event and total sunitinib concentration

In the time-to-event analysis, patients with a total sunitinib concentration lower than 108 ng/mL had a longer time to first dose reduction or withdrawal due to adverse effects compared with those exhibiting a total sunitinib concentration of 108 ng/mL or higher ($p = 0.03$) (Fig. 2A). However, TTF was not affected by the total sunitinib concentration (Fig. 2B). In addition, PFS and OS were not significantly different between the groups with higher and lower total sunitinib concentrations ($p = 0.79$ and $p = 0.85$, respectively).

3-4. Association of severe adverse effects and sunitinib CL/F

Out of 19 patients, 2 who underwent a sunitinib dosage change before the measurement of drug concentration experienced severe adverse effects. One experienced hypertension, and the other experienced hypoalbuminemia and lung infection. The median sunitinib CL/F values estimated using the Bayesian method in 19 patients with and without severe adverse effects were 11.4 and 18.0 L/h, respectively (Fig. 3A). According to the ROC analysis of the onset of severe adverse effects, the cutoff value of sunitinib CL/F was 15.3 L/h (Fig. 3B, sensitivity 0.89, specificity 0.80, AUC-ROC 0.83, $p = 0.02$). The patient characteristics for each group divided by the cutoff value of CL/F are presented in Table 3. The patients with a low sunitinib CL/F tended to be older compared with those with higher CL/F [median: 68.0 (60.5–71.5) *vs*.

56.0 (39.8–65.3) years, $p = 0.08$]. Other patient characteristics were not significantly different between the two groups.

3-5. Association of efficacy and sunitinib CL/F

The median day to the first CT scan after sunitinib therapy was 50.0 (36.0–73.0). The median sunitinib CL/F was not significantly different between non-progressive disease (PD) and PD groups (Fig. 4A). The PFS was not affected by the sunitinib CL/F (Fig. 4B).

3-6. Simulation in patients with lower and higher sunitinib CL/F

Fig. 5 presents the simulated sunitinib plasma concentration–time profiles in the patients with sunitinib CL/F values of 11.0 and 18.1 L/h, which were approximately median CL/F values for patients with and without severe adverse effects, respectively. Fig. 5A demonstrates the simulation and observed concentrations when these patients received 37.5 mg of sunitinib once a day. The sunitinib concentration at steady state in patient 1 with a CL/F of 11.0 L/h was approximately 1.5-fold higher than patient 2, who had a CL/F of 18.1 L/h. Fig. 5B shows that the simulation reflected a dose adjustment scenario for patient 1 with a CL/F of 11.0 L/h in the event that the patient restarts 25 mg of sunitinib once a day following discontinuation for 2 days after confirming that the sunitinib concentration was 90.0 ng/mL on day 7. The steady-state sunitinib

concentration in patient 1 with CL/F of 11.0 L/h receiving 25 mg of sunitinib once a day was similar to that in patient 2 with a CL/F of 18.1 L/h and receiving 37.5 mg.

4. DISCUSSION

This is the first report showing an association between the total sunitinib concentration and severe adverse effects in patients treated with a 2/1 schedule of sunitinib. Among 17 patients, the onset of severe adverse effects was observed in 7 patients (41.2%) on days 1–21. This indicates the need to manage the severe adverse effects, although the 2/1 schedule treatment had less sunitinib-related severe toxicity among patients with metastatic renal cell carcinoma.[7,19]

In this study, the median total sunitinib concentration in patients with severe adverse effects was significantly higher compared with that in patients without severe adverse effects. We observed a patient who exhibited a high total sunitinib concentration (sunitinib, 106 ng/mL; *N*-desethyl sunitinib, 27.9 ng/mL) on day 10 post-initiation and experienced grade 3 diarrhea during the 2/1 schedule of sunitinib.[20] The higher total sunitinib trough concentration was associated with the higher occurrence rate of hand–foot syndrome and thrombocytopenia in patients treated with a mixture of the 4/2 and 2/1 schedule.[21] The total sunitinib concentration was significantly higher in patients who discontinued treatment or had dosage reduction due to adverse effects within 6 weeks after the initiation of sunitinib compared with patients who continued treatment with the initial dosage in a mixture of the 4/2 and 2/1 schedules.[13] Since the median *N*-desethyl sunitinib concentration did not differ between the patients with and without severe adverse effects in this study, monitoring of total sunitinib concentrations

may be a useful marker to control adverse effects of sunitinib therapy. We conclude that the measurement of the total sunitinib concentration may prevent the onset of serious adverse effects even if the 2/1 schedule of sunitinib treatment is applied.

According to ROC analysis on the onset of severe adverse effects, the cutoff value of the total sunitinib concentration was 108 ng/mL. Total sunitinib trough concentration less than 108 ng/mL in the 2/1 schedule is effective in preventing the occurrence of severe adverse effects. In fact, patients with total sunitinib concentrations lower than 108 ng/mL had a longer time to first dose reduction or withdrawal due to adverse effects compared with those with a 108 ng/mL or higher total sunitinib concentration, without reduction in TTF. Since all responders in a phase I study had a total sunitinib trough concentration >50 ng/mL,[6] a target exposure threshold for total sunitinib trough concentration of >50 ng/mL for intermittent dosing (4/2 or 2/1 schedule) was recommended.[22] Therefore, we suggest that the optimal total sunitinib trough concentration at a steady state in the 2/1 schedule ranges from 50 to 108 ng/mL.

In this study, the median individual CL/F values of sunitinib estimated using the Bayesian method for patients in the severe adverse effects group (11.4 L/h) was significantly lower than those without severe adverse effects (18.0 L/h). Previously, age and gender were considered to be covariates for the CL/F of sunitinib.[23,24] The group with a low sunitinib CL/F tended to be older compared with the group exhibiting a high sunitinib CL/F. However, gender was not significantly associated with sunitinib CL/F in this study. A pharmacokinetic study reported that Asian ethnicity was a significant covariate associated with lower sunitinib clearance.[23] This may result from a polymorphism in the *ATP-binding cassette subfamily G member 2* (*ABCG2*), which

encodes the breast cancer resistance protein (BCRP), and the *ABCG2* 421C>A allele frequency is relatively high in Asians (~30%).[18] A previous study demonstrated that the loss of protein expression of BCRP from a genetic polymorphism is associated with an increase in the systemic exposure to sunitinib and sunitinib-induced toxicity.[25] A population pharmacokinetic model of sunitinib was established using the *ABCG2* 421C>A genotype as a predictive covariate for CL/F.[18] Our results indicated that the median CL/F of sunitinib in the patients with severe adverse effects was lower than that in patients with *ABCG2* 421C>A (14.3 L/h). Therefore, we conclude that an *ABCG2* genetic mutation may contribute to the increase in sunitinib concentration in the severe adverse effects group. Although none of the patients in this study concomitantly used potent CYP3A4 inhibitors, other medications may have affected CYP3A4-mediated sunitinib metabolism and contributed to lower sunitinib CL/F values for patients in the severe adverse effects group. With regard to treatment efficacy, the median sunitinib CL/F value was not significantly different between the non-PD and PD groups. In addition, PFS was not affected by the sunitinib CL/F. These results indicate that the sunitinib CL/F cannot be used to predict tumor response to sunitinib.

Based on our simulation in patients with lower and higher sunitinib CL/F, the sunitinib concentration at a steady state in the patient with a CL/F of 11.0 L/h was approximately 1.5 times higher than that in the patient with a CL/F of 18.1 L/h (Fig. 5A). Therefore, dose adjustment is recommended, especially for patients with low sunitinib CL/F values, as presented in Fig. 5B. Our simulation demonstrated that a one-step dose reduction (37.5 to 25 mg) in the patients with a sunitinib concentration of approximately 90.0 ng/mL on day 7 after sunitinib therapy would result in a

concentration similar to that of patients with a higher CL/F. The results of this study suggest a practical procedure for sunitinib TDM based on scientific evidence.

Several limitations of this study should be acknowledged. Since this study is retrospective, the sunitinib dose modifications and radiological evaluation were not conducted based on strict protocols. We only assessed sunitinib and *N*-desethyl sunitinib concentrations on days 9–15 after the initiation of sunitinib, and the concentrations at the time adverse effects developed or PD diagnosed were not evaluated in our study. Therefore, we considered that the total sunitinib concentrations on day 9–15 after the initiation of sunitinib therapy were not directly comparable to the therapeutic efficacy of sunitinib over the entire treatment period. In the analysis of the model-based pharmacokinetics, we did not perform the predictions of the *N*-desethyl sunitinib CL/F because a population pharmacokinetic model of this active metabolite in Japanese patients has not been reported. Since the sunitinib dose was adjusted on the basis of the total sunitinib concentrations, a population pharmacokinetic model including both sunitinib and *N*-desethyl sunitinib in the Japanese should be constructed in a future study. Furthermore, the main limitation of this study was the small sample size. Thus, further studies on larger cohorts are necessary to validate our findings.

5. WHAT IS NEW AND CONCLUSION

Maintaining a total sunitinib trough concentration of less than 108 ng/mL is safe to avoid the onset of serious adverse effects without increasing the treatment failure in patients with metastatic renal cell carcinoma treated with the 2/1 schedule of

sunitinib. The protocol for sunitinib TDM using a model-based analysis may help provide a safer chemotherapy treatment regimen.

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Figure legends

Fig. 1. (A) Association of total sunitinib concentration and severe adverse effects and (B) receiver operating characteristic (ROC) curve of the total sunitinib concentration for the prediction of severe adverse effects.

The box plot indicates the minimum, first quartile, median, third quartile, and maximum. The central rectangle spans the first quartile to the third quartile (the interquartile range). The outliers are shown as open circles.

Fig. 2. Kaplan–Meier curves for (A) time to first dose reduction or withdrawal from adverse effects and (B) time to treatment failure (TTF) for each group divided by the total sunitinib concentration.

The solid lines indicate the patients with total sunitinib concentrations lower than 108 ng/mL (n = 10), and the dash lines represent those with a total sunitinib concentration of 108 ng/mL or higher (n = 7).

Fig. 3. (A) Association of sunitinib apparent oral clearance (CL/F) and severe adverse effects and (B) receiver operating characteristic (ROC) curve of sunitinib CL/F for the prediction of severe adverse effects.

The box plot indicates the minimum, first quartile, median, third quartile, and maximum. The central rectangle spans the first quartile to the third quartile (the interquartile range). An outlier is indicated by an open circle.

Fig. 4. (A) Association of sunitinib apparent oral clearance (CL/F) and progressive disease (PD) evaluated by first computed tomography (CT) scan and (B) Kaplan–Meier curves for progression-free survival (PFS) for each group divided by sunitinib CL/F. The box plot indicates the minimum, first quartile, median, third quartile, and maximum. The central rectangle spans the first quartile to the third quartile (the interquartile range). An outlier is indicated as an open circle.
The solid line indicates the patients with a lower sunitinib CL/F than 15.3 L/h (n = 9), and the dash line indicates those with a sunitinib CL/F of 15.3 L/h or higher (n = 10).

Fig. 5. Simulated sunitinib plasma concentration–time profiles in patients with sunitinib apparent oral clearance (CL/F) of 11.0 (patient 1) and 18.1 L/h (patient 2), respectively. The initial dose of sunitinib was 37.5 mg once a day.
(A) Bayesian-simulated and observed concentrations of sunitinib on the 2/1 schedule.
(B) The simulation reflected a dose adjustment scenario for patient 1 with CL/F of 11.0 L/h, if the patient restarts 25 mg of sunitinib once a day following discontinuation for 2 days after day 7; patient 2 with a CL/F of 18.1 L/h did not undergo a dose change.
The solid lines represent the simulation in sunitinib CL/F of 11.0 L/h (patient 1), and the dash lines represent the simulation in sunitinib CL/F of 18.1 L/h (patient 2). The closed circles represent the observed sunitinib concentration. The arrows indicate the onset of severe adverse effects in patient 1.

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Table 1 Patient characteristics at the start of sunitinib therapy

Patients	17
Age (years)	62.0 (56.0–69.0)
Gender: Female/Male	6/11
Body weight (kg)	58.8 (54.8–67.6)
Laboratory data	
AST (IU/L)	18 (16–27)
ALT (IU/L)	19 (12–29)
eGFR (mL/min/1.73 m^2)	52.4 (45.3–60.5)
Histology: Clear cell/Papillary	14/3
Performance status: 0–1/2–4	13/4
Number of prior systemic therapy: 0/≥1	12/5
Dose of sunitinib: 37.5 mg/25 mg	12/5

Data are expressed as the number of patients or median with the interquartile range in parentheses.

AST: aspartate aminotransferase, ALT: alanine aminotransferase, eGFR: estimated glomerular filtration rate

Table 2 Relationship between total sunitinib concentration and adverse effects

		Total sunitinib concentration	
	All (n = 17)	< 108 ng/mL (n = 10)	≥ 108 ng/mL (n = 7)
Adverse effects (All grades/Grade ≥ 3)			
ALT increase	4/3	2/1	2/2
AST increase	4/2	2/0	2/2
Hypertension	3/2	1/0	2/2
Diarrhea	3/1	0/0	3/1
GGT increase	2/1	1/0	1/1
Lipase increase	1/1	0/0	1/1
Oral mucositis	3/1	0/0	3/1
Platelet count decrease	7/1	4/0	3/1

Data are expressed as the number of patients.

All adverse effects reported as grade 3 or higher in either group are shown.

Patients were counted once at the highest grade.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyltransferase

Table 3 Relationship between sunitinib apparent oral clearance and patients' characteristics

		Sunitinib CL/F		
	All (n = 19)	< 15.3 L/h (n = 9)	≥ 15.3 L/h (n = 10)	p
Age (years)	61.0 (52.0–69.0)	68.0 (60.5–71.5)	56.0 (39.8–65.3)	0.08[a)]
Gender: Female/Male	7/12	4/5	3/7	0.43[b)]
Body weight (kg)	59.5 (55.7–66.2)	60.5 (56.6–72.3)	59.2 (50.4–65.6)	0.32[a)]
Laboratory data				
AST (IU/L)	18 (16–28)	17 (16–27)	20 (17–35)	0.36[a)]
ALT (IU/L)	20 (12–34)	20 (13–28)	20 (11–36)	0.84[a)]
eGFR (mL/min/1.73 m^2)	52.4 (46.1–60.9)	52.4 (45.3–57.6)	55.5 (47.6–65.8)	0.50[a)]
Histology: Clear cell/Papillary	16/3	8/1	8/2	0.54[b)]
Performance status: 0–1/2–4	14/5	7/2	7/3	0.56[b)]
Number of prior systemic therapy: 0/≥1	13/6	7/2	6/4	0.37[b)]
Dose of sunitinib (mg/day)	37.5 (25.0–37.5)	37.5 (25.0–37.5)	37.5 (25.0–37.5)	0.91[a)]

Data are expressed as the number of patients or median with the interquartile range in parentheses.

[a)] Mann–Whitney U test. [b)] Fisher's exact test.

CL/F: apparent oral clearance, AST: aspartate aminotransferase, ALT: alanine aminotransferase, eGFR: estimated glomerular filtration rate

Fig. 1

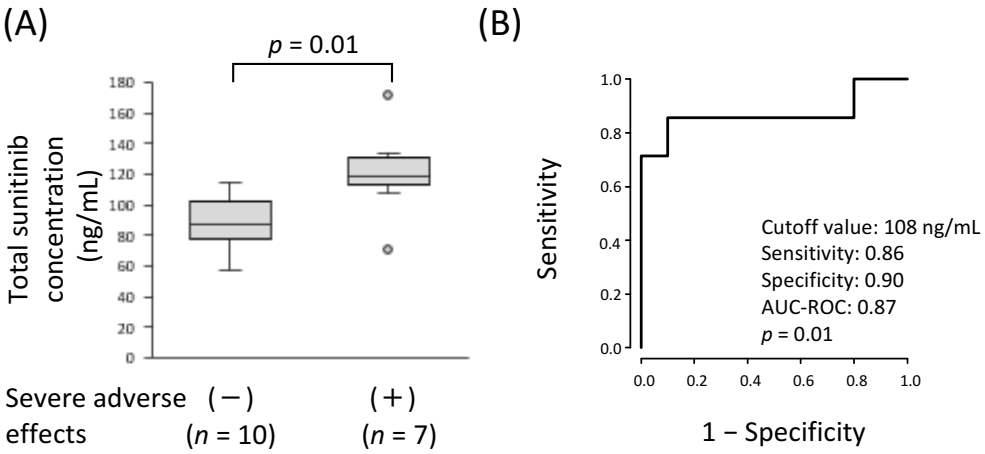

(A)
p = 0.01
Total sunitinib concentration (ng/mL)
180
160
140
120
100
80
60
40
20
0
Severe adverse effects
(−) (n = 10)
(+) (n = 7)
(B)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.2 0.4 0.6 0.8 1.0
1 − Specificity
Cutoff value: 108 ng/mL
Sensitivity: 0.86
Specificity: 0.90
AUC-ROC: 0.87
p = 0.01

Fig. 2

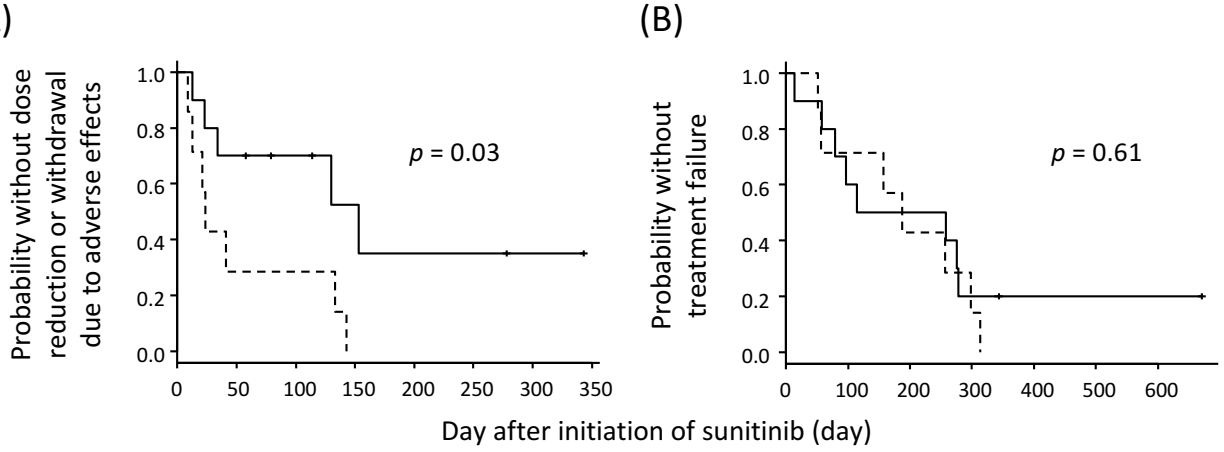

(A)
Probability without dose reduction or withdrawal due to adverse effects
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
p = 0.03
(B)
Probability without treatment failure
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
p = 0.61
Day after initiation of sunitinib (day)

Fig. 3

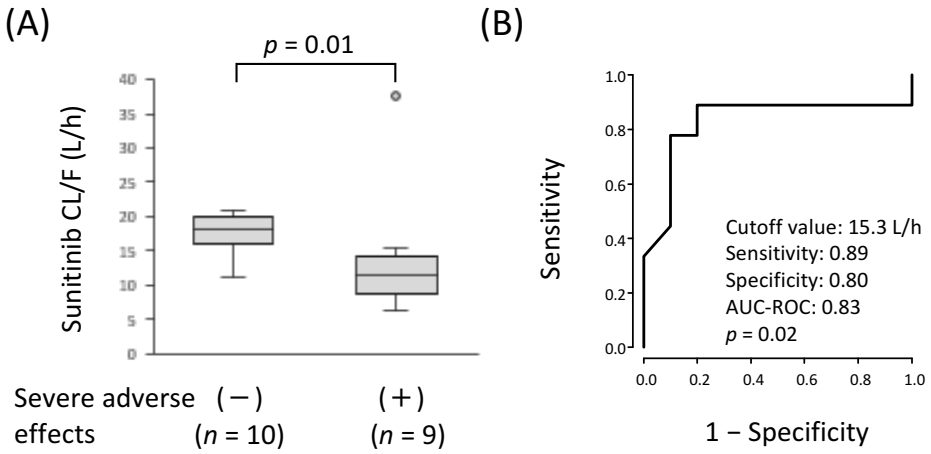
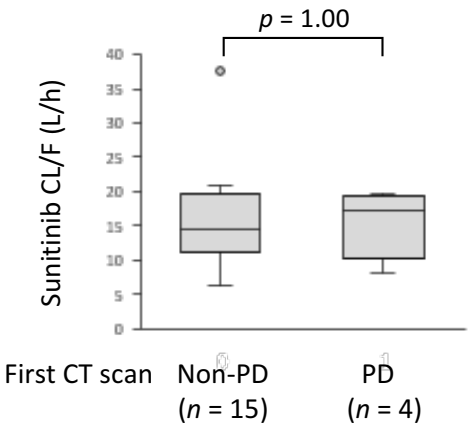

(A)
p = 0.01
Sunitinib CL/F (L/h)
40
35
30
25
20
15
10
5
0
Severe adverse effects
(−) (n = 10)
(+) (n = 9)
(B)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 − Specificity
Cutoff value: 15.3 L/h
Sensitivity: 0.89
Specificity: 0.80
AUC-ROC: 0.83
p = 0.02

Fig. 4

(A)


p = 1.00
Sunitinib CL/F (L/h)
40
35
30
25
20
15
10
5
0
First CT scan
Non-PD
(n = 15)
PD
(n = 4)

(B)

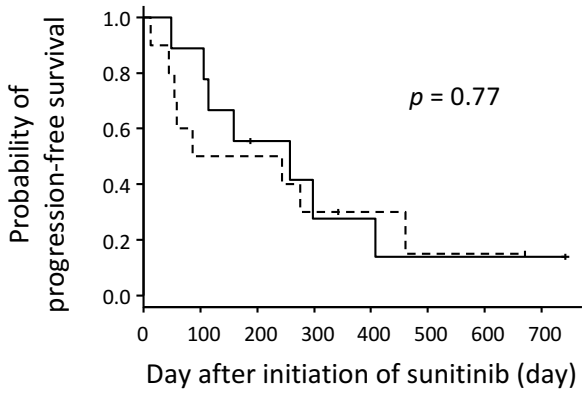
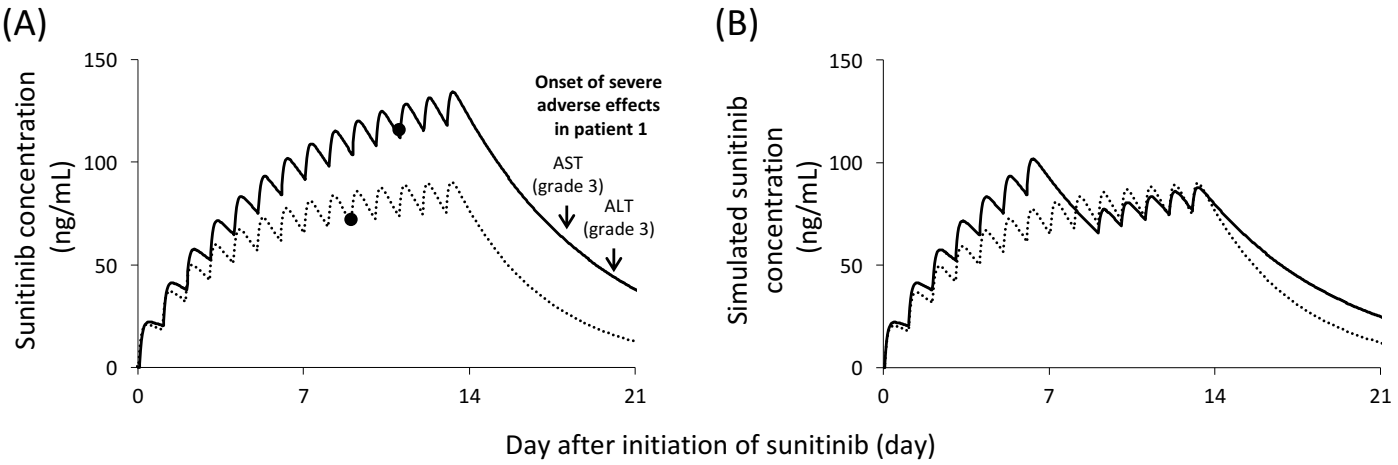

Probability of progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
p = 0.77
0
100
200
300
400
500
600
700
Day after initiation of sunitinib (day)

Fig. 5


(A)
(B)
Sunitinib concentration (ng/mL)
Simulated sunitinib concentration (ng/mL)
150
100
50
0
0
7
14
21
Onset of severe adverse effects in patient 1
AST (grade 3)
ALT (grade 3)
Day after initiation of sunitinib (day)