Assessment of Sunitinib-Induced Toxicities and Clinical Outcomes Based on Therapeutic Drug Monitoring of Sunitinib for Patients With Renal Cell Carcinoma

doi: 10.1016/j.clgc.2015.01.007

Original Study

Assessment of Sunitinib-Induced Toxicities and Clinical Outcomes Based on Therapeutic Drug Monitoring of Sunitinib for Patients With Renal Cell Carcinoma

Satoshi Noda,[1] Takashi Otsuji,[2] Masato Baba,[3] Tetsuya Yoshida,[3] Susumu Kageyama,[3] Keisei Okamoto,[3] Yusaku Okada,[3] Akihiro Kawauchi,[3] Hiroyuki Onishi,[4] Daiki Hira,[1] Shin-ya Morita,[1] Tomohiro Terada[1]

Abstract

The benefit of pharmacokinetic assessment of sunitinib remains unknown. We reported that patients with total sunitinib (sunitinib + its active metabolite SU12662) ≥ 100 ng/mL showed high incidence of Grade ≥ 3 toxicities and worsening clinical outcomes. Thus, pharmacokinetic assessment of sunitinib could be helpful for dose optimization.

Background: Sunitinib has been approved for the treatment of metastatic renal cell carcinoma (RCC). Sunitinib pharmacokinetics shows a large interpatient variability. **Patients and Methods:** A retrospective, observational clinical study of 21 patients with RCC was performed. Sunitinib was administered for 4 weeks of a 6-week cycle for the first cycle. We evaluated the association of sunitinib-induced toxicities and clinical outcomes with the trough total sunitinib concentration in a steady state during the first cycle. **Results:** The median total sunitinib concentration was 91.8 ng/mL (range, 49.8-205 ng/mL). There was an association between total sunitinib concentration and the severity of thrombocytopenia, anorexia, and fatigue. Patients with $\geq$ 100 ng/mL total sunitinib (n = 8), compared with patients with $<$ 100 ng/mL (n = 13), had a greater incidence of Grade $\geq$ 3 toxicities (6 patients [75.0%] vs. 3 patients [23.1%]). Patients with $<$ 100 ng/mL total sunitinib had significantly longer time to treatment failure (TTF) and progression-free survival (PFS) time than patients with $\geq$ 100 ng/mL (median TTF, 590 vs. 71 days; $P = .04$; median PFS, 748 vs. 238 days; $P = .02$). **Conclusion:** Results of this study suggest that therapeutic drug monitoring of sunitinib could be useful for avoiding severe toxicities. Dose reduction might be needed, especially when the total sunitinib concentration is $\geq$ 100 ng/mL, to avoid unnecessary early discontinuation of treatment.

Clinical Genitourinary Cancer, Vol. 13, No. 4, 350-8
Keywords: Individualized pharmacotherpy, Kidney cancer, Pharmacokinetics, Tolerability, Tyrosine kinase inhibitor

Introduction

Sunitinib is an oral multikinase inhibitor that targets vascular endothelial growth factor receptor, platelet-derived growth factor receptors, and stem-cell factor receptor. It has been approved by the US Food and Drug Administration for the treatment of advanced and/or metastatic renal cell carcinoma (RCC) as the first-line treatment.[1] Sunitinib frequently induces severe toxicities such as thrombocytopenia, anorexia, fatigue, hand-foot syndrome (HFS), and bleeding events.[1] In addition, sunitinib induces rare, but potentially life-threatening events such as intestinal perforation, interstitial lung disease, and would healing complication.[2-4] Because these toxicities are difficult to treat and anticipate, dose reduction or discontinuation is generally carried out in daily clinical settings. As a consequence, physicians must closely monitor all patients who have started sunitinib treatment. Against this background, a predictive marker for preventing severe sunitinib-induced toxicities is needed.

[1]Department of Pharmacy, Shiga University of Medical Science Hospital, Shiga, Japan
[2]Department of Pharmacy, Shiga Medical Center for Adults, Shiga, Japan
[3]Department of Urology, Shiga University of Medical Science Hospital, Shiga, Japan
[4]Department of Urology, Shiga Medical Center for Adults, Shiga, Japan

Submitted: Oct 20, 2014; Revised: Jan 6, 2015; Accepted: Jan 16, 2015; Epub: Jan 21, 2015

Address for correspondence: Tomohiro Terada, PhD, Department of Pharmacy, Shiga University of Medical Science Hospital, Seta Tsukinowa-cho, Otsu City, Shiga 520-2192, Japan
Fax: +81-77-548-2411; e-mail contact: teradat@belle.shiga-med.ac.jp

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.01.007

Therapeutic drug monitoring (TDM) has been widely used to improve efficacy and to avoid adverse events for various drugs.[5] At present, although many anticancer agents show large interindividual variability for pharmacokinetics (PK), TDM has not been routinely used in chemotherapy management. Recently, clinical studies have reported that trough imatinib plasma levels are associated with cytogenetic and molecular response in chronic myeloid leukemia.[6,7] Regarding toxicity, several studies have demonstrated that the area under the curve (AUC) of erlotinib was associated with the occurrence of skin toxicity.[8,9] Implementation of TDM might contribute to optimal dose adjustment for other oral molecular-targeted anticancer agents including sunitinib. In fact, considerable interindividual differences in sunitinib PK have been observed.[10] The reason for severe toxicity in some patients might be the interindividual variation in serum levels of sunitinib. However, a pharmacokinetic (PK) approach to evaluate the side effects of sunitinib is lacking. Furthermore, information on the associations between sunitinib PK and clinical outcomes and pharmacogenomic factors is insufficient.

Sunitinib is primarily metabolized by cytochrome P450 (CYP) 3A4 to the equally active SU12662. SU12662 is further metabolized to inactive moieties by CYP3A4.[11] Previous studies have reported that sunitinib is a substrate for adenosine triphosphate-binding cassette (ABC) transporters, ABCG2[12] and ABCB1,[13] which affect the intestinal absorption and biliary excretion of various drug substrates.[14] In this study, we evaluated polymorphism in *CYP3A5* (6986G>A), *ABCG2* (421C>A, 34G>A, 1143C>T), and *ABCB1* (1236C>T, 2677G>T/A, 3435C>T) (Table 1). Regarding the ABCB1 variants, we assessed the *ABCB1* 1236-2677-3435 TTT haplotype, which is associated with low expression.[15]

In the present study, the primary aim was to evaluate the association of sunitinib concentration with sunitinib-induced toxicity in patients with RCC. The secondary aim was to estimate the association of sunitinib PK with clinical outcome and genetic polymorphisms related to the PK of sunitinib.

Patients and Methods

Patients

This was a 2-institution study conducted at Shiga University of Medical Science Hospital and Shiga Medical Center for Adults. Twenty-one Japanese RCC patients treated with sunitinib were enrolled between September 2010 and March 2013. Eligibility criteria included histological confirmation and Eastern Cooperative Oncology Group performance status of 0, 1, or 2. This study was approved by the relevant institutional review boards.

Table 1 Selected SNPs Related to Sunitinib Pharmacokinetics

Gene	SNPs	rs Number	Region
CYP3A5	*CYP3A5* 6986G>A	rs776746	Intron
ABCG2	*ABCG2* 421C>A	rs2231142	Nonsynonymous Q141K
ABCG2	*ABCG2* 34G>A	rs2231137	Nonsynonymous V12M
ABCG2	*ABCG2* 1143C>T	rs2622604	Intron
ABCB1	*ABCB1* 1236C>T	rs1128503	Synonymous G412G
ABCB1	*ABCB1* 2677G>T/A	rs2032582	Nonsynonymous A893S/T
ABCB1	*ABCB1* 3435G>T	rs104642	Synonymous I1445I

Abbreviation: SNP = single-nucleotide polymorphism.

Treatment Plan

Sunitinib was administered at a dose of 50 mg, 37.5 mg, or 25 mg daily based on the treating physicians' recommendation for 4 weeks of a 6-week cycle for the first cycle. Subsequently, dose reduction or discontinuation was adjusted based on adverse events or disease progression.

Assessment of Safety and Efficacy

All adverse events were graded according to the Common Toxicity Criteria for Adverse Effects version 4.0. The worst clinically significant treatment-associated toxicities were analyzed. We also examined major bleeding events, as previously defined.[16] The best tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[17] Time for assessment was dictated by the individual institutional policies. To evaluate drug exposure and the safety/efficacy relationship, we grouped the population into patients with "low" exposure and "high" exposure. In this study, we used a total sunitinib (sunitinib + SU12662) concentration of 100 ng/mL as the cutoff value, which was previously reported as being associated with most patients experiencing dose-limiting toxicity.[18] Toxicity and clinical outcome due to sunitinib were compared between the 2 groups.

Assessment of Serum Level of Sunitinib

After informed consent had been obtained from the patients, blood samples were collected before administration at a steady state (days 10-28) after the initiation of sunitinib treatment during the first cycle. We retrospectively evaluated the serum concentrations of sunitinib and its major metabolite, SU12662, using stored blood samples. Blood samples were drawn into a sterilized vacuum tube for separation just before sunitinib administration. All samples were centrifuged at 1700*g* and 4°C for 10 minutes, and serum was separated and stored at −20°C.

Sunitinib and SU12662 were measured using high-performance liquid chromatography, as previously described.[19] The observed intraday and interday assay imprecision and inaccuracy were < 10%. The lower limits of quantification of sunitinib and SU12662 were 10 ng/mL and 5 ng/mL, respectively.

Single-Nucleotide Polymorphisms Related to the PK of Sunitinib

Genomic DNA was extracted from the blood using DNA Extract All Reagents (Applied Biosystems, Foster City, CA). Subsequently, genotyping was performed using TaqMan Single-Nucleotide Polymorphism (SNP) genotyping assay (Applied Biosystems) in a Step One Plus Real time Polymerase Chain Reaction system (Applied Biosystems). Amplification conditions were 95°C for 20 seconds, 40 cycles of 95°C for 3 seconds, and 60°C for 20 seconds.

Statistical Analysis

Descriptive data are expressed as mean ± SD or median. Continuous variables were compared using the Mann−Whitney *U* test. Categorical variable were compared using the χ^2 test or Fisher exact test. The correlation between serum concentration of sunitinib and blood cell count was determined using the Spearman test. The correlation between the severity of nonhematological toxicities and total sunitinib concentration was evaluated using the

Jonckheere–Terpsta test. Time-to-event variables were estimated using the Kaplan–Meier method and log rank test. Time to treatment failure (TTF) was defined as the period from the first day of sunitinib treatment until cessation of sunitinib treatment for any cause. Progression-free survival (PFS) was defined from the date of treatment initiation to the date of objective tumor progression or death. Overall survival (OS) was defined from the date of sunitinib initiation until the date of death. Patients lost to follow-up were censored at the time of last contact. The cutoff date for this analysis was March 31, 2014. Median follow-up was 482 days (range, 48-1001 days). Allele frequencies were tested for Hardy–Weinberg equilibrium using the χ^2 test. Correlations between genotypes related to sunitinib PK and the dose-adjusted total sunitinib concentration were evaluated using 1-way analysis of variance and Tukey test. All comparison tests were 2-sided. A $P < .05$ was considered to be statistically significant. All statistical analyses were performed using SPSS II version 22.0.

Results

Patient Characteristics

Twenty-one patients were treated with sunitinib. Baseline characteristics are shown in Table 2. The median age was 68 (range, 56-83) years, and 18 patients (85.7%) had clear-cell histology. Patients were treated with sunitinib starting at doses of 50 mg (n = 11), 37.5 mg (n = 5), and 25 mg (n = 5) daily. The median trough total sunitinib concentration was 91.8 (range, 49.8-205) ng/mL.

Association of Toxicities With Total Sunitinib Concentration

In the first cycle of sunitinib, a clear inverse correlation was found between the total sunitinib concentration and the blood platelet count at nadir ($r = -0.53$; $P = .01$), but not hemoglobin level ($r = 0.04$; $P = .86$) or leukocyte count ($r = 0.14$; $P = .55$; Figure 1).

A positive trend was observed between total sunitinib concentration and higher-grade toxicity of anorexia and fatigue (Figure 2A, B). In addition, total sunitinib concentration was not correlated with the severities of HFS and hypertension (Figure 2C, D). The mean total sunitinib concentration was greater in patients with bleeding events (n = 10) than in those without them (n = 11; 116 ± 43.4 vs. 77.2 ± 22.2 ng/mL, respectively; $P = .13$; Figure 2E).

Association of Dose Reduction or Discontinuation of Sunitinib With Total Sunitinib Concentration

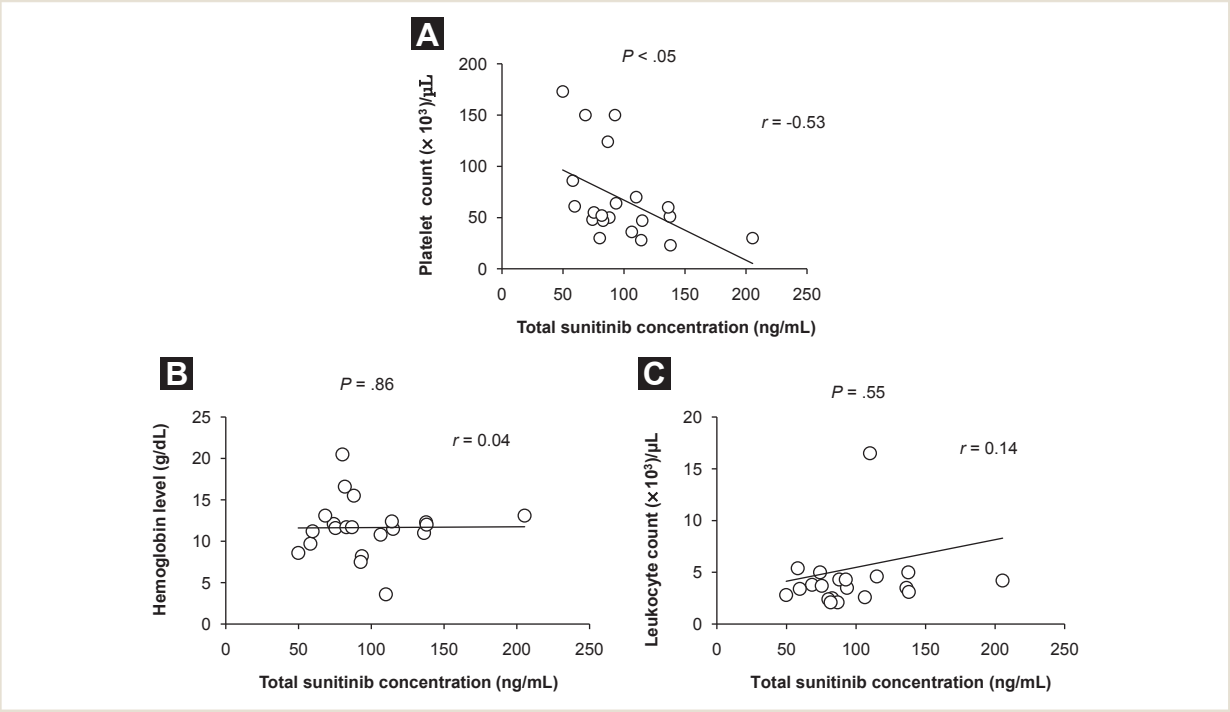
In the low-exposure group (total sunitinib < 100 ng/mL; n = 13), 3 patients (23.1%) experienced Grade 3 thrombocytopenia during the first cycle. Dose reductions from 50 mg to 37.5 mg

Table 2 Patient Characteristics

Characteristic	Total (n = 21)	Total Sunitinib Concentration		P
		<100 (n = 13)	≥100 (n = 8)	
Median Age (Range), Years	68 (56-83)	68 (56-83)	70 (59-79)	.92
Sex (Male/Female)	17/4	10/3	7/1	.50
Median Weight (Range), kg	56 (37-80)	56 (37-74)	50 (45-80)	.33
Median AST (Range), IU/L	22 (9-86)	22 (9-59)	26 (19-86)	.41
Median ALT (Range), IU/L	13 (6-104)	16 (7-59)	11 (6-104)	.46
Median eGFR (Range), mL/min/1.73m^2	41.8 (6.2-80.4)	41.5 (6.2-80.4)	50.8 (30.3-76.7)	.50
Median Sunitinib Concentration (Range), ng/mL	64.6 (30.6-137)	49.8 (30.6-75.6)	108 (64.7-137)	<.01
Median SU12662 Concentration (Range), ng/mL	22.5 (12.4-68.5)	22.7 (12.4-43.7)	22.3 (13.0-68.5)	.75
Median Total Sunitinib Concentration (Range), ng/mL	91.8 (49.8-205)	80.2 (49.8-93.5)	125 (106-205)	<.01
Initial Dose, n (%)				
50 mg	11 (52.4)	4 (30.8)	7 (87.5)	.03
37.5 mg	5 (23.8)	5 (38.4)	0 (0.0)	
25 mg	5 (23.8)	4 (30.8)	1 (12.5)	
Histology, n (%)				
Clear cell	18 (85.7)	11 (84.6)	7 (87.5)	.62
Papillary	3 (14.3)	2 (15.4)	1 (12.5)	
Previous Treatment, n (%)				
No	12 (57.1)	7 (53.8)	5 (62.5)	.67
Sorafenib	5 (23.8)	4 (30.8)	1 (12.5)	
Immunotherapy	4 (19.2)	2 (15.4)	2 (25.0)	
ECOG Performance Status, n (%)				
0	16 (76.2)	10 (76.9)	6 (75.0)	.93
1	3 (14.3)	2 (15.4)	1 (12.5)	
2	2 (9.5)	1 (7.7)	1 (12.5)	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate.

Figure 1 The Relationship Between Total Sunitinib Concentration and Hematological Toxicity. For the First Cycle of Sunitinib Treatment, (A) Platelet Count, (B) Hemoglobin Level, and (C) Leukocyte Count at Nadir Were Compared With Trough Total Sunitinib (Sunitinib + SU12662) at a Steady State in 21 Patients With Renal Cell Carcinoma. Each Circle Represents an Individual Patient



were performed in 2 patients, which resulted in attenuation of the thrombocytopenia. In this group, the toxicities of sunitinib therapy were mild (Grade $\leq$ 1 toxicities), except for the thrombocytopenia, and controllable. The final reasons for sunitinib discontinuation were disease progression (n = 5), interstitial lung disease (n = 2), Grade 3 anorexia (n = 2), and Grade 3 pancreatitis (n = 1).

In the high-exposure group (total sunitinib $\geq$ 100 ng/mL; n = 8), 6 of the 8 patients (75.0%) experienced Grade $\geq$ 3 toxicities during the first cycle. Because of its toxicities, dose reductions from 50 mg to 37.5 mg were performed in 5 patients. In 2 patients, the dose was reduced from 50 mg to 25 mg. In this group, 3 patients, who were managed as outpatients, were hospitalized because of grade 3 anorexia (n = 2) and intestinal perforation (n = 1). Additionally, 1 patient experienced protracted wound healing for the first cycle. As a consequence, sunitinib was discontinued in 7 patients who experienced Grade 3 anorexia (n = 3), Grade 3 fatigue (n = 3), and intestinal perforation (n = 1). Treatment of the patient who experienced intestinal perforation was started with sunitinib at 50 mg daily for 4 weeks of a 6-week cycle. This patient needed a dose reduction to 37.5 mg after 1 cycle of sunitinib because of Grade 3 thrombocytopenia. Six days after discontinuation of the second cycle of sunitinib, he presented with abdominal pain and muscle guarding. Computed tomography scans showed free air in the upper abdomen. Emergency laparotomy revealed localized perforation of the sigmoid colon. Resection of the sigmoid colon and colostomy were performed, and he recovered within 14 days. As shown in Figure 3, serum total sunitinib concentration was 205 ng/mL on day 16 of the first cycle. It was reported that sunitinib was effective at total plasma concentrations of 50 to 100 ng/mL in a vivo study.[20] Serum total sunitinib concentrations of the second cycle ranged from 90 to 160 ng/mL.

Association of Efficacy With Total Sunitinib Concentration

Eighteen of the 21 patients (85.7%) were included in the analysis of efficacy end points. A waterfall plot of the greatest percentage changes from baseline in the sum of the longest diameters of target lesions according to a total sunitinib concentration of $\geq$ 100 ng/mL, or < 100 mg/mL are displayed in Figure 4.

In the low-exposure group (total sunitinib < 100 ng/mL; n = 13), partial responses determined according to RECIST were achieved in 3 patients (23.1%). Stable disease was observed in 8 patients (61.5%). In 1 patient, the efficacy could not be confirmed because of transfer to another hospital. One patient was not assessable because of early unacceptable toxicity before the first assessment.

In the high-exposure group (total sunitinib $\geq$ 100 ng/mL; n = 8), the best response of stable disease was observed in 7 patients (87.5%). One patient was not assessable because of early unacceptable toxicity before the first assessment.

Figure 2 The Relationship Between Total Sunitinib Concentration and Nonhematological Toxicity. For the First Cycle of Sunitinib Treatment, (A) Anorexia, (B) Fatigue, (C) Hand-Foot Syndrome, (D) Hypertension, and (E) Bleeding Event Were Compared With Trough Total Sunitinib at a Steady State in 21 Patients With Renal Cell Carcinoma. All Adverse Events Were Graded Using the Common Toxicity Criteria for Adverse Effects Version 4.0. Each Circle Represents an Individual Patient

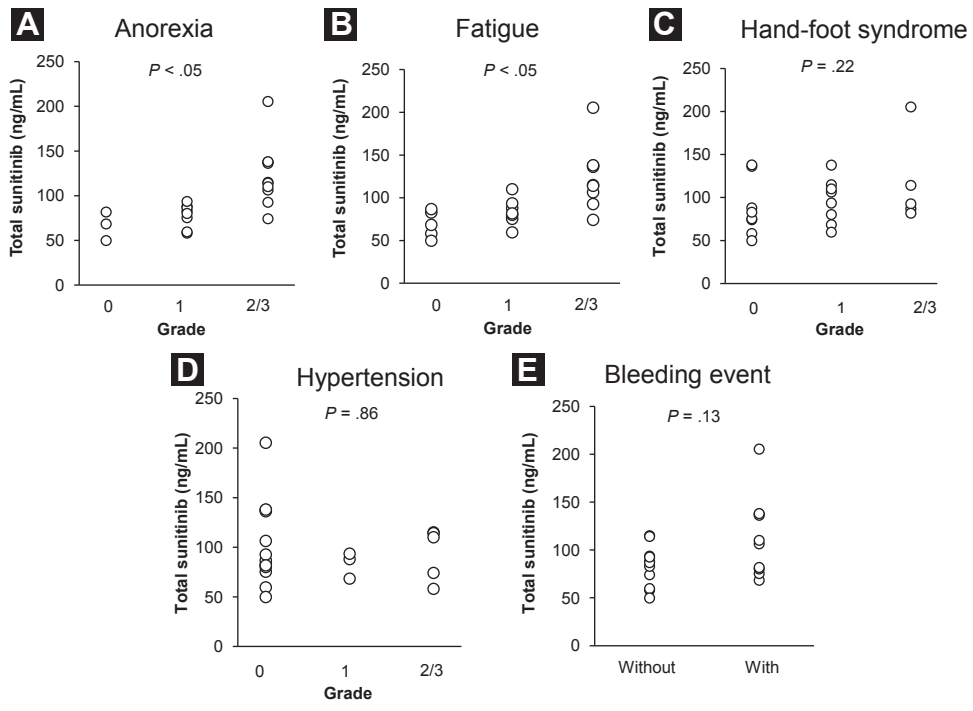
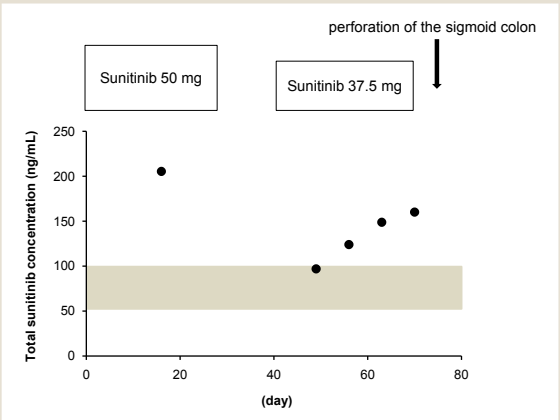


Figure 3 A Case of Perforation of the Sigmoid Colon Possibly Related to High Exposure to Sunitinib. Serum Concentrations of Total Sunitinib During Sunitinib Therapy in a Patient Who Experienced Intestinal Perforation. Arrow Indicates the Occurrence of Perforation of the Sigmoid Colon. Gray Area Shows the Therapeutic Range of Sunitinib (50-100 ng/mL)[20]



Association of TTF, PFS, and OS With Total Sunitinib Concentration

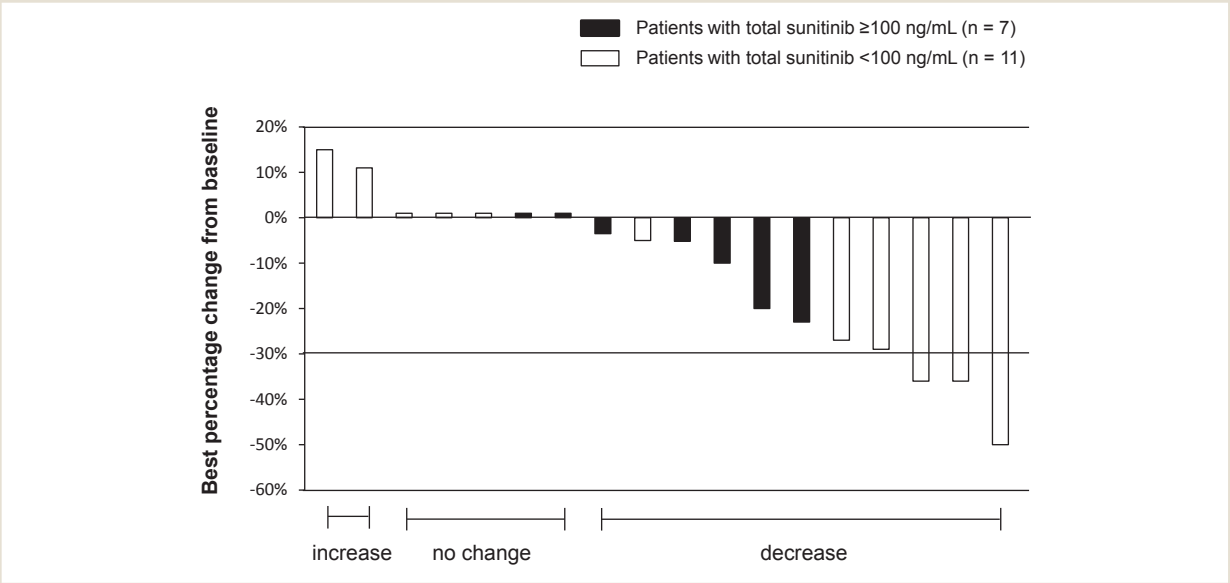
The median TTF, PFS, and OS were 163 days (95% confidence interval [CI], 9.12-317), 590 days (95% CI, 58.3-1122), and 939 days (95% CI, 585-1293), respectively. Additionally, a subgroup analysis of TTF, PFS, and OS was performed using total sunitinib concentration for the first cycle.

The patients with $<$ 100 ng/mL total sunitinib (n = 13) had significantly longer TTF than patients with $\geq$ 100 ng/mL (n = 8; median, 590 vs. 71 days; $P = .04$; Figure 5A). Patients with $<$ 100 ng/mL total sunitinib had significantly longer PFS than patients with $\geq$ 100 ng/mL (median, 748 vs. 238 days; $P = .02$; Figure 5B). Patients with $<$ 100 ng/mL total sunitinib showed only a tendency for significantly longer OS than patients with $\geq$ 100 ng/mL (median, 939 vs. 570 days; $P = .07$; Figure 5C).

Association of Total Sunitinib Concentration With SNPs Related to the PK of Sunitinib

Pharmacogenomic data were available for 21 patients. The allele frequencies of polymorphism in ABCG2, ABCB1, and CYP3A5 are shown in Table 3. These SNPs were in Hardy–Weinberg equilibrium ($P > .05$), except for the *CYP3A5* (6986G>A). However, the observed deviation was small with

Figure 4 Waterfall Plot of the Greatest Percentage Change From Baseline in the Sum of the Longest Diameters of Target Lesions. Open Squares, Patients With a Total Sunitinib Concentration < 100 ng/mL; Closed Squares, Patients With a Total Sunitinib Concentration ≥ 100 ng/mL



$P = .01$ for *CYP3A5* (6986G>A). As shown in Figure 6, no statistically significant associations between SNPs related to the PK of sunitinib and total sunitinib dose-adjusted concentration were observed.

Discussion

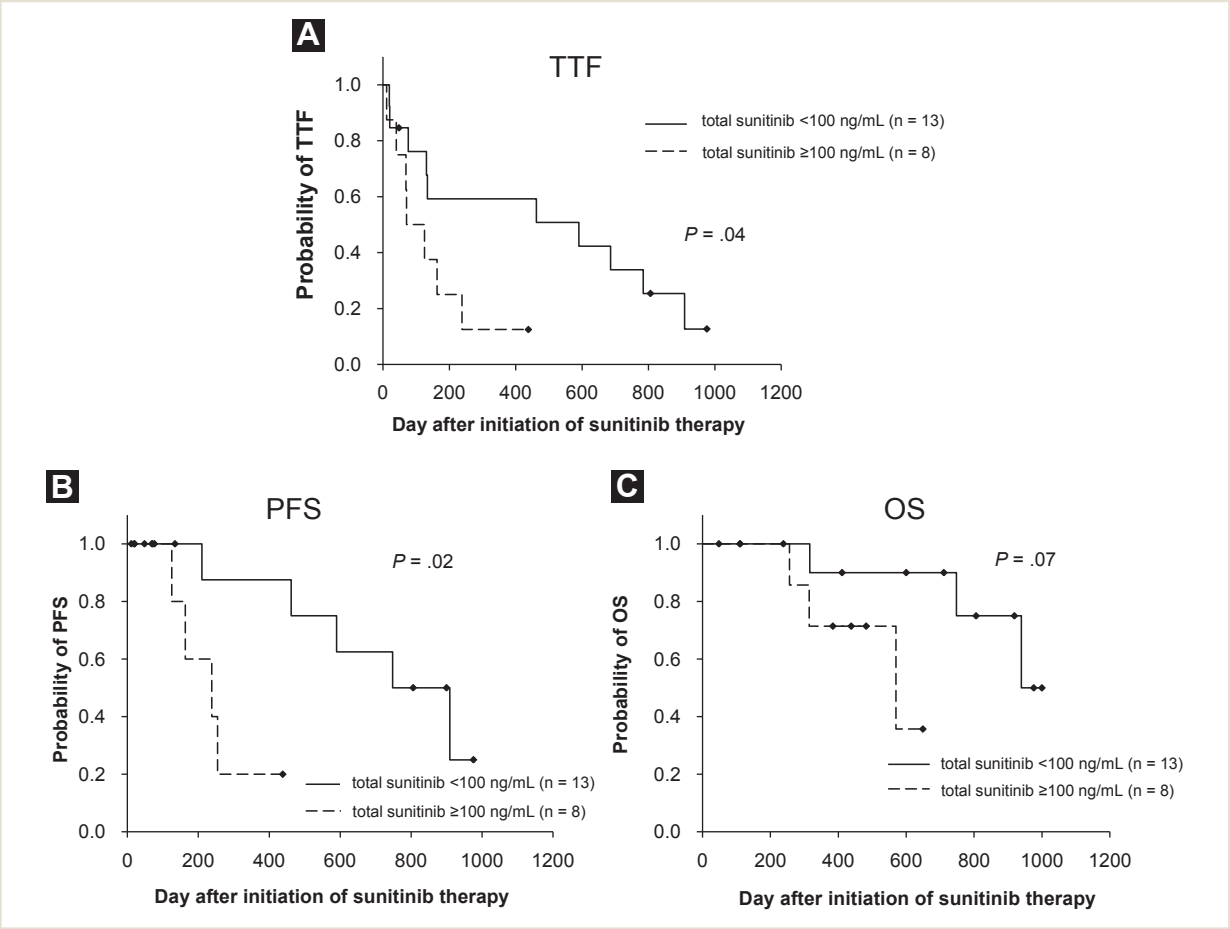
Despite the excellent efficacy of sunitinib, its severe toxicity is becoming a central issue in the treatment of RCC. Identifying a predictive marker of sunitinib toxicity is important to improve sunitinib therapy management. High exposure to sunitinib might be one of the reasons for the severe toxicities induced by it. In the present study, we showed that some patients with ≥ 100 ng/mL total sunitinib concentration were hospitalized because of its severe toxicities during outpatient therapy. Among them, 1 patient had to stop sunitinib permanently after 2 cycles because of intestinal perforation. Of interest is the fact that this patient had extremely high exposure to sunitinib (total trough sunitinib for the first cycle: 205 ng/mL). This patient had the rare genotype combination of ABCG2 and ABCB1; homozygosity for *ABCG2* 34G>A and the *ABCB1* 1236-2677-3435 TTT haplotype, suggesting that the functional loss of ABCG2 and ABCB1 might have contributed to the substantial exposure to sunitinib. Another reason for a high concentration in this patient is considered to be because of drug–drug interaction. During sunitinib therapy, this patient had taken azelnidipine, a CYP 3A4 inhibitor,[21] in combination with it, which could have been related to the high concentration of sunitinib.

A previous meta-analysis indicated that increased serum AUC to total sunitinib is associated with improved treatment outcomes and some adverse effects.[22] Although severe toxicity of sunitinib is becoming a central issue in the treatment of RCC, a threshold for the toxicity of sunitinib treatment has not been defined. Furthermore, a recent study demonstrated that total trough sunitinib concentration was highly correlated with its $AUC_{0\ to\ 24\ hours}$.[23] Therefore, we consider that total sunitinib trough concentration is a valid PK parameter for its toxicity. In a phase I study, a case presentation of 3 patients indicated that total sunitinib trough concentration ≥ 100 ng/mL might be associated with dose-limiting toxicity.[18] In agreement with this study, we showed that most of the patients with total trough sunitinib ≥ 100 ng/mL experienced unacceptable toxicities. This could have led to early treatment discontinuation or delayed administration, which resulted in suboptimal efficacy of sunitinib. In fact, in the present study, the high-exposure group (≥ 100 ng/mL total sunitinib) showed a shorter TTF and PFS. These observations suggest that ≥ 100 ng/mL total sunitinib trough concentration might be a limiting factor leading to treatment discontinuation.

Preclinical studies have demonstrated that sunitinib is effective at total plasma concentrations of 50 to 100 ng/mL.[20] In a clinical trial, Faivre et al[18] reported that the total sunitinib concentration obtained with a dose of 50 mg daily ranged from 50 to 100 ng/mL. Uemura et al[24] also reported that sunitinib was effective at plasma concentrations ≥ 50 ng/mL in patients with metastatic RCC. In the present study, 95.2% of patients (20/21) exceeded 50 ng/mL total sunitinib, and these patients showed either a partial response or stable disease as the best response. Additionally, considering sunitinib toxicity, when targeting ≥ 100 ng/mL total sunitinib, it is difficult to maintain sunitinib treatment for a long period of time. Therefore, the target range could be a total sunitinib trough concentration of 50 to 100 ng/mL during sunitinib therapy.

In this study, total sunitinib concentration was significantly associated with TTF and PFS. However, the difference between

Figure 5 Kaplan–Meier Curve of (A) Time to Treatment Failure (TTF), (B) Progression-Free Survival (PFS), and (C) Overall Survival (OS) According to Sunitinib Exposure in Patients With Renal Cell Carcinoma. Solid Lines, Patients With a Total Sunitinib Concentration < 100 ng/mL; Dotted Lines, Patients With a Total Sunitinib Concentration ≥ 100 ng/mL. Small Closed Diamond Marks Represent Censored Patients (End of Follow-Up)



PFS and TTF was large. This apparent difference might be explained by the fact that patients who discontinued sunitinib treatment because of its severe toxicities have a greater frequency compared with those who discontinued treatment because of progression of disease (12 patients [57.1%] vs. 5 patients [23.8%]). Considering that PFS includes time to disease progression from sunitinib discontinuation induced by toxicity, PFS might be longer than TTF in the present study.

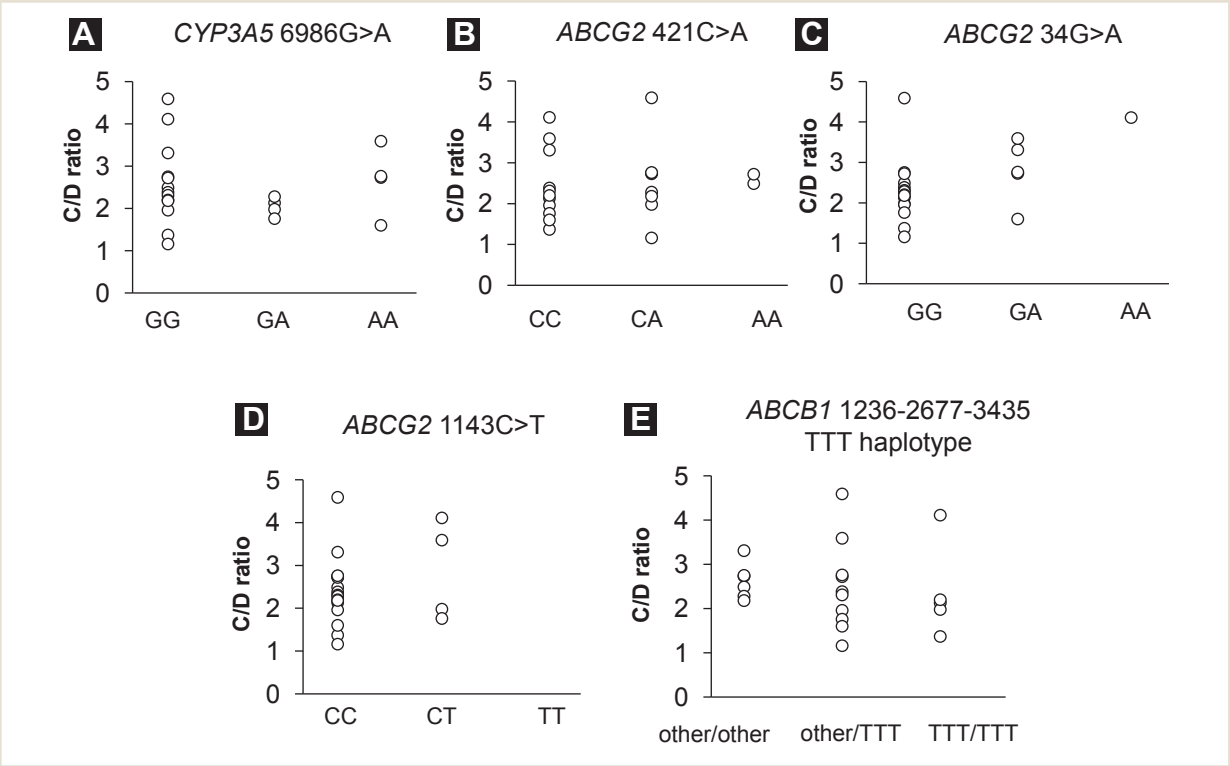
Our data showed that polymorphisms related to PK of sunitinib was not related to total sunitinib dose-adjusted concentration. However, previous preclinical and clinical studies reported that functional loss of ABCG2 was associated with increased sunitinib

Table 3 Polymorphism Genotype and Allele Frequency

Gene	SNPs	Patients	Homozygous Wild Type	Heterozygous	Homozygous Variant	Allele Frequency
CYP3A5	*CYP3A5* 6986G>A	21	13	4	4	0.286
ABCG2	*ABCG2* 421C>A	21	11	8	2	0.286
ABCG2	*ABCG2* 34G>A	21	15	5	1	0.167
ABCG2	*ABCG2* 1143C>T	21	17	4	0	0.095
ABCB1	*ABCB1* 1236C>T	21	2	6	13	0.761
ABCB1	*ABCB1* 2677G>T/A	21	3	10	8	0.619
ABCB1	*ABCB1* 3435G>T	21	4	11	6	0.547

Abbreviation: SNP = single-nucleotide polymorphism.

Figure 6 The Relationship Between Total Sunitinib Concentration and Single Nucleotide Polymorphisms Related to the Pharmacokinetics of Sunitinib. We Examined the Effect of Genetic Polymorphisms in (A) CYP3A5, (B-D) ABCG2, and (E) ABCB1. C/D Ratio Represents Total Sunitinib Dose-Adjusted Concentration



exposure and sunitinib-related toxicity.[12,25-27] Of interest, our patient who experienced high exposure to sunitinib had the ABCG2 and ABCB1 variant, and had received a CYP3A4 inhibitor in combination with sunitinib. Therefore, phenotypes of the PK of sunitinib are multifactorial, and not only genetics but also drug-drug interactions, poor compliance, and environment could have an effect on sunitinib PK.

Conclusion

The present study showed that several side effects of sunitinib were dose-dependent. Discontinuation occurred significantly more frequently in patients with total sunitinib trough concentration $\geq$ 100 ng/mL. Dose reduction might be needed, especially when the steady-state total sunitinib concentration is $>$ 100 ng/mL. These findings suggest that TDM of sunitinib could be helpful for avoiding severe side effects, resulting in prolonged TTF and PFS with sunitinib therapy. However, these results are debatable because the number of patients examined was very small and there were several differences in their background. To confirm these findings, large prospective PK studies should be performed.

Clinical Practice Points

- Sunitinib, an oral multitargeted tyrosine inhibitor, has shown single-agent activity in patients with metastatic RCC. Sunitinib PK show a large interpatient variability. However, information on pharmacokinetic assessment of sunitinib is limited.
- In this retrospective, observational study, we explored the PK relationship with safety or efficacy of sunitinib in 21 patients with RCC. We found that the severity of thrombocytopenia, anorexia, and fatigue appeared to be dose-dependent. Patients with $\geq$ 100 ng/mL total sunitinib (n = 8), compared with patients with $<$ 100 ng/mL (n = 13), had a greater incidence of Grade $\geq$ 3 toxicities (6 patients [75%] vs. 3 patients [23%]). Furthermore, we indicated that patients with $<$ 100 ng/mL total sunitinib had significantly longer TTF and PFS than patients with $\geq$ 100 ng/mL.
- These findings suggested that TDM of sunitinib could be helpful for avoiding severe toxicities, resulting in prolonged TTF and PFS with sunitinib therapy. However, this was a retrospective analysis of a small number of patients, which consisted of a heterogeneous population. Therefore, these results need to be validated in a large prospective study.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 22390029) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356:115-24.
2. Flaig TW, Kim FJ, La Rosa FG, et al. Colonic pneumatosis and intestinal perforations with sunitinib treatment for renal cell carcinoma. *Invest New Drugs* 2009; 27:83-7.
3. Boyle HJ, Chatté G, Rivoire M, et al. Lung toxicity in a patient treated with sunitinib. *Eur Respir J* 2012; 40:1300-3.
4. Feyerabend S, Schilling D, Wicke C, et al. Toxic dermatolysis, tissue necrosis and impaired wound healing due to sunitinib treatment leading to forefoot amputation. *Urol Int* 2009; 82:246-8.
5. de Jonge ME, Huitema AD, Schellens JH, et al. Individualised cancer chemotherapy: strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review. *Clin Pharmacokinet* 2005; 44:147-73.
6. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood* 2007; 109:3496-9.
7. Guilhot F, Hughes TP, Cortes J, et al. Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial. *Haematologica* 2012; 97:731-8.
8. Lu JF, Eppler SM, Wolf J, et al. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clin Pharmacol Ther* 2006; 80:136-45.
9. Hamada A, Sasaki J, Saeki S, et al. Association of ABCB1 polymorphisms with erlotinib pharmacokinetics and toxicity in Japanese patients with non−small-cell lung cancer. *Pharmacogenomics* 2012; 13:615-24.
10. Britten CD, Kabbinavar F, Hecht JR, et al. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. *Cancer Chemother Pharmacol* 2008; 61:515-24.
11. Adams VR, Leggas M. Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. *Clin Ther* 2007; 29:1338-53.
12. Mizuno T, Terada T, Kamba T, et al. ABCG2 421C>A polymorphism and high exposure of sunitinib in a patient with renal cell carcinoma. *Ann Oncol* 2010; 21: 1382-3.
13. Hu S, Chen Z, Franke R, et al. Interaction of the multikinase inhibitors sorafenib and sunitinib with solute carriers and ATP-binding cassette transporters. *Clin Cancer Res* 2009; 15:6062-9.
14. Noguchi K, Katayama K, Mitsuhashi J, et al. Functions of the breast cancer resistance protein (BCRP/ABCG2) in chemotherapy. *Adv Drug Deliv Rev* 2009; 61:26-33.
15. Kimchi-Sarfaty C, Oh JM, Kim IW, et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science* 2007; 315:525-8.
16. Je Y, Schutz FA, Choueiri TK. Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *Lancet Oncol* 2009; 10: 967-74.
17. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.
18. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; 24:25-35.
19. Noda S, Kageyama S, Tsuru T, et al. Pharmacokinetic/pharmacodynamic analysis of a hemodialyzed patient treated with 25 mg of sunitinib. *Case Rep Oncol* 2012; 5: 627-32.
20. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/ pharmacodynamic relationship. *Clin Cancer Res* 2003; 9:327-37.
21. Sugiyama Y, Mimura N, Kuwabara T, et al. Effect of benidipine on simvastatin metabolism in human liver microsomes. *Drug Metab Pharmacokinet* 2007; 22: 199-205.
22. Houk BE, Bello CL, Poland B, et al. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol* 2010; 66:357-71.
23. de Wit D, Gelderblom H, Sparreboom A, et al. Midazolam as a phenotyping probe to predict sunitinib exposure in patients with cancer. *Cancer Chemother Pharmacol* 2014; 73:87-96.
24. Uemura H, Shinohara N, Yuasa T, et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. *Jpn J Clin Oncol* 2010; 40:194-202.
25. Mizuno T, Fukudo M, Terada T, et al. Impact of genetic variation in breast cancer resistance protein (BCRP/ABCG2) on sunitinib pharmacokinetics. *Drug Metab Pharmacokinet* 2012; 27:631-9.
26. Mizuno T, Fukudo M, Fukuda T, et al. The effect of ABCG2 genotype on the population pharmacokinetics of sunitinib in patients with renal cell carcinoma. *Ther Drug Monit* 2014; 36:310-6.
27. Kim HR, Park HS, Kwon WS, et al. Pharmacogenetic determinants associated with sunitinib-induced toxicity and ethnic difference in Korean metastatic renal cell carcinoma patients. *Cancer Chemother Pharmacol* 2013; 72:825-35.