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

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Abstract (249 words)

Manuscript (4,694 words)

Conflict of interest

All authors declare no potential conflict of interest.

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 inter-patient 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 ≥100 ng/mL total sunitinib (n=8),

as compared with patients with <100 ng/mL (n=13), had a higher incidence of Grade ≥3 toxicities (75% vs. 23%). Patients with <100 ng/mL total sunitinib had significantly longer time to treatment failure (TTF), progression-free survival time (PFS) than patients with ≥100 ng/mL (median TTF 590 vs. 71 days, *P*=0.04; median PFS 748 vs. 238 days, *P*=0.02)

Conclusions

This study suggests that therapeutic drug monitoring of sunitinib could be useful for avoiding severe toxicities. Dose reduction may be needed, especially when the total sunitinib concentration is ≥100 ng/mL, to avoid unnecessary early discontinuation of treatment.

Key words: Sunitinib, Renal cell carcinoma, Pharmacokinetics, Therapeutic drug monitoring

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 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 event.[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 handle 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.

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 both 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 may 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 may 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 ATP-binding cassette 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 ABCB1 1236-2677-3435 TTT haplotype, which are 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 two-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 (ECOG) performance status of 0, 1, or 2. This study was approved by the relevant institutional review boards.

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 v4.0. 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.

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 by high-performance liquid chromatography, as previously described.[18] 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 (SNPs) *related to the PK of sunitinib*

Genomic DNA was extracted from the blood using DNA Extract All Reagents (Applied Biosystems, Foster City, CA, USA). Subsequently, genotyping was performed using TaqMan® SNP genotyping assay (Applied Biosystems) in a Step One Plus Real time PCR system (Applied Biosystems). Amplification conditions were 95˚C for 20 s, 40 cycles of 95˚C for 3 s, and 60˚C for 20 s.

Statistical analysis

Descriptive data are expressed as means ± SD or median. Continuous variables were compared using Mann-Whitney U-test. Categorical variable were compared by Chi-square test or Fisher's exact test. The correlation between serum concentration of sunitinib and blood cell count was determined using Spearman's test. The correlation between the severity of non-hematological toxicities and total sunitinib concentration was evaluated by 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 due to 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 cut-off date for this analysis was March 31, 2014. Median follow-up was 482 days (range 48-1001). Allele frequencies were tested for Hardy-Weinberg equilibrium using the Chi-square test. Correlations between genotypes related to sunitinib PK and the dose-adjusted total sunitinib concentration were evaluated by one-way analysis of variance and Tukey test. All comparison tests were two-sided. A p-value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS II v. 22.0.

Results

Patient characteristics

Twenty-one patients were treated with sunitinib. Baseline characteristics are shown in Table 2. The median age was 68 years (range 56-83), and 18 patients (85.7%) had clear cell histology. Patients were started on sunitinib 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 ng/mL (range 49.8-205). 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 concentration of 100 ng/mL as the cut-off value, which was previously reported as being associated with most patients experiencing dose-limiting toxicity.[19] Toxicity and clinical outcome due to sunitinib were compared between the two groups.

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*=0.01), but not hemoglobin level count (r=0.04, *P*=0.86) or leukocyte count (r=0.14, *P*=0.55) (Fig. 1).

A positive trend was observed between total sunitinib concentration and higher-grade

toxicity of anorexia and fatigue (Fig. 2a, b). In addition, total sunitinib concentration was not correlated with the severities of HFS and hypertension (Fig. 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*=0.13) (Fig. 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), three patients (23.1%) experienced grade 3 thrombocytopenia during the first cycle. Dose reductions from 50 mg to 37.5 mg were performed in 2 patients, which resulted in attenuation of the thrombocytopenia. In this group, the toxicities of sunitinib therapy were mild (grade ≤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 ≥100 ng/mL, n=8), six (75%) of the 8 patients experienced Grade ≥3 toxicities during the first cycle. Owing to 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, three patients, who were managed as outpatients, were hospitalized due to grade 3 anorexia (n=2) and intestinal perforation (n=1). Additionally, one 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). The patient who experienced intestinal perforation was started on 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 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. Serum total sunitinib concentrations of the second cycle ranged from 90 to 160 ng/mL.

Association of efficacy with total sunitinib concentration

Eighteen (85.7%) of the 21 patients were included in the analysis of efficacy end

points. 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 ≥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 by RECIST were achieved in 3 patients (23.1%). Stable disease was observed in 8 patients (61.5%). In one patient, the efficacy could not be confirmed due to transfer to another hospital. One patient was not assessable due to early unacceptable toxicity before the first assessment.

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

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 sub-group 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 ≥100 ng/mL (n=8) (median 590 vs. 71 days, *P*=0.04) (Fig. 5a). Patients with <100 ng/mL total sunitinib had significantly longer PFS than patients with ≥100 ng/mL (median 748 vs. 238 days, *P*=0.02) (Fig. 5b). Patients with <100 ng/mL total sunitinib showed only a tendency for significantly longer OS than patients with ≥100 ng/mL (median 939 vs. 570 days, *P*=0.07) (Fig. 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*>0.05), except for the CYP3A5 (6986G>A). However, the observed deviation was small with *P*=0.01 for CYP3A5 (6986G>A). As shown in Fig. 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 using it. Identifying a predictive marker of sunitinib toxicity is important to improve sunitinib therapy management. A previous report indicated that one RCC patient showed severe adverse events such as grade 3 hypertension, grade 3 facial acne, and grade 3 elevation of amylase, and had maximum concentration and AUC of sunitinib that were 2.5-fold higher than those of four other patients with similar clinical characteristics.[12] High exposure to sunitinib may 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 due to its severe toxicities during outpatient therapy. Among them, one patient had to stop sunitinib permanently after 2 cycles due to 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). To identify the cause of the high concentration of sunitinib in this patient, we checked co-administered drugs. During the sunitinib therapy, this patient had taken azelnidipine, a CYP 3A4 inhibitor, as previously reported,[20] in combination with it, which could have been related to the high concentration of sunitinib.

The development of TDM strategies should lead to the selection of an optimal regimen and dose for each individual patient based on drug PK. However, the usefulness of TDM of sunitinib is limited by the lack of established therapeutic ranges. A previous meta-analysis of metastatic RCC studies indicated that increased serum AUC to sunitinib and SU12662 is associated with improved treatment outcomes and some adverse effects.[21] Although severe toxicity of sunitinib is becoming a central issue in the treatment of RCC using it, a threshold for the toxicity of sunitinib treatment has not been defined. A recent study demonstrated that total trough sunitinib concentration were highly correlated with its $AUC_{0\text{-}24h}$.[22] 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 three patients indicated that total sunitinib trough concentration ≥ 100 ng/mL may be associated with dose-limiting toxicity.[19] 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 may be a limiting factor leading to treatment discontinuation.

Preclinical studies have demonstrated that sunitinib is effective at total plasma concentrations of 50-100 ng/ml.[23] In a clinical trial, Faivre et al.[19] 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 50-100 ng/mL during sunitinib therapy.

In this study, total sunitinib concentration was significantly associated with TTP and PFS. However, it was not significantly associated with OS. This discrepancy may partly contribute to the availability of sequential administration of target therapy after the discontinuation of sunitinib treatment. Guidelines recommend everolimus[25] and axitinib[26] for patients with advanced RCC refractory to prior systemic therapy, including sunitinib. In the present study, nine (42.9%) of 21 patients were subsequently treated with target therapy, including everolimus (n=4) and axitinib (n=5), after sunitinib discontinuation. These observations suggest that additional treatment could be

beneficial for patients who discontinued sunitinib due to severe toxicity or progressive disease.

To identify the cause of the large inter-patient variability in sunitinib exposure in this study, we checked genetic polymorphism related to sunitinib PK. Previous preclinical and clinical studies reported that functional loss of ABCG2 was associated with increased sunitinib exposure.[12,27,28] Another study reported that ABCG2 421C>A polymorphism may be mostly associated with the risk of sunitinib-related toxicity in mRCC patients.[29] In disagreement with these studies, our data showed that polymorphism related to PK of sunitinib, including ABCG2, was not related to total sunitinib dose-adjusted concentration. A recent pharmacogenomic study on the PK of sunitinib indicated that none of the SNPs in candidate genes for the PK of sunitinib appeared to be significantly associated with the clearance of sunitinib and SU12662 in 114 RCC patients treated with sunitinib.[30] Phenotypes of the PK of sunitinib are multifactorial, and not only genetics but also drug-drug interactions, poor compliance, and environment could have an impact on sunitinib PK. Therefore, we need to perform prospective PK/pharmacogenomic study in RCC patients treated with sunitinib.

Conclusions

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 ≥100 ng/mL. Dose reduction may be needed, especially when the steady-state total sunitinib concentration is above 100 ng/mL. These findings suggest that therapeutic drug monitoring of sunitinib could be helpful for avoiding severe side effects, resulting in prolonged TTF and PFS upon sunitinib therapy. However, these results are debatable because the number of patients examined was very small and there were several differences in their back ground. In order to confirm these findings, large prospective PK studies should be performed.

Clinical practice point

- Sunitinib, an oral multitargeted tyrosine inhibitor, has shown single-agent activity in patients with metastatic RCC. Sunitinib pharmacokinetics shows a large inter-patient variability. However, information on pharmacokinetic assessment of sunitinib is limited.
- In this retrospective, observational study, we explored pharmacokinetic 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 ≥100 ng/mL total sunitinib (n=8), as compared with patients with <100 ng/mL (n=13), had a higher incidence of Grade ≥3 toxicities (75% vs. 23%). Furthermore, we indicated that patients with <100 ng/mL total sunitinib had significantly longer TTF, PFS than patients with ≥100 ng/mL.
- These findings suggested that TDM of sunitinib could be helpful for avoiding severe toxicities, resulting in prolonged TTF and PFS upon sunitinib therapy. However, this was a retrospective analysis of a small number of patients consisted of heterogeneous population. Therefore, these results need to be validated in a large prospective study.

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

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Legends for figures

Fig. 1 The relationship between total sunitinib concentration and hematological toxicity

For the first cycle of sunitinib treatment, platelet count (a), hemoglobin level (b), and leukocyte count (c) at nadir were compared with trough total sunitinib (sunitinib + SU12662) at a steady state in 21 patients with renal cell carcinoma (RCC). Each *symbol* represents an individual patient.

Fig. 2 The relationship between total sunitinib concentration and non-hematological toxicity

For the first cycle of sunitinib treatment, anorexia (a), fatigue (b), hand-foot syndrome (c), hypertension (d), and bleeding event (e) were compared with trough total sunitinib at a steady state in 21 patients with RCC. All adverse events were graded using the Common Toxicity Criteria for Adverse Effects v4.0. Each *symbol* represents an individual patient.

Fig. 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. Arrows indicate the occurrence of perforation of the sigmoid colon. Gray area shows the therapeutic range of sunitinib (50-100 ng/ml) (reference 23).

Fig. 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.

Fig. 5 Kaplan-Meier curve of time to treatment failure (TTF) (a), progression-free survival (PFS) (b), and overall survival (OS) (C) 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).

Fig. 6 The relationship between total sunitinib concentration and SNPs related to the PK of sunitinib

We examined the effect of genetic polymorphism in CYP3A5 (a), ABCG2 (b-d), and ABCB1 (e). C/D ratio represents total sunitinib dose-adjusted concentration.

Table 1 Selected SNPs related to sunitinib PK

gene	SNPs	rs number	Region
CYP3A5	CYP3A5 6986G>A	rs776746	Intron
ABCG2	ABCG2 421C>A	rs2231142	Non-synonymous Q141K
ABCG2	ABCG2 34G>A	rs2231137	Non-synonymous V12M
ABCG2	ABCG2 1143C>T	rs2622604	Intron
ABCB1	ABCB1 1236C>T	rs1128503	Synonymous G412G
ABCB1	ABCB1 2677G>T/A	rs2032582	Non-synonymous A893S/T
ABCB1	ABCB1 3435G>T	rs104642	Synonymous I1445I

Table 2　Patient Characteristics

Chracteristic	total (n=21)	total sunitinib concentration		*P*
		<100 (n=13)	≥100 (n=8)	
Median Age (range), yr	68 (56-83)	68 (56-83)	70 (59-79)	0.92
Gender (Male/Female)	17/4	10/3	7/1	0.50
Median Weight (range), kg	56 (37-80)	56 (37-74)	50 (45-80)	0.33
Median AST (range), IU/L	22 (9-86)	22 (9-59)	26 (19-86)	0.41
Median ALT (range), IU/L	13 (6-104)	16 (7-59)	11 (6-104)	0.46
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)	0.50
Median sunitinib concentration (range), ng/mL	64.6 (30.6-137)	49.8 (30.6-75.6)	108 (64.7-137)	<0.01
Median SU12662 concentration (range), ng/mL	22.5 (12.4-68.5)	22.7 (12.4-43.7)	22.3 (13.0-68.5)	0.75
Median total sunitinib concentration (range), ng/mL	91.8 (49.8-205)	80.2 (49.8-93.5)	125 (106-205)	<0.01
Initial dose, n (%)				
50 mg	11 (52.4)	4 (30.8)	7 (87.5)	0.03
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)	0.62
papillary	3 (14.3)	2 (15.4)	1(12.5)	
Prior treatment, n (%)				
No	12 (57.1)	7 (53.8)	5 (62.5)	0.67
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)	0.93
1	3 (14.3)	2 (15.4)	1 (12.5)	
2	2 (9.5)	1 (7.7)	1 (12.5)	

AST, aspartate aminotransferase; ALT, aranine aminotransferase; eGFR, estimated glomerular filtration rate; ECOG, Eastern Cooperative Oncology Group

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

Figure

Fig.1

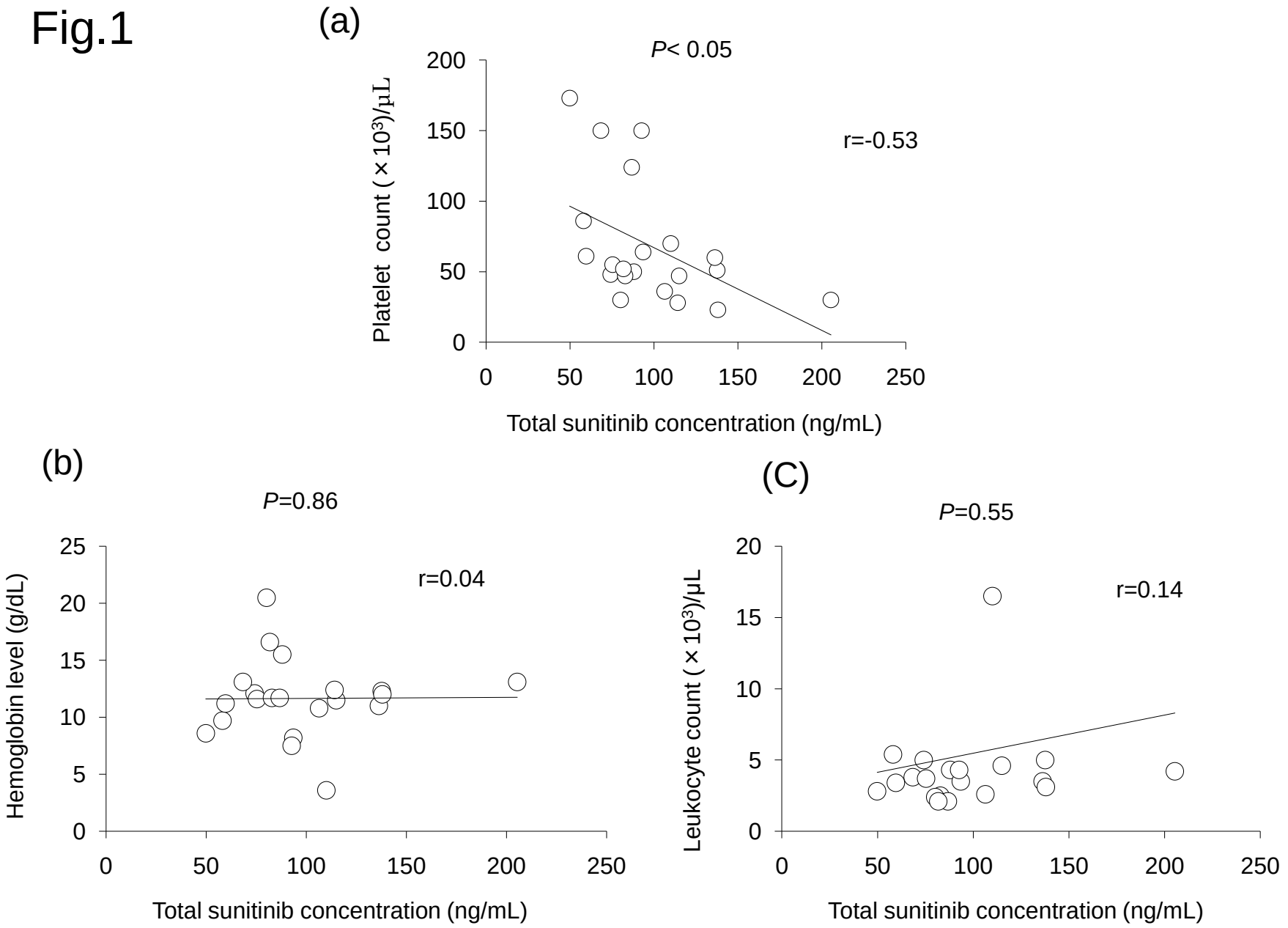

(a)
P< 0.05
r=-0.53
Platelet count (× 10³)/μL
Total sunitinib concentration (ng/mL)
(b)
P=0.86
r=0.04
Hemoglobin level (g/dL)
Total sunitinib concentration (ng/mL)
(C)
P=0.55
r=0.14
Leukocyte count (× 10³)/μL
Total sunitinib concentration (ng/mL)

Fig. 2

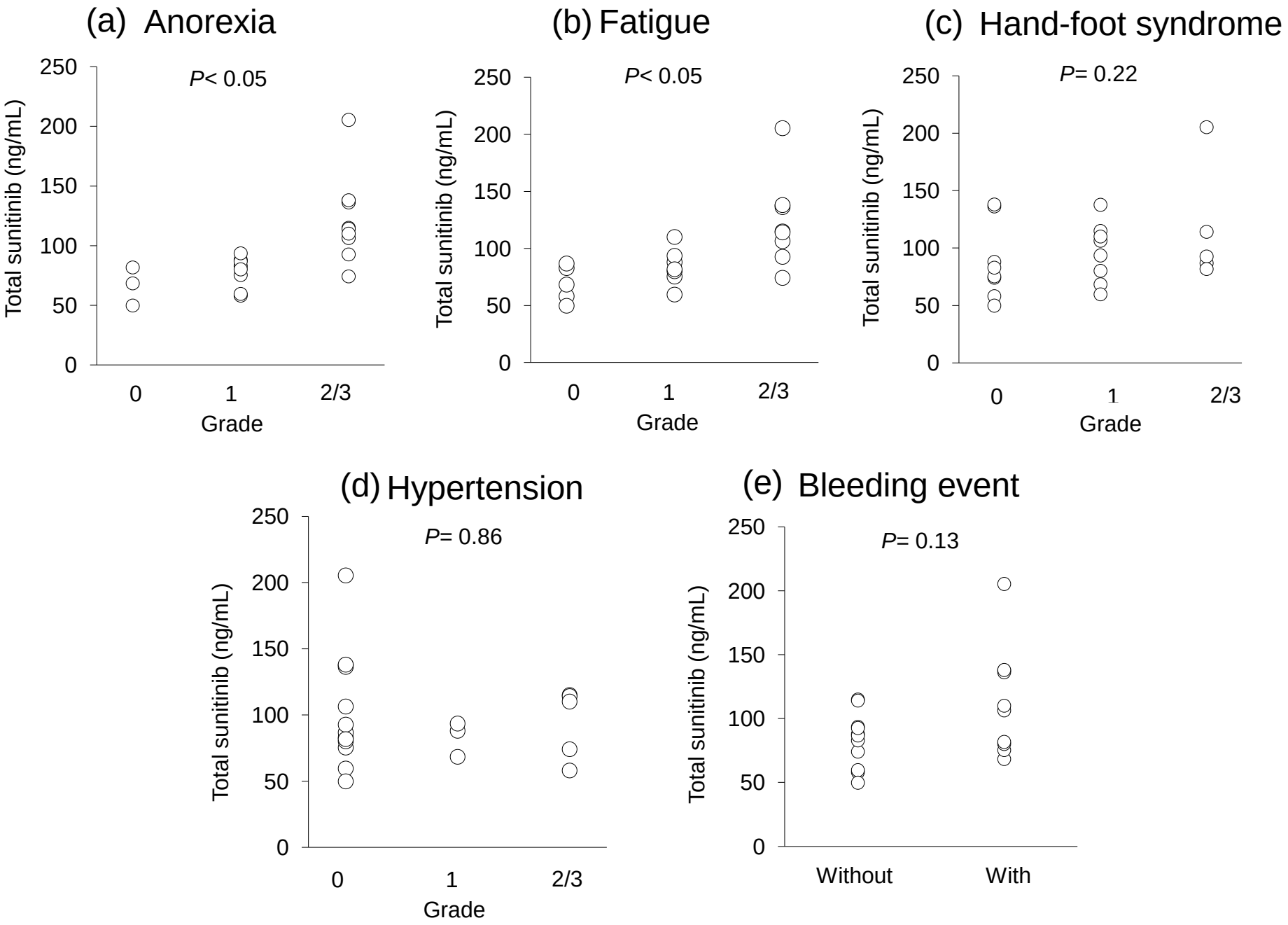

(a) Anorexia
P< 0.05
Total sunitinib (ng/mL)
250
200
150
100
50
0
0
1
2/3
Grade
(b) Fatigue
P< 0.05
Total sunitinib (ng/mL)
250
200
150
100
50
0
0
1
2/3
Grade
(c) Hand-foot syndrome
P= 0.22
Total sunitinib (ng/mL)
250
200
150
100
50
0
0
1
2/3
Grade
(d) Hypertension
P= 0.86
Total sunitinib (ng/mL)
250
200
150
100
50
0
0
1
2/3
Grade
(e) Bleeding event
P= 0.13
Total sunitinib (ng/mL)
250
200
150
100
50
0
Without
With

Fig. 3

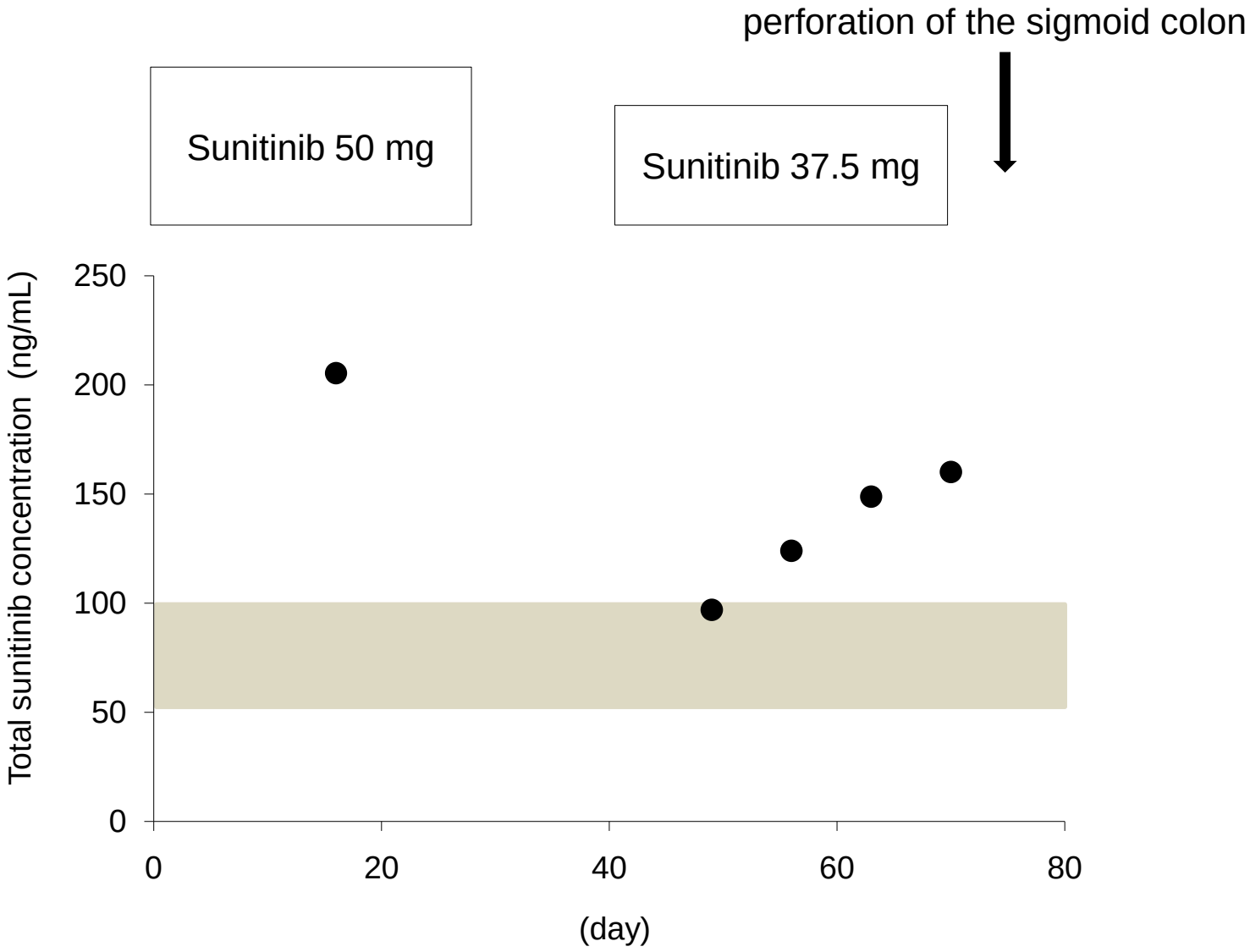

perforation of the sigmoid colon
Sunitinib 50 mg
Sunitinib 37.5 mg
Total sunitinib concentration (ng/mL)
250
200
150
100
50
0
0
20
40
60
80
(day)

Fig. 4

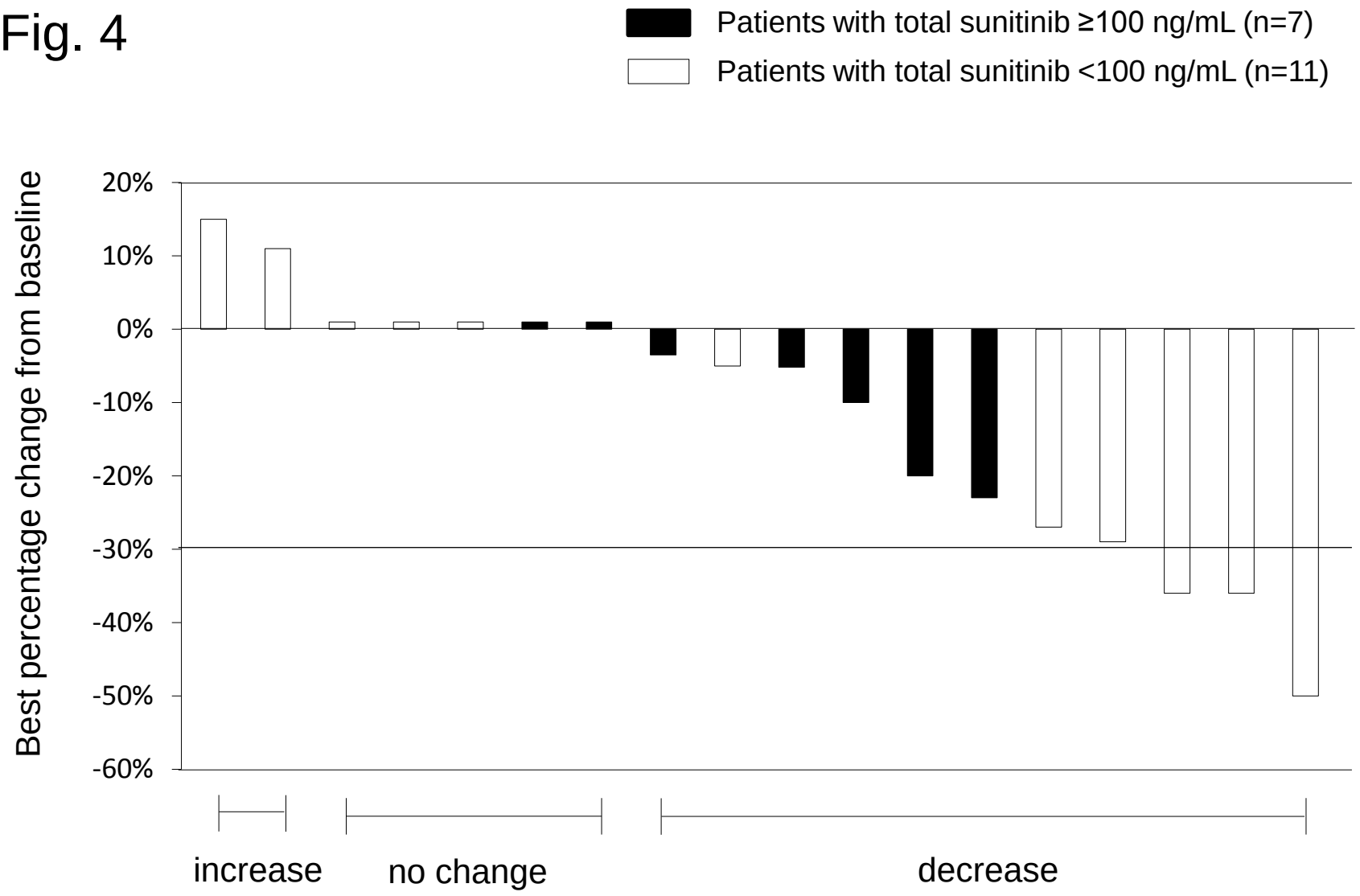

Patients with total sunitinib ≥100 ng/mL (n=7)
Patients with total sunitinib <100 ng/mL (n=11)
Best percentage change from baseline
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
-60%
increase
no change
decrease

Fig. 5

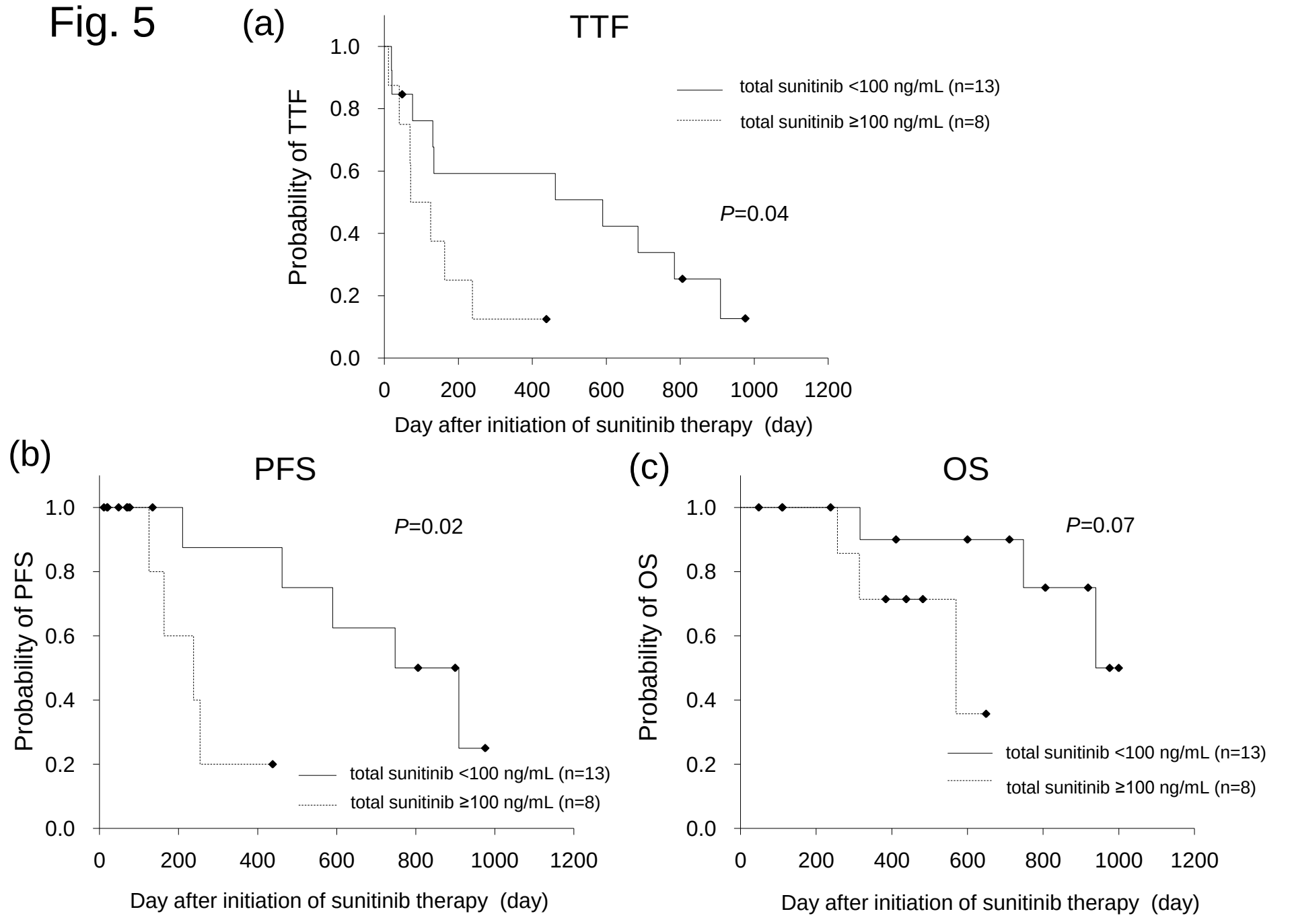
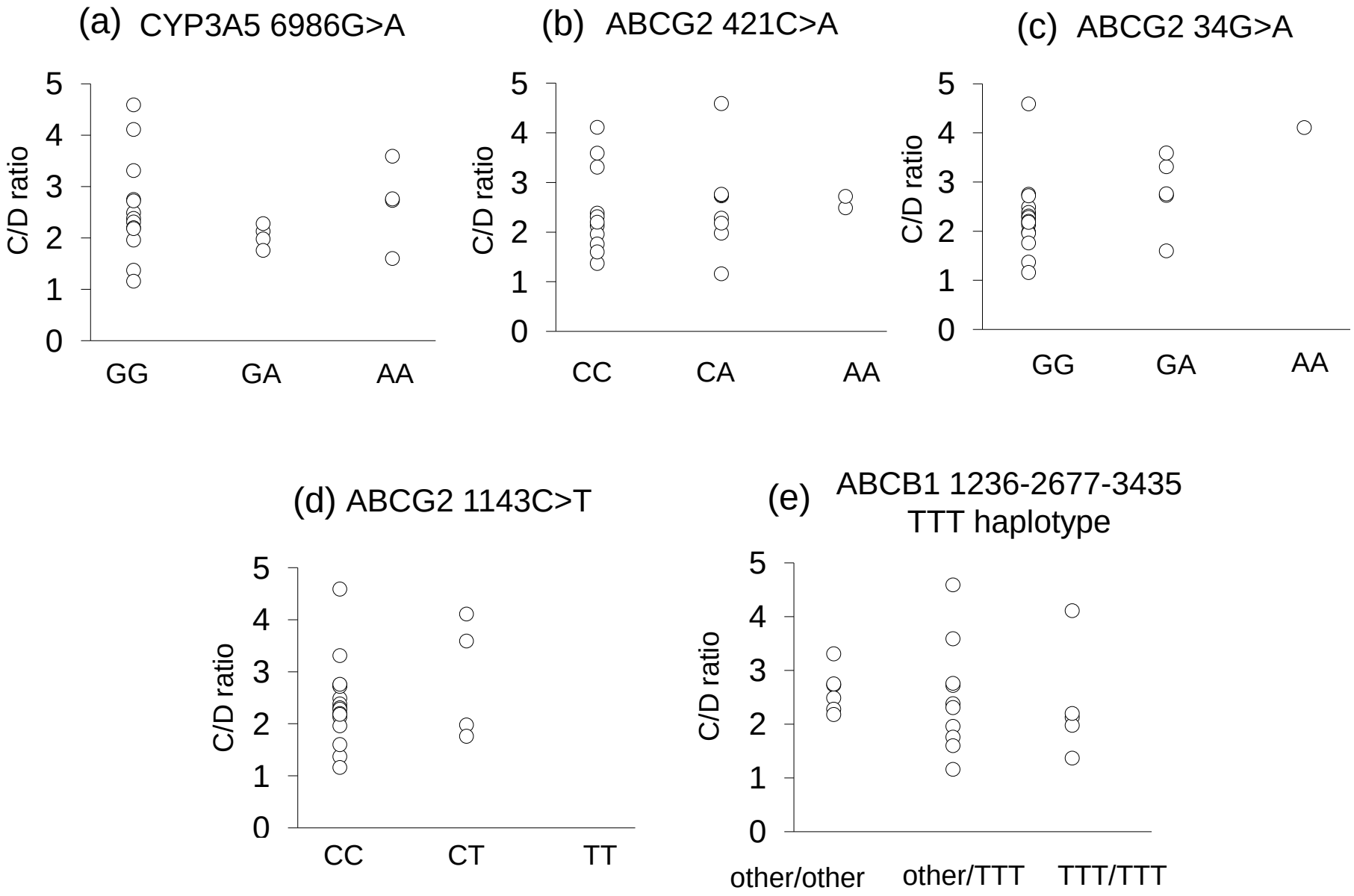

(a)
TTF
Probability of TTF
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
1000
1200
Day after initiation of sunitinib therapy (day)
total sunitinib <100 ng/mL (n=13)
total sunitinib ≥100 ng/mL (n=8)
P=0.04
(b)
PFS
Probability of PFS
P=0.02
Day after initiation of sunitinib therapy (day)
total sunitinib <100 ng/mL (n=13)
total sunitinib ≥100 ng/mL (n=8)
(c)
OS
Probability of OS
P=0.07
Day after initiation of sunitinib therapy (day)
total sunitinib <100 ng/mL (n=13)
total sunitinib ≥100 ng/mL (n=8)

Fig. 6


(a) CYP3A5 6986G>A
C/D ratio
0
1
2
3
4
5
GG
GA
AA
(b) ABCG2 421C>A
C/D ratio
0
1
2
3
4
5
CC
CA
AA
(c) ABCG2 34G>A
C/D ratio
0
1
2
3
4
5
GG
GA
AA
(d) ABCG2 1143C>T
C/D ratio
0
1
2
3
4
5
CC
CT
TT
(e) ABCB1 1236-2677-3435
TTT haplotype
C/D ratio
0
1
2
3
4
5
other/other
other/TTT
TTT/TTT