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Fractioned Dose Regimen of Sunitinib for Patients with Gastrointestinal Stromal Tumor: A Pharmacokinetic and Treatment Efficacy Study[1]

Yen-Yang Chen*,[2], Chun-Nan Yeh†,[2], Chi-Tung Cheng†, Chao-En Wu‡, Kun-Chun Chiang§, Tsung-Wen Chen†, Chih-Chi Wang¶, Jen-Shi Chen‡ and Ta-Sen Yeh*

*Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Kaohsiung, Taiwan; †GIST Team, Department of Surgery, Chang Gung Memorial Hospital, Linko, Chang Gung University, Taoyuan, Taiwan; ‡Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital–Linko Medical Center, Taoyuan, Taiwan; §Department of Surgery, Chang Gung Memorial Hospital–Keelung, Taiwan; ¶Department of Surgery, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Kaohsiung, Taiwan

Abstract

AIM: Sunitinib has shown benefit in patients with imatinib (IM)–resistant gastrointestinal stromal tumor (GIST). However, its advantages are somewhat diminished because of associated toxicities. Herein, we clarify the efficacy and safety of fractioned dose regimen of sunitinib by a pharmacokinetic and efficacy study. *MATERIALS AND METHODS:* Between 2001 and March 2013, a total of 214 patients with metastatic GIST was treated at Chang Gung Memorial Hospital. Among them, 55 (11.6%) patients who received sunitinib were investigated. One group of patients was administered with standard dose of once-daily sunitinib (standard dose group) and the other group was administered with standard total daily dose of sunitinib in fractioned doses (fractioned dose group). *RESULTS:* Thirty-two male and 23 female patients with a median age of 55 years received sunitinib. The median duration of sunitinib administration was 9.2 months. The clinical benefit was 65.2%. The mean peak blood level of sunitinib in patients with fractioned doses was significantly lower than that in those with once-daily dose (83.4 *vs* 50.1 ng/ml, $P = .01$). The rates of adverse effects of hand-foot syndrome, mucositis, and yellow skin were significantly decreased by fractioned doses of sunitinib. However, the progression-free and overall survival did not differ between patients with different treatment regimens. *CONCLUSION:* The fractioned dose regimen of sunitinib appears to be a safe and effective treatment for patients with IM-resistant/intolerant GISTs. Significantly decreased toxicity of this regimen could be explained by significantly lower peak sunitinib blood level. However, the treatment efficacy is not reduced by this regimen.

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Address all correspondence to: Chun-Nan Yeh, MD, Department of Surgery, Chang Gung Memorial Hospital and University, 5, Fu-Hsing Street, Kwei-Shan, Taoyuan, Taiwan. E-mail: chen.y9964@gmail.com

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[2] These authors contributed equally to this paper.

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Introduction

Gastrointestinal stromal tumors (GISTs) primarily arise from mesenchymal tissue in the gastrointestinal (GI) tract and abdomen. Although GISTs are rare, representing only an estimated 0.1% to 3% of all GI tract tumors [1], they account for the most common mesenchymal malignancy of the GI tract [2]. GISTs appear to be related to the interstitial cells of Cajal [3] and express the cell surface transmembrane receptor KIT, which has tyrosine kinase activity. Gain-of-function mutations of KIT are frequent in GISTs and result in constitutive activation of KIT signaling and lead to uncontrolled cell proliferation and resistance to apoptosis [4,5]. The KIT tyrosine kinase inhibitor imatinib (IM) mesylate has shown a promising clinical result for patients with advanced GIST [6], and several trials have shown a promising effect of this targeted therapy [6,7]. Our previous study showed that IM mesylate significantly affected survival in patients with GIST [8–10]. However, progression of GIST eventually develops and emerges as a challenge.

Sunitinib is a multitargeted tyrosine kinase inhibitor that predominantly targets vascular endothelial growth factor receptors and is used for treatment of metastatic renal cell carcinoma and GIST [11]. In addition to vascular endothelial growth factor receptors, sunitinib inhibits other receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFRs), KIT, Fms-like tyrosine kinase-3, colony-stimulating factor 1, and RET, which are involved in a great variety of malignancies [12]. In GIST, sunitinib is administered as a second-line targeted therapy, offering a new treatment option for patients who are refractory to IM. Although continuous once-daily dosing of sunitinib appears to be a safe and effective dosing regimen for patients with IM-resistant GIST, several adverse events (AEs), such as diarrhea, cutaneous toxicity, hypertension, myelosuppression, and thyroid dysfunction, have been reported [12]. These drug-related toxicities may reduce the treatment duration and patient compliance and therefore diminish treatment advantages of sunitinib. In this study, we investigated the efficacy, safety, and pharmacokinetics (PK) of administering the total daily dose of sunitinib in fractioned doses when treating GIST patients with IM intolerance or failure. The goal was to treat GIST patients with a regimen that has similar efficacy and a better safety profile.

Methods

Patient Population

Between 2001 and March 2013, a total of 214 patients who had histologically confirmed, recurrent, or metastatic GIST that expressed CD117 or CD34 was treated at the Department of Medical Oncology and Surgery in Chang Gung Memorial Hospital in Taiwan. Failure of prior IM therapy, demonstrated by disease progression (based on Response Evaluation Criteria in Solid Tumors) [13] or discontinuation of IM due to toxicity, was one of the inclusion criteria in this study. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate cardiac, hepatic, renal, coagulation, and hematologic functions. Key exclusion criteria included lack of recovery from the acute toxic effects of previous anticancer therapy or IM treatment, discontinuation of IM therapy within 2 weeks or of any other approved/investigational drugs for GIST within 4 weeks before starting sunitinib treatment, clinically significant cardiovascular events or diseases in the previous 12 months, diabetes mellitus with clinical evidences of peripheral vascular disease or diabetic ulcers, or a diagnosis of any second malignancy within the previous 5 years. Patients could have previously received chemotherapeutic regimens (the last chemotherapy treatment must have been at least 4 weeks before study entry) and undergone radiotherapy, or surgery, or both. The study was approved by the local Institutional Review Board of Chang Gung Memorial Hospital (101-0274C), and a written informed consent for drug administration and the analysis of tumor-associated genetic alteration was obtained independently from each patient.

Study Design and Evaluation of Efficacy and Safety

A retrospective study was conducted to evaluate the effects of sunitinib in inducing objective responses in Taiwanese GIST patients. Patients received 50 mg interruptedly (4 weeks on and 2 weeks off) or 37.5 mg continuously of sunitinib in 12.5-mg capsules taken daily through mouth with food. We classified them into two groups as follows: one group of patients was administered with the above regimens once daily (standard dose group, i.e., four capsules (12.5 mg per capsule) per day, 4 weeks on and 2 weeks off, or three capsules continuously), and the other group of patients was administered with the above regimens in fractioned doses (fractioned dose group, i.e., one capsule (12.5 mg per capsule) four times per day, 4 weeks on and 2 weeks off, or one capsule three times a day continuously without rest).

The patients received regular physical examinations and evaluations of performance status, body weight, complete blood counts, and serum chemistries. The administration of each dose and any AEs were recorded for each patient. Standard computed tomography was performed on each patient every 3 months in the first 3 years and every 6 months for the following 2 years to assess patients' responses.

Measurement of efficacy was based on objective tumor assessments using Response Evaluation Criteria in Solid Tumors with a minor modification to allow use of standard radiographic protocols for spiral computed tomography. Time to response was defined as the interval from the start of sunitinib treatment to the date of achieving an objective response (complete response or partial response). Time to progression was defined as the interval from the start of sunitinib treatment to the date of reaching disease progression. Progression-free survival (PFS) was defined as the duration of time between sunitinib initiation and tumor progression or death from any causes. Overall survival (OS) was defined as survival after administration of sunitinib, and death was the endpoint of the study. Response rate, PFS, OS, time to response, duration of response, and time to progression were recorded. Safety and tolerability were assessed by analysis of AEs, physical examinations, vital signs, Eastern Cooperative Oncology Group performance status, and abnormal laboratory values (for example, complete blood count with differential, serum electrolyte measurements, and electrocardiogram). Cardiac function was assessed at screening, at day 28 of all treatment cycles, and at the end of treatment with a 12-lead electrocardiogram and multigated acquisition scans. Toxic effects were recorded in accordance with the National Cancer Institute Common Toxicity Criteria [14].

PK Analysis of Sunitinib

Blood samples were collected from selected patients in the study for PK analysis of sunitinib. The blood samples were collected 5 to 6 hours after drug administration to measure the peak levels of sunitinib. Each 8-ml blood sample was collected into heparinized polypropylene tubes, centrifuged at 1000*g* for 10 minutes for plasma

separation, and stored at below −20 °C until analysis. Plasma concentrations of sunitinib and CGP74588 were determined by using a validated liquid chromatography–tandem mass spectrometry assay. The lower limit of quantification was 4 ng/ml for both sunitinib and CGP74588.

Analysis of KIT and PDGFRA Mutations

Sections were prepared from formalin-fixed, paraffin-embedded, pretreated specimens that were trimmed to enrich tumor cells. Polymerase chain reaction amplification of genomic DNA for KIT and PDGFRA was performed and amplification was analyzed for mutations as previously described [15].

Statistical Analysis

All data are presented as percentages of patients or means with SDs. Pearson Chi-square test and Fisher exact test were used for nominal variables. Survival rates were calculated and plotted with the Kaplan-Meier method and compared between groups with a log-rank test. All statistical analyses were performed using the SPSS computer software package (version 10.0; SPSS, Chicago, IL). A P value of less than .05 was considered to be statistically significant.

Results

Clinical Features

Table 1 summarizes the demographic features of 55 GIST patients who received sunitinib during the study period. There were 32 male and 23 female patients with a median age of 55 years old (ranging from 15 to 88 years). The stomach was the most common site for GISTs treated with sunitinib (23 patients; 35%), followed by the jejunum and ileum (15 patients; 22%), duodenum (4 patients), and the colorectum (6 patients; 13%; Table 1).

Table 1. Demographic and Genetic Data of 55 GIST Patients with IM Failure or Intolerance Treated with Sunitinib

	n (%; *N* = 55)
Age (median/range, years)	55.0/15-88
Gender (M/F)	32/23
Location	
Stomach	23 (26.6)
Duodenum	4 (12.5)
Jejunum and ileum	15 (23.4)
Ileum	5 (14.1)
Others	7 (18.8)
Colon-Rectum	6 (4.7)
Tumor recurrence	
Liver	22
Loco-regional	19
Both	14
Genetic spectrum	39 (84.4)
Exon 11	24
Deletion mutation	
Deletion and insertion mutation	
Missense mutation	
Exon 9 (insertion mutation)	8
Exon 13	1
No mutation (wild type)	5
PDGFRA (exon 18)	1
Median duration of sunitinib use (months)	9.24

M, male; F, female; PDGFRA, platelet-derived growth factor α.

Table 2. PK between Metastatic GIST Patients Receiving Divided and Non-Divided Doses of Sunitinib

	Divided Group (24 Samples per 12 Patients)	Non-Divided Group (24 Samples per 12 Patients)	*P* Value
PK (ng/ml)			.01
Mean ± SD	50.1 ± 12.4	83.4 ± 36.8	
Range	19.7-64.8	44.3-168.3	

Mann-Whitney *U* test.

PK Analysis of Sunitinib

The peak plasma level of sunitinib of patients in the standard dose group was significantly higher than that of patients in the fractioned dose group (mean, 83.4 *vs* 50.1 ng/ml; P = .01; Table 2).

Adverse Events

Table 3 listed hematologic and non-hematologic AEs between two groups of patients. Generally, fractioned doses of sunitinib caused similar or relatively lower rates of AEs when compared with standard doses of sunitinib.

In addition, the patients who received fractioned doses of sunitinib developed significant lower rates of yellow skin discoloration, grade 3/4 hand-foot skin reaction (HFSR), and mucositis when compared with those who received standard doses of sunitinib. In the standard dose group, the most common treatment-related non-hematologic AEs were HFSR (65%), hypertension (54%), diarrhea (42%), and mucositis (38%). The most frequent treatment-related grade 3/4 non-hematologic AEs among these patients were HFSR (35%), hypertension (8%), and anorexia (4%). However, in the fractioned dose group, the most common treatment-related non-hematologic AEs were hypertension (59%), diarrhea (52%), HFSR (45%), and GI bleeding (21%). The most frequent treatment-related grade 3/4 non-

Table 3. AEs between Divided and Non-Divided Doses of Sunitinib for Metastatic GIST Patients

	Divided Dose (*n* = 29; %)		Non-Divided Dose (*n* = 26; %)		*P* Value	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Hematologic						
Anemia	17 (58.62)	9 (31.03)	16 (61.54)	5 (19.23)	.823	.315
Leukopenia	17 (58.62)	2 (6.90)	15 (57.69)	3 (11.54)	1.0	.659
Neutropenia	14 (48.28)	3 (10.34)	12 (46.15)	3 (11.54)	.888	1.0
Thrombocytopenia	16 (55.17)	3 (10.34)	15 (57.69)	1 (3.85)	.841	.613
Non-hematologic						
Anorexia	4 (13.79)	2 (6.90)	6 (23.08)	1 (3.85)	.490	1.0
Nausea	2 (6.90)	0 (0)	2 (7.69)	0 (0)	1.0	1.0
Vomiting	2 (6.90)	0 (0)	3 (11.54)	1 (3.85)	.659	.473
Diarrhea	15 (51.72)	1 (3.45)	11 (42.31)	0 (0)	.484	1.0
Constipation	0 (0)	0 (0)	2 (7.69)	0 (0)	.219	1.0
Alopecia	2 (6.90)	0 (0)	1 (3.85)	0 (0)	1.0	1.0
Yellow skin	2 (6.90)	0 (0)	9 (34.62)	0 (0)	**.017**	1.0
HFSR	13 (44.83)	3 (10.34)	17 (65.38)	9 (34.62)	.177	**.030**
Mucositis	1 (3.45)	0 (0)	10 (38.46)	0 (0)	**.002**	1.0
Fever	1 (3.45)	0 (0)	2 (7.69)	1 (3.85)	.589	.473
Fatigue	4 (13.79)	1 (3.45)	9 (34.62)	0 (0)	.111	1.0
Insomnia	0 (0)	0 (0)	2 (7.69)	0 (0)	.219	1.0
AST/ALT	3 (10.34)	1 (3.45)	0 (0)	0 (0)	.238	1.0
HTN	17 (58.62)	1 (3.45)	14 (53.85)	2 (7.69)	.718	.598
GI bleeding	6 (20.69)	5 (17.24)	1 (3.85)	1 (3.85)	.105	.197
Jaundice	0 (0)	0 (0)	0 (0)	0 (0)	1.0	1.0
Creatinine	2 (6.90)	0 (0)	4 (15.38)	0 (0)	.406	1.0
Thyroid function	1 (3.45)	0 (0)	1 (3.85)	0 (0)	1.0	1.0

AST/ALT, aspartate aminotransferase/alanine aminotransferase; HTN, hypertension.

hematologic AEs among these patients were GI bleeding (17%), HFSR (10%), anorexia (7%), and diarrhea (3%). Not only the distribution patterns of AEs were slightly different between the two groups, but the occurrences were also a little different.

The hematologic abnormalities among patients who received sunitinib in standard doses and in fractioned doses included reduced levels of hemoglobin (62% and 59%), leukocytes (58% and 59%), and platelets (58% and 55%), respectively.

Spectrum of Mutations

Tumor specimens suitable for genetic analysis were available from 39 (70.9%) of the 55 GIST patients with IM failure or intolerance. Overall, 32 (85.7%) of the 39 examined GISTs had activated mutations of KIT exons 9 and 11. Eight of 39 (20.5%) GISTs had exon 9 mutation, 24 (61.5%) had exon 11 mutation, and 5 (12.8%) had no mutation of KIT. One PDGFRA exon 18 mutation was found. One patient had concurrent deletion mutation in exon 11 and missense mutation in exon 13; however, the exon 13 mutation was followed by the deletion mutation in exon 11. This patient developed acquired resistance and expired from disease progression. All eight GISTs that had KIT exon 9 mutation displayed in-frame duplication of nucleotides, resulting in insertion of alanine (A) and tyrosine (Y) at codons 502 and 503. The KIT exon 11 mutations in the 24 GIST patients included insertion and deletion mutations, deletion mutations, and missense mutations.

Treatment Outcomes

The median follow-up time after initiation of sunitinib was 9.2 months. Overall, 1 patient (1.8%) had a complete response, 20 (36.4%) had partial responses, 13 had stable diseases (23.6 %), and 21 had progressive diseases (38.2%). A clinical benefit was observed in 61.8% of GIST patients. During the median 9.2-month follow-up after sunitinib use, the median PFS and OS of these 55 GIST patients were 9.5 and 22.6 months, respectively (Figures 1 and 2). The median PFS for the 29 patients who were in the fractioned dose group

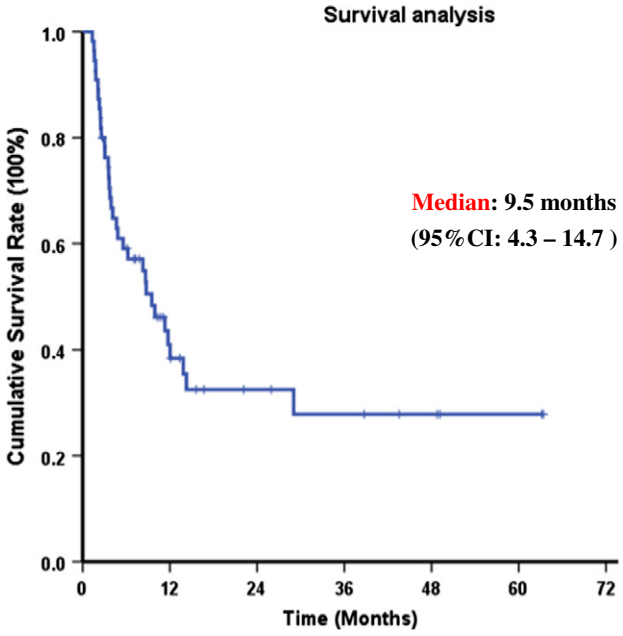


Figure 1. PFS of all patients after initiation of sunitinib.

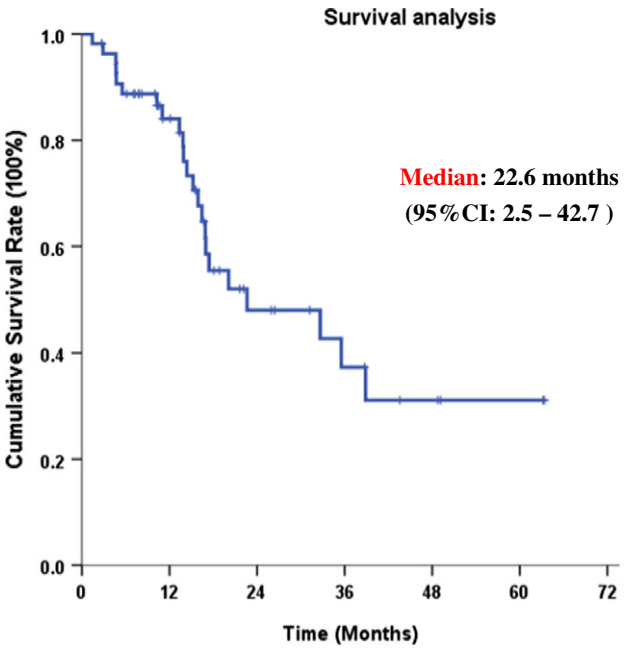
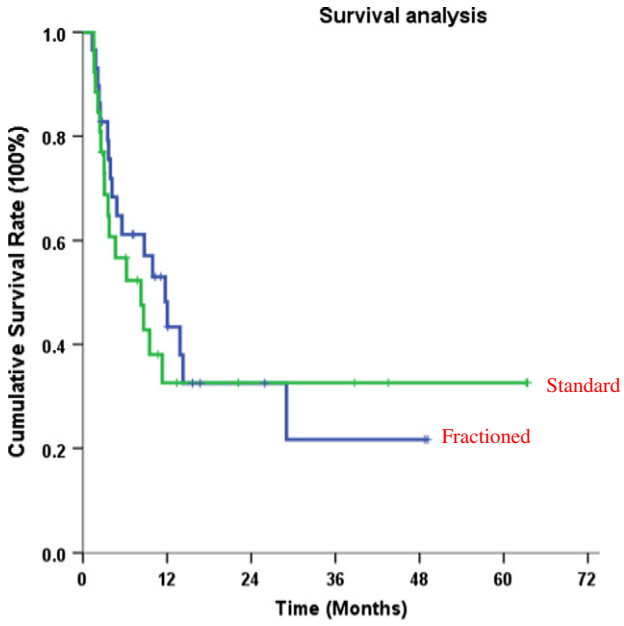


Figure 2. OS of all patients after initiation of sunitinib.

was 11.7 months, which is similar to the median PFS of 8.3 months for the 26 patients in the standard dose group (P = .664; Figure 3). At the same time, the median OS was 20.1 months for the 29 patients



	Fractioned	Standard
N	29	26
Median	11.7	8.3
95%CI	7.1-16.4	2.5-14.0
Log-rank test		p=0.664

Figure 3. PFS of two groups after initiation of sunitinib.

who were in the fractioned dose group and 38.9 months for the 26 patients who were in the standard dose group, which also did not reach statistical significance (P = .439; Figure 4).

Discussion

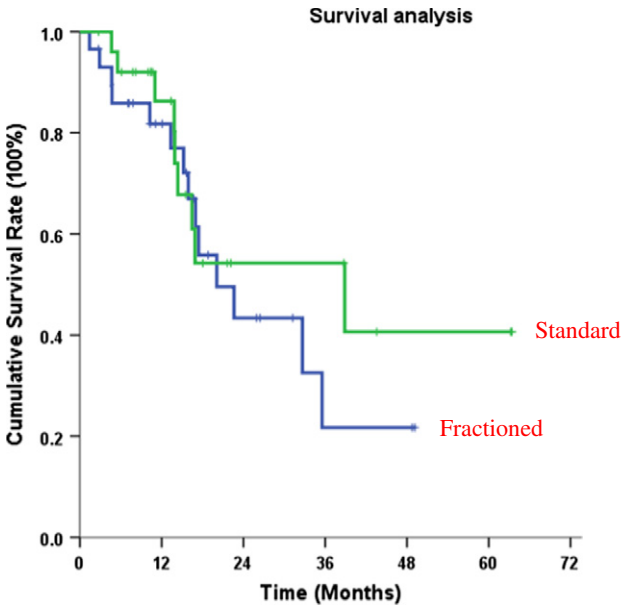
This study provided a novel alternative dosing schedule of sunitinib to treat IM-resistant/intolerant GIST patients. We demonstrated a clinical response rate of 38.2% for all patients treated with sunitinib and a median duration of response of 9.5 months. This is similar to the response rate and slightly higher duration of response to the results in the previous phase III trial of sunitinib for treatment of advanced GIST after IM failure [16], which reported a response rate of 30% and a response duration of 27.3 weeks. The median duration of response of 9.5 months is also slightly longer than that seen in another sunitinib treatment experience, which was a global open-label study that provided sunitinib access to patients with advanced IM resistant/intolerant GIST. That study reported 8.3 months of PFS in all intention-to-treat population of 1124 patients [17].

The standard once-daily sunitinib regimen resulted in median PFS of 8.3 months and median OS of 38.9 months. However, the fractioned dose regimen of sunitinib led to median PFS of 11.7 months and median OS of 20.1 months. Although no statistically significant differences were found, the fractioned dose regimen achieved even longer PFS for these GIST patients who were resistant or intolerant to IM. The results suggested that sunitinib treatment either as standard regimen or as fractioned dose regimen have similar efficacy. The fractioned doses of sunitinib did not compromise the clinical effects for GIST patients.

The most important reason for using fractioned doses of sunitinib was the hope of decreasing occurrence of AEs. The study demonstrated that fractioned doses of sunitinib caused similar or relatively lower rates of AEs when compared with standard doses of sunitinib. Sunitinib in fractioned dose regimen exhibited an improved safety profile when compared with the standard dose regimen, especially in all grades of mucositis and yellow skin discoloration and grade 3/4 of HFSR. These improvements of AEs grading in divided dose regimen may help GIST patients to continue sunitinib treatment with or without dosing interruption and/or dose reduction.

Our previous study demonstrated that sunitinib treatment made the skin more susceptible to physical damage and such injury was associated with increased expression of FasL in keratinocytes [18]. We observed higher plasma levels of sunitinib in patients who developed high-grade HFSR than in patients without HFSR. The induction of keratinocyte FasL/Fas in our animal experiments and HFSR patients may result from the combined effects of sunitinib toxicity and physical pressures. Therefore, the lower peak plasma levels of sunitinib resulted from the fractioned doses of sunitinib may partly explain the lower incidence of grade 3/4 HFSR and other AEs [18].

In conclusion, fractioned dose regimen of sunitinib appears to be a safe and effective treatment for patients with IM-resistant/intolerant GISTs. Significantly decreased toxicity of this regimen could be explained by significantly lower peak sunitinib blood level. The treatment efficacy is not reduced by this regimen; however, a more comprehensive study is still warranted due to limited case numbers.



	Fractioned	Standard
N	29	26
Median	20.1	38.9
95%CI	10.8-29.4	6.5-71.2
Log-rank test		p=0.439

Figure 4. OS of two groups after initiation of sunitinib.

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