JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2023, 1–8
https://doi.org/10.1093/jjco/hyac202
Original Article

OXFORD

Original Article

Sunitinib therapy for imatinib-resistant and/or intolerant gastrointestinal stromal tumors: comparison of safety and efficacy between standard and reduced dosage regimens

Kenta Sasaki[1,2], Tatsuo Kanda[3,*], Yoshifumi Matsumoto[1], Takashi Ishikawa[4], Seiichi Hirota[5] and Yasuo Saijo[1]

[1]Department of Medical Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Department of Internal Medicine, Sanjo General Hospital, Sanjo, Japan, [3]Department of Surgery, Sanjo General Hospital, Sanjo, Japan, [4]Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan and [5]Department of Surgical Pathology, Hyogo Medical University School of Medicine, Nishinomiya, Japan

*For reprints and all correspondence: Tatsuo Kanda, M.D., Ph.D., Department of Surgery, Sanjo General Hospital, Tsukanome, Sanjo, Niigata 955-0055, Japan. E-mail: kandat@herb.ocn.ne.jp

Received 28 June 2022; Editorial Decision 3 November 2022; Accepted 11 December 2022

Abstract

Background: Sunitinib therapy for patients with imatinib-resistant and/or intolerant gastrointestinal stromal tumors (GISTs) often causes severe adverse events (AEs) that lead to treatment discontinuation.

Methods: We retrospectively reviewed the clinical records of imatinib-resistant and/or intolerant GIST patients who underwent sunitinib therapy in our institutions between 2007 and 2020. Forty-one patients were enrolled and divided into two groups on the basis of the starting dosage: the standard dosage group (50 mg/day, 21 patients) and the reduced dosage group (37.5 mg/day, 20 patients). Tolerability, safety and clinical efficacy of the two groups were compared.

Results: Three patients (14%) in the standard dosage group and another three (15%) in the reduced dosage group ($P = 1.000$) discontinued sunitinib therapy because of AEs. The incidences of grade 3 or more severe treatment-related AEs were 90 and 75%, respectively ($P = 0.238$). Two possible treatment-related deaths were noted in the standard dosage group. Clinical efficacy was comparable between the two groups: median time to treatment failure and overall survival were 4.5 months [interquartile range (IQR), 3.6–9.0] and 13.7 months (IQR, 7.5–22.9) in the standard dosage group and 4.6 months (IQR, 2.7–17.0) and 13.4 months (IQR, 9.3–36.8) in the reduced dosage group, respectively.

Conclusions: The reduced dosage of 37.5 mg sunitinib tended to decrease toxicity and the incidences of severe AEs and treatment-related deaths. This reduced dosage regimen showed equivalent clinical efficacy including patient survival. The reduced dosage of 37.5 mg sunitinib can be adopted as an alternative therapy for patients with imatinib-resistant and/or intolerant GISTs.

Key words: dosage, GIST, sunitinib

Introduction

Sunitinib malate, an oral multikinase inhibitor, is recommended for the second-line treatment of unresectable and/or metastatic gastrointestinal stromal tumors (GISTs) after imatinib failure (1–3). A randomized clinical trial has demonstrated that sunitinib therapy improved time to progression of imatinib-failure GIST patients from 6.4 to 27.3 weeks with acceptable tolerability (4), confirming the efficacy and safety of sunitinib therapy for GISTs. Unfortunately, sunitinib therapy is still not widely adopted in clinical practice mainly because real-world clinical data are limited (5,6).

Sunitinib malate is inherently designed as a multikinase inhibitor targeting KIT, platelet-derived growth factor receptors, and all isoforms of vascular endothelial growth factor receptors (VEGFRs). Because of this, molecularly targeted therapy with this drug tends to give rise to a variety of adverse events (AEs) including hematological toxicities, gastrointestinal toxicities, hand-foot skin reaction, hypertension and hypothyroidism. These drawbacks have hindered the adoption of sunitinib therapy for GISTs in clinical practice. A post-marketing survey conducted in 2012 revealed that 16% of patients who underwent sunitinib therapy for GISTs discontinued the treatment within the first six weeks in Japan, and AEs accounted for 60% of the causes of early discontinuation (7). The low feasibility of sunitinib therapy in clinical practice remains an unresolved issue in Japan.

The dosage for sunitinib therapy is set at 50 mg/day regardless of age, sex, weight or stature on the basis of the results of a pharmacokinetic study and clinical trials (4,8). There is concern whether the same dosage as that for Caucasians should be adopted for Asians who generally have a smaller stature, although several studies conducted in Asian countries (9–11) have shown comparable results to the global phase III study.

We started sunitinib therapy as a second-line treatment for patients with imatinib-resistant and/or intolerant GISTs in 2007. Over the years, we have encountered a number of patients who had to interrupt sunitinib therapy in the early phase. We are well aware of the need to improve the treatment particularly in terms of tolerability and to make it suitable for clinical practice. A Europe and US cooperative research group has reported that the continuous dosing regimen of 37.5 mg daily may be an alternative to standard sunitinib therapy in terms of both efficacy and safety (12). That study aimed to explore efficacy improvement by reducing or eliminating treatment-off time and to provide a rationale for sunitinib dosage reduction in GIST treatment after imatinib failure. In 2011, we changed our dosage to 37.5 mg/day, aiming to improve tolerability particularly in the early phase of sunitinib therapy.

We herein report the clinical outcomes of GIST patients who underwent this treatment in our institutions. To gain a better understanding of the practical benefits, we also retrospectively compare the outcomes with those of the standard dosage regimen with regard to safety and efficacy including patient survival.

Patients and methods

Patient selection

We reviewed the hospital registry of patients who underwent sunitinib therapy for imatinib-resistant and/or intolerant GISTs in Niigata University Medical and Dental Hospital and its affiliated hospital, Sanjo General Hospital, from July 2007 to November 2020. Forty-one unresectable and metastatic GIST patients were identified, and their clinical data were retrospectively collected from the medical records of the hospitals. The diagnosis of GIST was confirmed on the basis of pathology including immunohistochemical analysis for KIT expression in all the 41 patients. The enrolled patients were classified into two groups on the basis of the starting dosage for sunitinib therapy, namely, 50 mg/day (standard dosage group) and 37.5 mg/day (reduced dosage group) and the clinical outcomes, namely, tolerability, safety and efficacy, of sunitinib therapy were compared.

Dosing of sunitinib therapy

We initiated sunitinib therapy for imatinib-resistant and/or intolerant GIST patients with the standard dosage regimen (4), in which sunitinib was given orally at 50 mg/day in six-week cycles with four weeks on and two weeks off-treatment in 2007. To facilitate smooth induction of the treatment, we adopted a modified regimen in which the starting dosage was reduced to 37.5 mg/day regardless of age, sex, weight or stature in 2011. In the modified regimen, the patients were allowed to continue the therapy after four weeks without off-treatment if AEs were mild.

Dosing reduction or interruption was done according to the guidelines for sunitinib therapy although the attending physician made the final decision on the basis of the patient's condition. Sunitinib therapy was continued until the disease progressed, unacceptable AEs occurred or the patient refused to continue.

Tolerability and safety

To evaluate the tolerability of the two dosage regimens for sunitinib therapy, we selected AE-associated discontinuation, early discontinuation within the first 28 days regardless of cause and dose intensity in the early phase as the indices. Dose intensity in the early phase was calculated by taking the sum of the actual doses during the first 12 weeks, equivalent to the period of two cycles of the standard dosage regimen.

We selected the overall incidences of treatment-related AEs (TAEs) and the incidences of grade 3 (G3) or more severe TAEs as the indices of safety. Safety data were retrospectively collected from reviews of medical records and laboratory data of the hospitals. Each AE was evaluated as treatment-related or not and graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 5.0 (13).

Evaluation of clinical efficacy

We analyzed objective response, time to treatment failure (TTF) and overall survival (OS) to evaluate the clinical efficacy of the treatments. Patients were followed on an outpatient basis, and tumor status was regularly evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (14). The median interval of CT or MRI was 2.3 months (interquartile range [IQR], 1.4–4.0).

Statistical analysis and ethics

Differences between the two groups were assessed using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. TTF was defined as the time from the initiation of sunitinib therapy to disease progression or sunitinib discontinuation, and OS was defined as the time from the initiation of sunitinib therapy to death from any cause.

Survival curves were generated with the Kaplan–Meier method and compared by the log-rank test. A P value of <0.05 was considered statistically significant.

This study was performed in accordance with the Helsinki Declaration (1964, amended in 2000) of the World Medical Association, and was approved by the Ethics Review Committee of each institution (no. 2019–0265 and no. R3–21). Consent to participate was sought in accordance with the opt-out method of Niigata University Medical and Dental Hospital and Sanjo General Hospital.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The standard dosage group (50 mg/day) included 21 patients and the reduced dosage group (37.5 mg/day), 20 patients. Except the four patients in the reduced dosage group, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores for the enrolled patients were 0 or 1. The most common primary site in both groups was the jejunum and the ileum, followed by the stomach. The most common metastatic site in both groups was the peritoneum, followed by the liver. The standard dosage group included two imatinib-intolerant patients and the reduced dosage group, one. The standard and reduced dosage groups had similar clinical and pathological features. On the other hand, the year sunitinib therapy was started differed between the two groups because we switched the treatment schedule from the standard dosage regimen to the reduced one in 2011. In addition, age and kinase mutation showed statistically significant difference between the two groups.

Tolerability and sunitinib dose intensity

The median cumulative dose of sunitinib during the first 12 weeks was 2200 mg (IQR, 2050–2700) (78.6% of 2800 mg planned dose) in the standard dosage group and 1556 mg (IQR, 1378–1903) (74.1% of 2100 mg planned dose) in the reduced dosage group: the dose of the standard dosage group was significantly higher than that of the reduced dosage group ($P < 0.0001$).

The total numbers of patients who discontinued sunitinib therapy owing to AEs were three (14%) in the standard dosage group and three (15%) in the reduced dosage group, and there was no significant difference between the two groups ($P = 1.000$). As regards early discontinuation, none of the patients in the standard dosage group discontinued sunitinib therapy in the first 28 days whereas two patients in the reduced dosage group discontinued the therapy ($P = 0.232$).

Only one patient continued sunitinib therapy for more than four weeks without off-treatment in the reduced dosage group, but this patient started the off-treatment six weeks after treatment initiation.

Treatment-related adverse events

TAEs during sunitinib therapy are summarized in Table 2. The overall incidences of TAEs were 100% in the standard dosage group and 95% in the reduced dosage group. With regard to G3 or more severe TAEs, the incidences of the two groups were not significantly different (90 vs. 75% $P = 0.238$). In addition, the TAE profiles of the two groups were similar, although the incidence of G3 or more severe thrombocytopenia was lower in the reduced dosage group (20%) than the standard dosage group (52%), with marginally significant difference ($P = 0.052$). Two patients in the standard dosage group died of possible TAEs [thrombotic microangiopathy (TMA) and cerebral infarction] whereas no patient in the reduced dosage group died of TAEs ($P = 0.488$).

One patient with treatment-related death (TRD) was a 67-year-old man who had a history of pancreaticoduodenectomy for duodenal GIST four years before. The patient started sunitinib therapy for imatinib-resistant hepatic metastases and showed partial response after the first cycle of the treatment. The dosage was reduced to 37.5 mg/day owing to repetitive G3 thrombocytopenia from the third cycle. On the 28th day of the sixth cycle, the patient was hospitalized because of severe fatigue associated with G3 thrombocytopenia (46 000/mm^3). In conjunction with the decreased thrombocyte count (16 000/mm^3), the patient rapidly developed multiorgan failure on the next day and finally expired. The diagnosis of TMA was made after the patient's death on the basis of microthrombus formation in pathology, schistocytes in blood smears, and low plasma level of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13).

The other patient with TRD was a 44-year-old man who suffered from imatinib-resistant hepatic and peritoneal metastases from mesenteric GIST. Sunitinib therapy was continued with the standard dosage although the patient had started to use an angiotensin II receptor blocker for hypertension from the 13th day of the treatment. Four days after completion of the third cycle of sunitinib therapy, the patient suddenly presented with hemiplegia. MRI revealed an infarct of the left internal capsule, and the diagnosis of TRD was made because he had no other significant risk of cerebrovascular diseases than sunitinib-induced hypertension.

Clinical efficacy and survival

Tumor responses are shown in Table 3. RECIST-defined objective response rate and disease control rate (partial response plus stable disease) were 19 and 71% in the standard dosage group and 30 and 65% in the reduced dosage group, respectively.

Median TTF and OS of the standard dosage group were 4.5 months (IQR, 3.6–9.0) and 13.7 months (IQR, 7.5–22.9), respectively, and those of the reduced dosage group were 4.6 months (IQR, 2.7–17.0) and 13.4 months (IQR, 9.3–36.8), respectively (Fig. 1). Although the Kaplan–Meier estimation seemed to indicate an improvement in OS after 12 months in the reduced dosage group, the log-rank test showed no significant difference between the two groups ($P = 0.119$).

A total of 33 patients died as of the data cut-off date, namely, 19 in the standard dosage group and 14 in the reduced dosage group. The current status and the causes of death are shown in Table 4.

Treatments after sunitinib

Because regorafenib was approved for imatinib- and sunitinib-resistant GISTs in Japan in August 2013, we investigated its use following sunitinib therapy (Table 5). Regorafenib was prescribed for two patients (10%) in the standard dosage group and seven patients (35%) in the reduced dosage group, owing to the different timing of sunitinib therapy between the two groups.

To clarify the influence of regorafenib on OS, we again analyzed OS after excluding patients who underwent regorafenib therapy as the third-line treatment (Fig. 2). The median survival times were 12.7 months in the standard dosage group and 12.1 months in the reduced dosage group ($P = 0.326$), and were shorter than those shown in Fig. 1.

Table 1. Patient characteristics

	Sunitinib starting dosage		*P* value
	50 mg/day ($N = 21$)	37.5 mg/day ($N = 20$)	
Age, years median (range)	60 (44–77)	70.5 (44–85)	0.03
Gender			
Men	16 (73%)	13 (65%)	0.43
Women	5 (27%)	7 (35%)	
ECOG PS			
0	14 (67%)	10 (50%)	0.12
1	7 (33%)	6 (30%)	
2	0 (0%)	4 (20%)	
Body weight, kg median (range)	57.6 (40.0–87.2)	53.0 (40.9–66.4)	0.24
Tumor burden[a], cm median (range)	10.0 (3.5–33.0)	8.4 (1.9–21.0)	0.08
Primary tumor site			
Stomach	7 (32%)	7 (35%)	0.65
Duodenum	4 (18%)	1 (5%)	
Jejunum and ileum	9 (45%)	10 (50%)	
Others	1 (5%)	2(10%)	
(Colon, rectum, mesentery)			
Metastatic site[b]			
Peritoneum	19 (90%)	15 (75%)	0.24
Liver	9 (43%)	6 (30%)	0.39
Bone	1 (5%)	2 (10%)	0.61
Others	2 (10%)	2 (10%)	1.00
Reason for sunitinib use			
Imatinib resistance	19 (90%)	19 (95%)	1.00
Imatinib intolerance	2 (10%)	1 (5%)	
Kinase mutation[c]			
KIT exon 9	6 (29%)	1 (5%)	0.006
KIT exon 11	9 (43%)	5 (25%)	
PDGFRA	1 (5%)	0 (0%)	
Wild type	1 (5%)	0 (0%)	
Unknown	4 (19%)	14 (70%)	
Year of sunitinib start			
~2010	19 (90%)	1 (5%)	0.000
2011~	2 (10%)	19 (95%)	

[a]Tumor burden was defined as the sum of the longest diameters of all measurable tumors. [b]Total percentages add up to more than 100% because a part of patients have metastases in multiple sites. [c]Mutational analysis failed in four patients because of low DNA quality and was not conducted in 14. ECOG PS, Eastern Cooperative Oncology Group performance status; PDGFRA, platelet-derived growth factor receptor alpha.

Discussion

We have presented the clinical outcomes of sunitinib therapy for imatinib-resistant and/or intolerant GISTs in our institutions. Based on our first four-year experience of sunitinib therapy, we changed the starting dosage from 50 to 37.5 mg/day. This modification enabled us to compare the outcomes of the two regimens even though the groups were temporally unmatched.

At the time of treatment modification, we hypothesized that the reduced dosage would suppress the number of TAE and substantially increase the dose intensity, consequently leading to improved patient survival. Contrary to our expectations, the treatment modification failed to improve the efficacy and safety of sunitinib therapy because the standard dosage group and the reduced dosage group showed comparable tumor response and patient survival. With regard to OS, although the reduced dosage group seemed to show survival improvement in the late phase, subset analysis revealed that the apparent improvement was due to the use of regorafenib, a third-line tyrosine kinase inhibitor (TKI). Furthermore, the two groups also showed similar tolerability, which was assessed from the discontinuation due to AEs and the early discontinuation within the first 28 days.

Sunitinib malate is also used to treat metastatic renal cell carcinoma (RCC) because it effectively shuts down the VEGFR signaling pathway. The safety issue of sunitinib for Asian RCC patients has been thoroughly investigated. Several studies from Asian countries have reported higher incidences of dosage reduction and G3 or more severe AEs in sunitinib therapy than studies conducted in the west (15–17). Yamada *et al.* (18) addressed the relationship between dosage and safety in fifty patients who underwent sunitinib therapy for metastatic RCC. The starting dosage for sunitinib therapy was individually determined on the basis of patient age, body weight, laboratory data and PS, and consequently 22 (44%) of the patients started sunitinib therapy at a reduced dosage ($\leq$ 37.5 mg/day). Time-dependent Cox proportional hazards regression analysis revealed that the reduced starting dosage was a significant favorable factor that largely decreased the risk of unacceptable AEs leading to treatment discontinuation (hazard ratio 0.08, 95%

Table 2. Treatment-related adverse events

	Sunitinib starting dosage						*P* value
	50 mg/day ($N = 21$)			37.5 mg/day ($N = 20$)			(Grade ≥ 3)
	Any grade	Grade ≥ 3	Grade 5	Any grade	Grade ≥ 3	Grade 5	
Any AEs	21 (100%)	19 (90%)	2 (10%)	19 (95%)	15 (75%)	0	0.238
Thrombocytopenia	14 (67%)	11 (52%)	0	12 (60%)	4 (20%)	0	0.052
Neutropenia	11 (52%)	8 (38%)	0	11 (55%)	8 (40%)	0	1.000
Anemia	5 (24%)	3 (14%)	0	4 (20%)	2 (10%)	0	1.000
Hand-foot skin reaction	15 (71%)	2 (10%)	0	12 (60%)	2 (10%)	0	1.000
Hypertension	10 (48%)	3 (14%)	0	8 (40%)	2 (10%)	0	1.000
Hypothyroidism	5 (24%)	0	0	2 (10%)	0	0	NA
Appetite loss	8 (38%)	3 (14%)	0	11 (55%)	3 (15%)	0	1.000
Fatigue	4 (19%)	0	0	7 (35%)	0	0	NA
Diarrhea	7 (33%)	1 (5%)	0	4 (20%)	0	0	1.000
AST/ALT increased	2 (10%)	1 (5%)	0	4 (20%)	0	0	1.000
Fever	3 (14%)	0	0	3 (15%)	0	0	NA
Oral mucositis	5 (24%)	0	0	5 (25%)	1 (5%)	0	0.488
Dysgeusia	2 (10%)	0	0	3 (15%)	0	0	NA
Arthralgia	2 (10%)	0	0	0	0	0	NA
Creatinine increased	1 (5%)	0	0	1 (5%)	0	0	NA
Blood bilirubin increased	0	0	0	1 (5%)	0	0	NA
Electrocardiogram QT prolonged	0	0	0	1 (5%)	0	0	NA
Hyponatremia	0	0	0	1 (5%)	1 (5%)	0	0.488
Liver abscess	1 (5%)	1 (5%)	0	0	0	0	1.000
Ruptured aneurysm	1 (5%)	1 (5%)	0	0	0	0	1.000
TMA	1 (5%)	1 (5%)	1 (5%)	0	0	0	1.000
Shock	1 (5%)	1 (5%)	0	0	0	0	1.000
Cerebral infarction	1 (5%)	1 (5%)	1 (5%)	0	0	0	1.000
Nephrotic syndrome	0	0	0	1 (5%)	1 (5%)	0	0.488
Intestinal perforation	0	0	0	1 (5%)	1 (5%)	0	0.488
Hemorrhagic cystitis	0	0	0	1 (5%)	1 (5%)	0	0.488

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; TMA, thrombotic microangiopathy.

Table 3. Tumor response

	Sunitinib starting dosage		*P* value
	50 mg/day ($N = 21$)	37.5 mg/day ($N = 20$)	
Complete response	0 (0%)	0 (0%)	0.770
Partial response	4 (19%)	6 (30%)	
Stable disease	11 (52%)	7 (35%)	
Progressive disease	5 (24%)	6 (30%)	
Not evaluable	1 (5%)	1 (5%)	

confidence interval 0.03–0.21). In addition, that study disclosed that patients undergoing sunitinib therapy at ≤37.5 mg/day showed better progression-free survival (PFS) than patients receiving 50 mg/day (median PFS, 120 days *vs.* 41 days), although the difference was not statistically significant. These findings suggest that preventing the occurrence of severe AEs is crucial for sunitinib therapy and initiation with the reduced dosage is a clinically acceptable choice.

The present study revealed that nearly all patients in the reduced dosage group and the standard dosage group developed AEs. However, AEs in the reduced dosage group were generally modest. The incidences of G3 or more severe AEs were 90% in the standard dosage group and 75% in the reduced dosage group, and the incidences of G3 or more severe thrombocytopenia were 52 and 20%, respectively. Particularly noteworthy is that no TRD occurred in the reduced dosage group, although we were unable to validate this statistically.

Komatsu *et al.* (6) conducted a retrospective study of post-marketing registry data of 470 Japanese GIST patients and found that 70% of the patients suffered from G3 or more severe AEs and that women, the elderly (≥65 years), a history of radiotherapy, and renal impairment were associated with G3 or more severe AEs. In

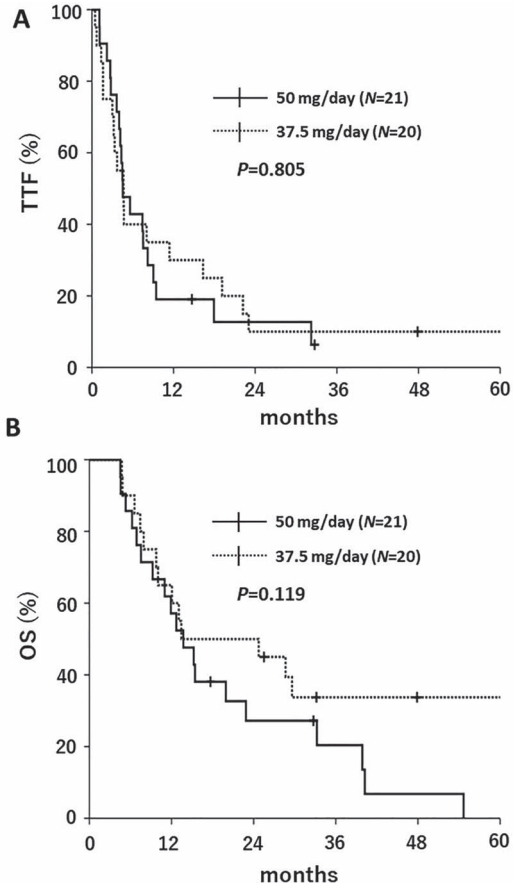

Figure 1. Kaplan–Meier curves of time to treatment failure (A) and overall survival (B) in the standard dosage group and the reduced dosage group.

Table 4. Status of patients

	Sunitinib starting dosage	
	50 mg/day ($N = 21$)	37.5 mg/day ($N = 20$)
Died, cause of death	19	14
GIST	16	14
Treatment-related death	2	0
Other disease[a]	1	0
Surviving	2	6

[a]This patient died of regorafenib-associated fulminant hepatitis.

our study, the median age of the patients in the reduced dosage group was 70.5 years, which was significantly higher than that in the standard dosage group (60.0 years). In terms of body weight, the reduced dosage group weighed less than the standard dosage group, although the difference was not statistically significant (53.0 vs. 57.6 kg). These findings indicate that the reduced dosage group is composed of patients having considerable risk of severe AEs. Sunitinib therapy for GIST is principally conducted on an outpatient basis, and this has made careful management rather difficult. Taken together with the clinical background, the low incidence of G3 or more severe AEs found in the present study is likely to be clinically significant.

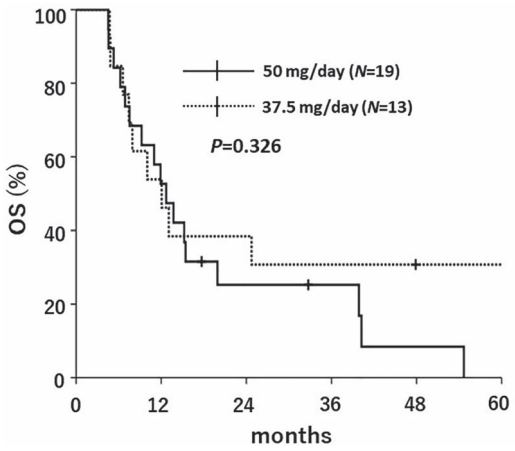

Figure 2. Kaplan–Meier curves of overall survival in the standard dosage group and the reduced dosage group excluding regorafenib-treated patients.

A fixed dosage of 50 mg/day has been adopted as the standard dosage for sunitinib therapy regardless body weight because early pharmacokinetic studies have clarified that the plasma trough levels of sunitinib and its active metabolites considerably varied in each patient and showed no significant correlation to body weight (8,9). On the other hand, it is known that sunitinib-induced toxicity leading to dose reduction is associated with plasma trough concentration (19). Several researchers have recommended therapeutic drug monitoring (TDM)-guided dose adjustment in sunitinib therapy (20–22). Individualization of dosing with TDM is a rational solution; however, it has practical challenges including cost, sampling timing and accessibility of testing. Low compliance (58%) with TDM-based intervention for sunitinib therapy was reported together with the possible clinical benefits (22), suggesting that many clinicians still prefer practice-based dosing in cancer treatment. The incorporation of TDM into clinical oncology practice is anticipated.

We have shown the clinical outcomes, namely, the safety and efficacy, of the two regimens in sunitinib therapy for GISTs. The reduced dosage regimen of 37.5 mg/day tended to decrease toxicity and G3 or more severe AEs, whereas patient survival was equivalent to that of the standard dosage regimen of 50 mg/day. These findings suggest that the reduced dosage regimen is a safer treatment than the standard dosage regimen and has the potential to decrease life-threatening AEs and TRDs. However, the results should be carefully interpreted because this study has many limitations, including a retrospective design and a small sample size. We adopted a comparative study design to analyze the clinical outcomes of the two regimens although this study was an observational and non-randomized one. Because of this, the profiles of the two patient groups were considerably different. In addition, the two patient groups of this study were temporally unmatched. We should keep in mind the possibility that the accumulated clinical experiences in treatment may have contributed to the improvement of patient management and that may lead to the decrease of life-threatening AEs and TRDs in the reduced regimen group.

In conclusion, the reduced dosage of 37.5 mg/day tended to decrease toxicity and the incidence of G3 or more severe AEs and TRDs. This modified regimen also showed equivalent tumor

Table 5. Treatment after sunitinib

	Sunitinib starting dosage		*P* value
	50 mg/day ($N = 21$)	37.5 mg/day ($N = 20$)	
Regorafenib	2 (10%)	7 (35%)	0.215
Imatinib	6 (29%)	3 (15%)	
Others[a]	4 (19%)	2 (10%)	
BSC	9 (43%)	8 (40%)	

BSC, best supportive care.
[a]Include sunitinib and investigational new tyrosine kinase inhibitors.

response and patient survival to the standard dosage regimen of 50 mg/day. Preventing the occurrence of severe AEs will contribute to the physical and mental well-being of patients and serve as a bridge to the next TKI therapy. The reduced dosage regimen of 37.5 mg/day is an alternative for standard sunitinib therapy and may be suitable for Japanese GIST patients, particularly the elderly and low body weight patients.

Acknowledgements

Part of this study was published in the 19th Annual Meeting of the Japanese Society of Medical Oncology. The authors' contributions are as follows: T.K. and Y.S. conceptualized the study. K.S., T.K., Y.M. and T.I. were the attending physicians of the enrolled patients and were responsible for data collection. S.H. contributed to diagnosis and gene analysis. K.S., T.K. and Y.S. drafted the manuscript. All authors have read and approved the final version of the manuscript.

Funding

This study was supported by research stipends from Niigata University and Sanjo General Hospital and did not receive any specific grants from public, commercial or not-for-profit sectors.

Conflict of interest statement

None declared.

References

1. Casali PG, Blay JY, Abecassis N, et al. Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2022;33:20–33.
2. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN task force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 2010;8:S-1–41.
3. Nishida T, Blay JY, Hirota S, Kitagawa Y, Kang YK. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. *Gastric Cancer* 2016;19:3–14.
4. Demetri DG, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;368:1329–38.
5. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. *Cancer* 2015;121:1405–13.
6. Komatsu Y, Ohki E, Ueno N, et al. Safety, efficacy and prognostic analyses of sunitinib in the post-marketing surveillance study of Japanese patients with gastrointestinal stromal tumor. *Jpn J Clin Oncol* 2015;45:1016–22.
7. Final results of post-marketing survey of Sutent ®. https://pfizerpro.jp/cs/sv/sutent/safety/index.html
8. 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.
9. Shirao K, Nishida T, Doi T, et al. Phase I/II study of sunitinib malate in Japanese patients with gastrointestinal stromal tumor after failure of prior treatment with imatinib mesylate. *Invest New Drugs* 2010;28:866–75.
10. Chen YY, Yeh CN, Cheng CT, et al. Sunitinib for Taiwanese patients with gastrointestinal stromal tumor after imatinib treatment failure or intolerance. *World J Gastroenterol* 2011;17:2113–9.
11. Yoon DH, Ryu MH, Ryoo BY, et al. Sunitinib as a second-line therapy for advanced GISTs after failure of imatinib: relationship between efficacy and tumor genotype in Korean patients. *Invest New Drugs* 2012;30:819–27.
12. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. *Eur J Cancer* 2009;45:1959–68.
13. National Cancer Institute. *Common terminology criteria for adverse events (CTCAE) version 5.0*. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published November 27, 2017.
14. 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.
15. Yoo C, Kim JE, Lee JL, et al. The efficacy and safety of sunitinib in korean patients with advanced renal cell carcinoma: high incidence of toxicity leads to frequent dose reduction. *Jpn J Clin Oncol* 2010;40:980–5.
16. Tomita Y, Shinohara N, Yuasa T, et al. Overall survival and updated results from a phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma. *Jpn J Clin Oncol* 2010;40:1166–72.
17. Kim HS, Hong MH, Kim K, et al. Sunitinib for Asian patients with advanced renal cell carcinoma: a comparable efficacy with different toxicity profiles. *Oncology* 2011;80:395–405.
18. Yamada Y, Ohno Y, Kato Y, et al. Optimal dose of sunitinib for long-term treatment in Japanese patients with renal cell carcinoma. *Cancer Chemother Pharmacol* 2019;84:987–92.
19. Gandhi KA, Joshi A, Mehta P, et al. Feasibility of therapeutic drug monitoring of sunitinib and its implications on response and toxicity in patients with metastatic renal cell cancer. *Cancer Chemother Pharmacol* 2022;89:751–9.
20. Lankheet NAG, Kloth JSL, Gadellaa-van Hooijdonk CGM, et al. Pharmacokinetically guided sunitinib dosing: a feasibility study in patients with advanced solid tumours. *Br J Cancer* 2014;110:2441–9.
21. Kloth JS, Binkhorst L, de Wit AS, et al. Relationship between sunitinib pharmacokinetics and administration time: preclinical and clinical evidence. *Clin Pharm* 2015;54:851–8.
22. Westerdijk K, Krens SD, van der Graaf WTA, et al. The relationship between sunitinib exposure and both efficacy and toxicity in real-world patients with renal cell carcinoma and gastrointestinal stromal tumour. *Br J Clin Pharmacol* 2021;87:326–35.