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Original Research

Sunitinib versus imatinib dose escalation after failure of imatinib standard dose in patients with advanced Gastrointestinal stromal tumors – a real-world multi-center study

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ABSTRACT

Background: Whether to escalate imatinib dosage or directly switch to sunitinib in gastrointestinal stromal tumors (GISTs) failing on standard dose 400 mg/d of imatinib is still controversial.
Methods: We evaluated progression-free survival (PFS), overall survival (OS), and time to sunitinib failure (TTSF) of patients selecting imatinib dose escalation or directly switching to sunitinib after the failure of imatinib 400 mg/d therapy from 3 tertery referring centers between January 2008 to December 2016.
Results: A total of 240 patients receiving sunitinib (37.5 mg continuous daily dose or 50 mg 4 weeks on with 2 weeks off) for at least 8 weeks were examined. After failure on imatinib 400 mg/d, 100 (49.3%) patients had dose escalation to 600 mg or 800 mg per day (IM group, imatinib group), and 103 (50.7%) directly switched to sunitinib (SU group, sunitinib group). The PFS in the SU and IM groups was 12 months and 5.0 months ($P < 0.001$), respectively. TTSF or OS in both groups was not statistically significantly different.
Conclusions: After the progression of imatinib standard-dose treatment in recurrent/metastatic GISTs, the PFS of patients directly switching to sunitinib was significantly longer compared with the PFS of patients with imatinib dose escalation. However, when the patients continued with sunitinib therapy after the failure of IM dose escalation, TTSF and OS in the IM group were similar to those in the SU group. Further exploration of the characteristics of the population benefiting from imatinib dose escalation are warranted.

Introduction

Gastrointestinal stromal tumors (GISTs) represent the most common mesenchymal tumors of the alimentary tract. They are more common in the stomach (50–60%), followed by the small intestine (25%) [1]. Most of them develop due to KIT- or PDGFRA (platelet derived growth factor receptor alpha)-activating mutations (80%). Surgery and TKI (tyrosine kinase inhibitor) therapy are the main choices of treatment. However, the long-term use of TKIs is prone to drug resistance [2,3].

Imatinib standard dose (400 mg/d) was approved as the first-line treatment for GISTs, including patients with KIT-positive unresectable and/or metastatic GISTs [4]. Besides, phase III studies (EORTC 62,005 and S0033, European organisation for Research and Treatment of Cancer) assessed the efficacy of imatinib dose escalation as an option for patients whose disease progressed on the 400 mg/day dose [5,6]. Sunitinib is an oral multi-targeted TKI with antiangiogenic and anti-tumor activities resulting from the blockade of several RTKs (receptor tyrosine kinases), including KIT, PDGFRs, and VEGFRs (vascular endothelial growth factor receptors). A randomized phase III placebo-controlled study showed that sunitinib provided significant, sustained clinical benefits in patients with imatinib-resistant or imatinib-intolerant GIST [7].

Targeted drugs of GIST have been rapidly updated. Ripretinib and avapritinib were approved by FDA for treatment options for GISTs in the

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last two years [8]. However, according to results from the phase III INTRIGUE trial (NCT03673501), ripretinib was not superior to sunitinib for PFS [9]. At present, imatinib and sunitinib recommended as first- and second-line therapies are still standard care for GISTs.

Studies showed that both imatinib dose escalation and sunitinib were effective as second-line treatment for GIST after resistance to imatinib standard dose first-line treatment [10,11]. Up to day, evidence-based better choice in second-line therapy is still unclear, being both imatinib dose escalation and sunitinib reasonable options. Aim of this retrospective study from three major GIST referral centers in southern China was performed to compare the efficacy of sunitinib and imatinib dose escalation as second-line therapy in patients with GIST previously treated with imatinib 400 mg/d.

Materials and methods

Patient selection

All procedures performed in this study involving human participants were approved, and informed consent was exempted by the ethics committee of The First Affiliated Hospital of Sun Yat-sen University. Data of patients with recurrent/metastatic GISTs treated with sunitinib from January 2008 to December 2016 in three tertiary teaching hospitals in southern China, including The First Affiliated Hospital of Sun Yat-sen University, the Sun Yat-sen University Cancer Center, and the Fujian Medical University Union Hospital, were analyzed from prospectively registered databases.

The main inclusion criteria for selecting patients for the study were as follows: adult patients (≥18 years), both sex; histologically proven metastatic GISTs previously treated with 400 mg imatinib as first-line therapy; sunitinib or imatinib escalating to 600 mg or 800 mg as second-line therapy after 400 mg imatinib treatment failed; and full documentation of treatment data, including but not confined to age, sex, ECOG (Eastern Cooperative Oncology Group), primary location, metastatic location, previous operation history, treatment duration, efficacy, safety, and so forth. The main exclusion criteria were as follows: cases without follow-up data and cases complicated with other malignant tumors. Patient selection was shown in Fig. 1.

Treatment after imatinib 400 mg/d progression

Based on the physicians' decision, patients' financial condition, and other factors, all patients progressing after the first-line treatment of imatinib 400 mg/d received either imatinib dose escalation or sunitinib as second-line treatment. Imatinib was administered orally at a dose of 600 mg or 800 mg per day (300 mg/400 mg bid). Sunitinib was administered orally 50 mg/d 4 weeks on with 2 weeks off or 37.5 mg continuous daily dose (CDD).

Some patients had a chance to receive cytoreductive surgery because of the favorable effect of second-line treatment. A few patients underwent palliative surgery considering the complications such as visceral compression, intestinal obstruction, uncontrollable gastrointestinal tract bleeding, and so on.

Detection of KIT and PDGFR gene mutations

Genetic mutations detection involved exons 9, 11, 13, and 17 of the KIT gene and exons 12 and 18 of the PDGFRA gene. Formalin-fixed, paraffin-embedded tumor tissue samples taken prior to imatinib treatment and/or after imatinib resistance were collected for primary and secondary gene mutation analyses. Genomic DNA was extracted from the tumor samples using an e.Z.N.A. FFPE (formalin-fixed, paraffin-embedded) DNA Kit (Omega Bio-Tek Inc., GA, USA).

Statistical analysis

The primary end point of this study was progression-free survival (PFS). Secondary end points were overall survival (OS), time to sunitinib failure (TTSF), and treatment safety. PFS was defined as the time from the escalation dose of imatinib or directly sunitinib to the occurrence of disease progression. TTSF was defined as the time from second-line therapy to the occurrence of disease progression of sunitinib. OS was defined as the time from second-line therapy to the occurrence of death or the end of follow-up. Response to treatment defined as the clinical

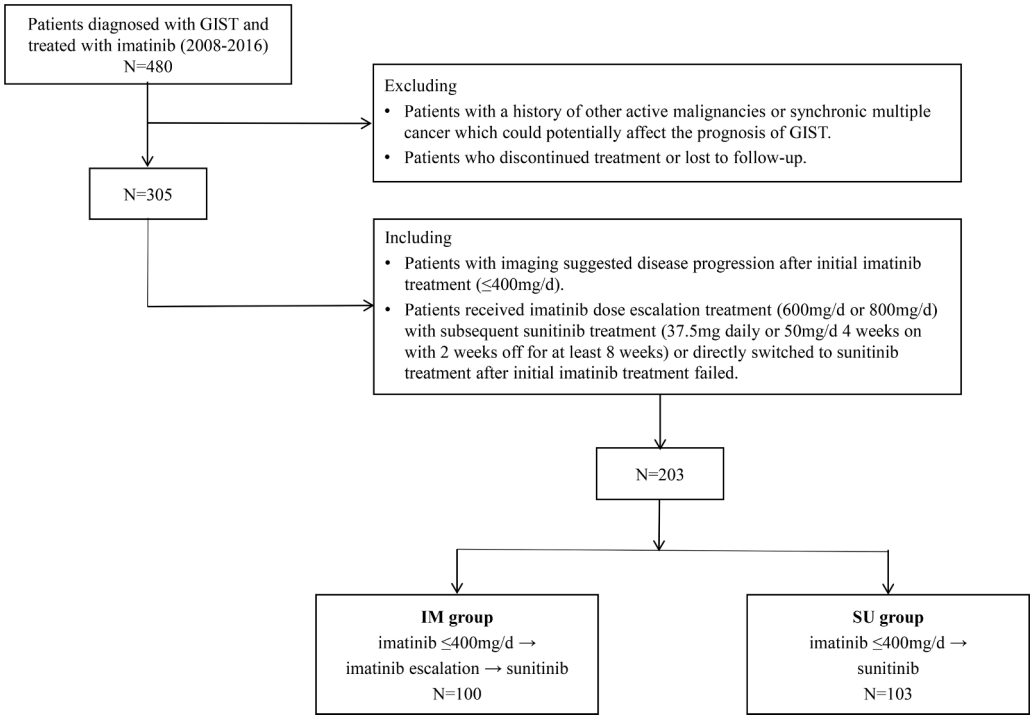

Fig. 1. Flowchart of advanced gastrointestinal stromal tumor patients recruited in the study.

benefit rate (percentage of patients who had achieved complete response, partial response, and stable disease) was evaluated according to RECIST (response evaluation criteria in solid tumors) 1.1 criteria. Toxicity was assessed by the Common Toxicity Criteria of the National Cancer Institute (CTC version 4.0).

All statistical analyses were performed using the SPSS 25.0 platform (SPSS Inc., IL, USA). PFS/TTSF and OS curves were constructed by the Kaplan–Meier method and compared using a log-rank test. Cox proportional-hazards models were used to estimate the simultaneous effects of prognostic factors on PFS so as to adjust for confounding variables. The factors with $P<0.2$ in the univariate Cox analysis or when considered clinically significant were included in the multivariate Cox model. Continuous variables were expressed as means ± standard deviation, and the mean differences between two groups were compared using the t-test. Frequency and percentage descriptions were used for categorical variables, and the chi-squared ($\chi 2$) test was used to compare the incidence of different events. If the theoretical frequency was lower than 1, Fisher's exact test was used.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. A total of 203 patients from 3 medical centers were enrolled between January 2008 and December 2016. A total of 149 patients had undergone genetic testing, including 79 patients with primary KIT exon 11 mutation, 39 with KIT exon 9 mutation, and 26 with KIT/PDGFRA wild type (WT).

Table 1
Clinical and pathological features of imatinib escalation and sunitinib groups.

Features	IM group ($n = 100$)	SU group ($n = 103$)	*P* value
Median age	52.2 (50.0–54.4)	52.0 (49.7–54.3)	0.892[a]
Sex			0.073[b]
-Male	73.0% (73/100)	61.2% (63/103)	
-Female	27.0% (27/100)	38.8% (40/103)	
Location of the primary tumor			0.420[b]
-Esophagus	2.0% (2/100)	2.9% (3/103)	
-Stomach	26.0% (26/100)	37.9% (39/103)	
-Duodenum	17.0% (17/100)	16.5% (17/103)	
-Jejunum or Ilium	39.0% (39/100)	28.2% (29/103)	
-Colon or rectum	4.0% (4/100)	1.9% (2/103)	
-EGIST	12.0% (12/100)	12.6% (13/103)	
Location of metastasis sites			0.930[b]
-None or Unknow	5.0% (5/100)	4.9% (5/103)	
-Single-organ metastasis			
Liver	28.0% (28/100)	31.1% (32/103)	
Peritoneum	44.0% (44/100)	36.9% (38/103)	
Lung	1.0% (1/100)	1.0% (1/103)	
Bone	1.0% (1/100)	1.9% (2/103)	
-Multiple-organ metastases	21.0% (21/100)	24.3% (25/103)	
Primary genotype			0.308[b]
-*KIT* exon 11 mt	42.0% (42/100)	35.9% (37/103)	
-*KIT* exon 9 mt	20.0% (20/100)	18.4% (19/103)	
-*PDGFRA* D842V mt	1.0% (1/100)	3.9% (4/103)	
-Wild type	9.0% (9/100)	16.5% (17/103)	
-Unknown	28.0% (28/100)	25.2% (26/103)	
Operation			0.012[b]
-Yes	20.0% (20/100)	7.8% (8/103)	
-No	80.0% (80/100)	92.2% (95/103)	
The best assessment of sunitinib			0.132[b]
-Not available	2.0% (2/100)	0	
-Complete response	2.0% (2/100)	0	
-Partial response	11.0% (11/100)	15.5% (16/103)	
-Stable disease	61.0% (61/100)	65.0% (67/103)	
-Progressive disease	24.0% (24/100)	19.4% (20/103)	

[a] P values were determined with the t-test.
[b] P values were determined with the chi-squared ($\chi 2$) test.

Twenty-eight patients had undergone surgery in the period from failure of imatinib first-line therapy to death or the end of follow-up. After the progression of the imatinib standard dose therapy, 100 patients (49.3%) received the imatinib dose escalation to 600 mg/d or 800 mg/d, and 103 patients (50.7%) switched to sunitinib 50 mg/d 4 weeks on and 2 weeks off or 37.5 mg/d CDD treatment. The proportion of male patients was slightly higher in the IM group, but with no statistically significant difference ($P = 0.073$). The IM group had more patients undergoing surgery during the treatment period with statistically significant differences ($P = 0.012$). Other characteristics of the two groups were balanced, with no obvious selection deviation.

Progression-free survival

The median follow-up were 74.0 months in IM group and 60.0months in SU group. The mPFS for all the patients was 8.0 months (95% CI 6.9–9.1). The mPFS in the SU group was 12.0 months [95% confidence interval (CI) 10.3–13.7] compared with 5.0 months (95% CI 3.6–6.4, $P < 0.001$, Fig. 2) in the IM group. After imatinib first-line treatment progression, sunitinib therapy significantly reduced the risk of tumor progression, according to the Cox proportional-hazards regression model [$P < 0.001$; hazard ratio (HR) = 0.348, 95% CI 0.251–0.482].

Univariate and multivariate analyses of PFS

The univariate analysis showed that age, sex, location of the primary tumor, metastatic sites, primary genotype, and surgery were all not related to PFS. The multivariate analysis revealed that sunitinib treatment was the only independent risk factor for a good prognosis (HR = 0.307, $P < 0.001$, Table 2).

PFS in subgroups

The subgroup analysis revealed that sunitinib was associated with better mPFS than imatinib dose escalation in all subgroups of patients with KIT exon 11 mutation (11.5 months, 95% CI 7.5–15.5 vs 4.0 months, 95% CI 3.3–4.7, $P < 0.001$, Fig. 3A), exon 9 mutation (16.5 months, 95% CI 10.9–22.1 vs 7.0 months, 95% CI 2.9–11.1, $P < 0.001$, Fig. 3B), or KIT/PDGFRA WT (8.5 months, 95% CI 6.6–10.4 vs 4.0 months, 95% CI 3.4–4.6, $P = 0.006$, Fig. 3C).

Time to sunitinib failure

The mPFS in the SU group was 12.0 months (95% CI 10.3–13.7) compared with 15.0 months in the IM group (95% CI 13.1–16.9, $P = 0.301$, Fig. 4). No matter which genotype, no significant difference was found in mPFS between the two groups (Supplement 1).

Overall survival

After imatinib first-line treatment progression, the median OS for all patients was 23.0 months (95% CI 20.7–25.3). Less difference was observed in OS between the SU and IM groups (25.0 months, 95% CI 21.9–28.1 vs 21.5 months, 95% CI 18.9–24.1, $P = 0.738$, Fig. 5). Regardless of which genotype, no significant difference was found in mOS between the two groups (Supplement 2).

Safety

The most common treatment-related adverse events (AEs) in the sunitinib group were hand-foot syndrome, fatigue, neutropenia, hypertension, and thrombocytopenia. Most AEs of sunitinib were from mild to moderate in severity. Patients with grade 3–4 adverse reactions could tolerate sunitinib after dose interruption followed by dose reduction. In the imatinib escalation group, AEs included edema, fatigue,

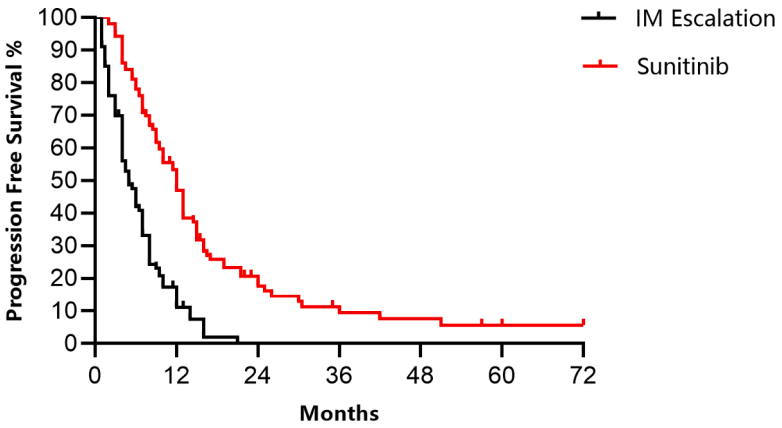

Fig. 2. PFS in the SU and IM groups.

Table 2
Univariate and multivariate analysis by each variable in the entire cohort.

Variable	Univariate HR	*P* value[a]	Multivariate HR	*P* value[a]
Intervention		<0.001		<0.001
Imatinib escalation	Reference		Reference	
Sunitinib	0.348		0.319	
Age (years)		0.472		
≤60	Reference			
>60	1.137			
Sex		0.436		
Male	Reference			
Female	0.881			
Location of the primary tumor		0.987		0.800
Stomach	Reference		Reference	
Non-stomach	o.997		0.956	
Location of metastasis sites		0.448		0.570
-Single-organ metastasis				
Liver	Reference		Reference	
Peritoneum	1.107	0.578	1.170	0.394
Others	1.142	0.435	1.155	0.505
-Multiple-organ metastases	1.302	0.575	1.460	0.439
-None or UN	0.520	0.134	0.628	0.299
Primary genotype		0.115		0.056
KIT exon 11 mt	Reference		Reference	
KIT exon 9 mt	0.656	0.048	0.662	0.071
KIT/PDGFRA WT	0.971	0.905	1.148	0.589
Others or UN	0.703	0.062	0.674	0.048
Operation	1.179	0.456	0.961	0.862

Abbreviations: HR, hazard ratio; mt, mutation. WT: wild-type; UN:unknown.
[a] P values were determined with the Cox proportional-hazards regression model.

granulocytopenia, and skin rash, which were more severe than those found in the previous 400 mg/d treatment, particularly edema and fatigue. No new adverse event specific or inconsistent with previously reported adverse reactions was observed. No treatment-related death occurred.

Discussion

In GISTs with metastasis or/and recurrence, the standard dose of imatinib is still effective, but the emergence of drug resistance is often inevitable [12]. At the time when only sunitinib is available for second-line treatment, whether to choose an imatinib dose-escalation regimen or to switch to sunitinib after the failure of standard dose of imatinib treatment was still unclear. This comparative study was conducted on the efficacy of the two regimens; it was a real-world study with a large sample size of patients.

For the dose-escalation regimen of imatinib, the recommended dose was 800 mg/d [13]. However, Chinese patients have poor tolerance to 800 mg/d. Li et al. indicated that the efficacy of the increasing dose of imatinib to 600 mg/d was equivalent to that of 800 mg/d in Chinese patients [14]. The IM group of this study was allowed to include patients who received imatinib 600 mg/d as second-line therapy.

Sunitinib, as a multi-target TKI, has shown favorable efficacy in recurrent or metastatic GISTs with imatinib failure; also, its long-term safety and efficacy have been confirmed in a global therapeutic application study [15]. Our study found that mPFS in the SU group was significantly better than that in the IM group in the whole cohort, suggesting that sunitinib might be a better option than imatinib escalation in GISTs with the failure of imatinib standard-dose treatment. Table 3 summarizes previous studies about the comparison of the treatment efficacy of imatinib dose escalation and sunitinib in GISTs. In most studies, the mPFS of sunitinib was about 10 months, while that of imatinib escalation was about 5 months. A significant difference was found between the two schemes, indicating that sunitinib might be beneficial to GISTs failing in imatinib standard-dose therapy. Our results were consistent with those described earlier.

In addition, the clinical efficacy of sunitinib on GISTs was affected by the KIT genotype to a certain extent. Reichardt et al. reported that for directly switching to sunitinib as second-line treatment, the mPFS of patients with a primary KIT exon 9 mutation was obviously better than that of patients with exon 11 mutation [21], which was consistent with our results. No significant difference in mPFS between KIT exon 9 mutation and exon 11 mutation was found in the SU group (16.5 m vs 11.5 m, $P = 0.121$, supplement 3B) in our study. However, patients with KIT exon 9 mutation had a trend of better benefits.

In terms of gene subgroups, patients with advanced GISTs with KIT exon 11 mutations were more likely to switch directly to sunitinib rather than imatinib escalation [18]. We also explored the difference in the efficacy of the two schedules in patients with primary KIT exon 11 mutation, KIT exon 9 mutation, and KIT/PDGFRA WT. The results showed that sunitinib had better PFS than imatinib dose escalation in all three subgroups, which was in accordance with the whole cohort.

Our study also showed no significant difference in TTSF and OS between the IM and SU groups. It seemed that the survival outcome was equivalent in the two groups, yet the SU group had a trend of longer OS. Most previous studies showed no statistically significant difference in OS between the two groups, but revealed a trend that sunitinib provided superior results than imatinib escalation, except the study by Hsu et al (Table 3). Despite no statistically significant difference in TTSF between the two groups, the IM group had longer TTSF. Prior studies suggested that the plasma drug concentration of imatinib might affect its therapeutic efficacy [22,23]. Therefore, the reason why imatinib dose escalation had a certain curative effect might be that its plasma drug concentration had reached the level that could inhibit tumor progression. In addition, several studies confirmed that the higher dose of imatinib was more beneficial to KIT exon 9 mutation than the standard

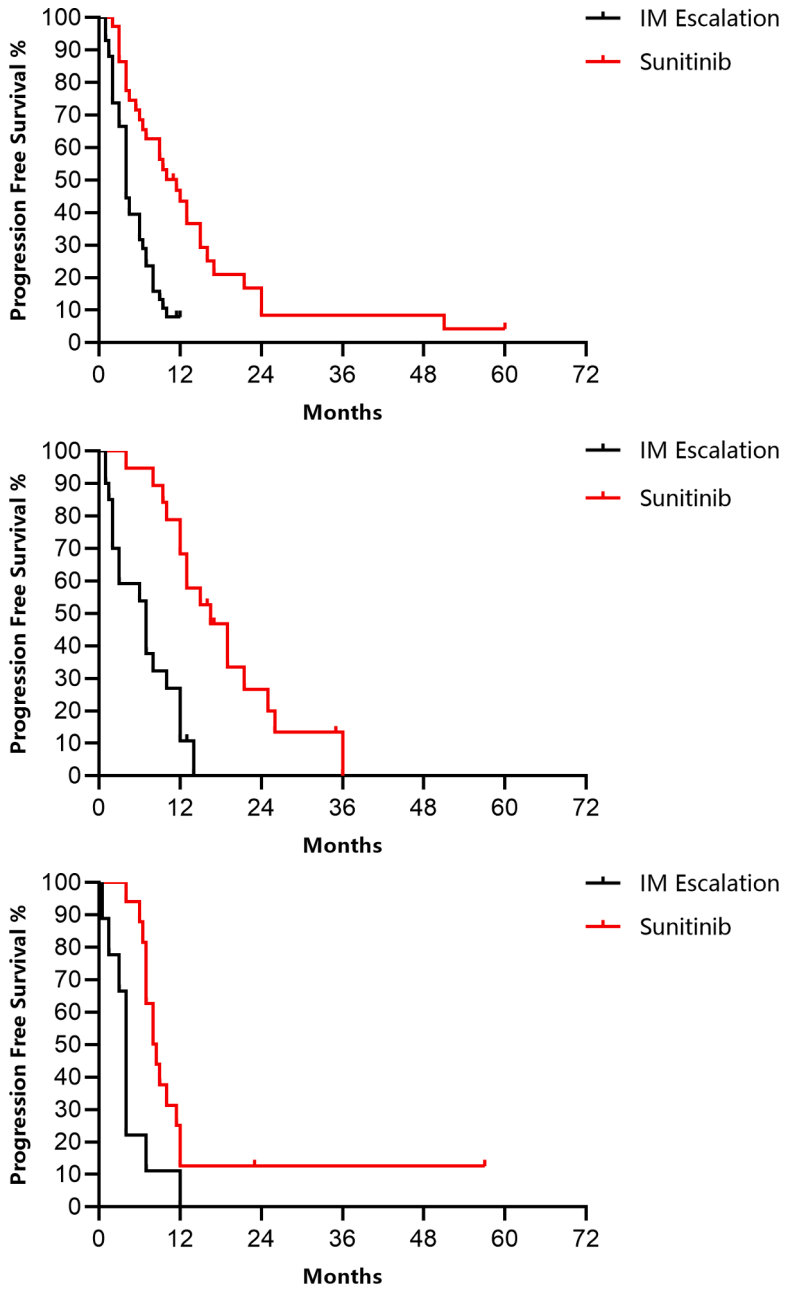

Fig. 3. PFS of different TKI therapies in gene subgroups.

dose; therefore, patients with the genotype were recommended to take a high dose of imatinib as the initial treatment [24–26]. Our study with the initial treatment dose of 400 mg/d as the inclusion standard included 39 patients (37.9%) with KIT exon 9 mutation. This was because mutation analysis was not performed in most patients due to certain limitations until 2011–2012 when gene testing became popular. Therefore, the genotype of most patients was unknown at the time of initial treatment. Consequently, a considerable number of patients with KIT exon 9 mutation were included, favoring the TTSF in the IM group to some extent. However, except for KIT exon 9 mutation, which genotype could benefit from higher dose was not clear. Also, whether the benefits from the higher dose in patients excluding KIT exon 9 mutation were related to the plasma imatinib concentration was unclear.

The patients in the IM group in our study were those who could still receive sunitinib treatment after the progression of imatinib dose escalation. In clinical practice, a situation may arise in which sunitinib cannot be applied because of physical status, economic condition, and other reasons. Moreover, in the course of our study, the standard third-line targeted drugs of GIST were not yet marketed in China, and almost all the treatment after the progression of sunitinib was palliative maintenance therapy (BSC, best supportive care). The lack of later-line treatment might be an important reason why researchers advised some patients to give priority to imatinib dose escalation after the progression of first-line therapy. At present, later-line targeted drugs in imatinib-resistant GISTs include at least sunitinib, regorafenib, and ripretinib [27–29]. Under the circumstance that PFS in the IM group was significantly worse than that in the SU group, reducing the frequency of progression and making efforts to strive for an opportunity to receive more active later-line treatment as far as possible may help improve OS.

This was a retrospective study with some inherent limitations as follows. First, although the sample of this study was close to clinical practice, it did not mean that it had good representativeness. The study was limited to an Asian population with a small sample size, and whether the results were applicable to other populations remained to be

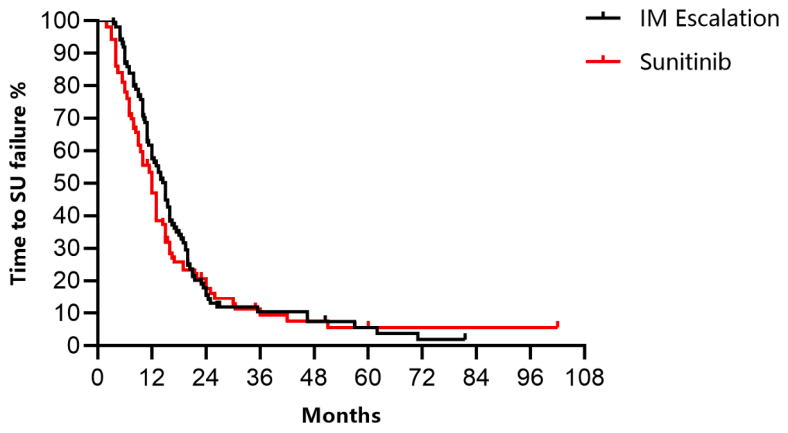

Fig. 4. TTSF in the SU and IM groups.

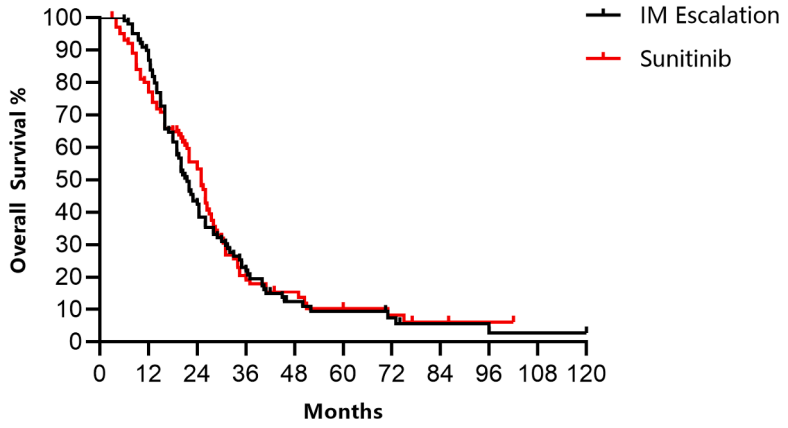

Fig. 5. OS in the SU and IM groups.

Table 3
Summary of IM escalation versus sunitinib in GISTs with progression of imatinib first-line therapy.

References	Number of cases/male proportion	Median age (year)	Primary tumor site/most common metastatic site	Imatinib escalation proportion (600/800 mg)	Gene mutation	Response evaluation criteria	Median PFS	Median OS
Hsu et al. [16]	91/62.6%	58	NA	69.2%	67 available, exon 11 62.7%, exon 9 20.9%, others 16.4%	RECIST	7.4 months (IM escalation), 9.9 months (sunitinib)	30.0 months (IM escalation), 35.5 months (sunitinib)
Vincenzi et al. [17]	123/55.0%	58	Stomach 57.0% / liver 58.0%	64.2%	Exon 11 76.0%, others 24.0%	RECIST or Choi	5.0 months (IM escalation), 10.0 months (sunitinib)	58.0 months (IM escalation), 62.0 months (sunitinib)
Dong et al. [18]	75/80.0%	53	Stomach 32.0% / liver 47.4%	50.7%	Exon 11 76.7%, exon 9 8.0%, others 5.3%	RECIST	4.0 months (IM escalation), 14.0 months (sunitinib)	20.0 months (IM escalation), 21.0 months (sunitinib)
Hsu et al. [19]	324/62.2%	61	NA	71.2%	NA	NA	NA	37.5 months (IM escalation), 16.0 months (sunitinib)
Yang et al. [20]	40/62.5%	57	Small intestine 37.5% / Peritoneum 70.0%	27.5%	25 available, exon 11 56%, exon 9 20.0%, others 24.0%	Choi	4.0 months (IM escalation), 9.0 months (sunitinib)	19.0 months (IM escalation), 26.0 months (sunitinib)

Abbreviations: IM, imatinib; NA, not available; PFS, progression-free survival; OS, overall survival;.
RECIST, response evaluation criteria in solid tumours.

verified. The selection of the sample population was often prone to a range of selection bias, including physicians' judgment, patients' general condition, concomitant diseases, tumor-related complications, and so on, for the diagnosis of the target population and the implementation of the study. This study was hoped to restore the clinical outcomes of different treatment options in real clinical scenarios. The three hospitals in our study are all teaching hospitals and major referred center for patients of GIST in China. In addition, the diagnosis and treatment of patients is guided by consensus or guidelines to minimize the gap of the three hospitals as much as possible. Besides, information bias inevitably

occurred during data collection, including recall bias, report bias (such as lack of central image evaluation), and so on.

Conclusions

In conclusion, sunitinib was a more effective TKI with an improved PFS for GISTs after the progression of standard dose of imatinib. Under the circumstance that the OS in the two groups was similar, it was suggested that the curative effect of imatinib dose escalation followed by sunitinib was also considerable, and we could not deny its feasibility. The characteristics of the population benefiting from imatinib dose escalation in conjunction with plasma imatinib concentration monitoring need further exploration.

CRediT authorship contribution statement

Shaoqing Huang: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Xing Liu:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Xiaodan Guo:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Hui Wu:** Supervision, Investigation, Resources, Writing – review & editing. **Huishan Lu:** Supervision, Investigation, Resources, Writing – review & editing. **Zhizhong Pan:** Supervision, Investigation, Resources, Writing – review & editing. **Shirong Cai:** Supervision, Investigation, Resources, Writing – review & editing. **Xiaojun Wu:** Supervision, Investigation, Resources, Writing – review & editing. **Xinhua Zhang:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2023.101641.

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