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Review

Cytoreductive surgery for metastatic gastrointestinal stromal tumors followed by sunitinib compared to followed by imatinib-a multi-center cohort study

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ABSTRACT

Background: The progression-free survival (PFS) is not optimal when imatinib was recommended for treatment of gastrointestinal stromal tumor (GIST) undergoing surgery after tumor local or multifocal progression.

Methods: We evaluate PFS of patients undergoing R0 resection or optimal cytoreductive surgery followed by sunitinib therapy compared with imatinib after tumor unifocal or multifocal progression.

Results: From January 2006 to June 2017, ninety-seven patients from thirteen medical centers were enrolled. Fifty-six patients continued imatinib therapy and 41 patients switched sunitinib treatment directly after R0 resection or optimal cytoreductive surgery. The PFS of sunitinib group was longer than that of imatinib group (30.0 months vs 12.0 months, $p = 0.009$). In subgroup analysis, the PFS of the sunitinib and imatinib groups were 25.5 months and 12.0 months in patients with tumor multifocal progression ($p = 0.008$), and 39.0 months and 13.0 months in patients with unifocal progression ($p = 0.156$), respectively. PFS of postoperative sunitinib group was also superior to the total PFS of postoperative imatinib group (PFS of postoperative imatinib plus PFS of subsequent sunitinib therapy (30.0 months vs 21.0 months, $p = 0.012$). The overall survival in the sunitinib and imatinib groups were 37.0 months and 33.0 months, respectively ($p = 0.794$).

Conclusions: Surgery followed by sunitinib in GIST patients with unifocal or multifocal progression on imatinib may improve PFS, compared with surgery followed by imatinib.

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract [1]. Despite the beneficial effects of imatinib (IM) as standard first-line treatment for metastatic GIST, resistance and intolerance to imatinib remain substantial clinical problems, and nearly 50% of patients show secondary resistance within 2 years [2,3].

Some studies have demonstrated that cytoreductive surgery in GIST patients with limited disease progression on imatinib therapy is feasible, but progression-free survival (PFS) remains unsatisfactory [4–6]. Meanwhile, the role of cytoreductive surgery in patients with multifocal progress disease is controversial because of the poor PFS [4–7]. It is worth noting that the postoperative TKI was imatinib in all previous studies regarding cytoreductive surgery in metastatic GIST with resistance to imatinib.

Sunitinib (SU) is a small molecule, multi-targeted tyrosine kinase inhibitor that targets VEGF receptors, PDGF receptors, c-KIT, FLT3 and RET. An international phase III trial demonstrated the efficacy and safety of sunitinib in patients with imatinib-resistant GISTs [8]. Therefore, we hypothesized that cytoreductive surgery followed by sunitinib in patients with progression in imatinib might be superior to surgery followed by imatinib. To our knowledge, there have not been any studies to evaluate the difference between these therapies.

The objective of this study was to investigate the optimal postoperative TKI therapy after cytoreductive surgery in GIST patients with unifocal or multifocal progression on imatinib.

Methods

Patient selection

All procedures performed in this study involving human participants were approved by Beijing Cancer Hospital Ethical Committee. The clinical trial registration number is NCT03424876. The records of all patients with metastatic GIST undergoing cytoreductive surgery in13 Chinese medical centers were retrieved. The inclusion criterions were as follows: pathological diagnosis of metastatic GIST was confirmed; imatinib first line therapy failed because of progressive disease; patient underwent optimal cytoreductive surgery after tumor progression; patient had to receive a minimum of one month of imatinib or sunitinib treatment after cytoreductive surgery. Unifocal progressive disease was defined as a single radiographic progressive site observed after imatinib resistance. Multifocal progressive disease was defined as more than one radiographic progressive site observed after imatinib resistance.

Cytoreductive surgery and postoperative management

All the patients with multifocal progression received cytoreductive surgery when they had complication including visceral compression, bowel obstruction, uncontrollable bleeding of digestive tract. All patients underwent evaluation by multidisciplinary teams to determine whether surgery and the selection of postoperative TKI therapy were suitable. Extent of resection was defined as macroscopically complete with a negative microscopic margin (R0), macroscopically complete with a positive microscopic margin (R1), or macroscopically incomplete (R2). Optimal cytoreductive surgery was defined as the diameter of every residual tumor less than 1 cm, or the proportion of residual tumors less than 25% [4,5].

Postoperative imatinib was administered orally at doses of 400 mg or 600 mg once daily. Postoperative sunitinib was administered orally at a dose of 50 mg once daily on a 4-weeks-on, 2-weeks-off (4/2) schedule or 37.5 mg once-daily as a continuous daily dose (CDD) schedule after cytoreductive surgery for 4–6 weeks. The patients were divided into imatinib and sunitinib groups according to the respective postoperative TKI.

Detection of KIT & PDGFR gene mutations

Detection of gene mutations included at least exon 9, 11, 13, and 17 of c-kit gene and exon 12 and 18 of PDGFRA gene. For patients with secondary resistance, exon 14 and 18 of c-kit gene were included. 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 sample using the e.Z.N.A.® FFPE DNA Kit (OMEGA Bio-Tek Inc., Norcross, GA, USA).

Statistical analysis

PFS was defined as the interval between the date of cytoreductive surgery to GIST progression after postoperative sunitinib or imatinib treatment, or to death from any cause. Overall survival (OS) was defined as the interval between the date of cytoreductive surgery to death from any cause. The response rate was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1). Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Based on previous studies, PFS in patients who continued imatinib therapy after cytoreductive surgery was estimated to be 9 months [4–6]. We assumed PFS in the sunitinib treatment group to be 20 months. Assuming a sample ratio of 1:1 with a default rate of 10%, and a one-sided level of significance of 0.05, a two-sided log-rank test with an overall sample size of 87 subjects (43 in the imatinib group and 44 in the sunitinib group) achieves 90.2% power at a 0.05% significance level to detect a hazard ratio of 0.45.

All statistical analyses used the SPSS 19.0 platform (SPSS Inc., Chicago, IL, USA). PFS and OS curves were constructed according to the Kaplan-Meier method and were compared using a log-rank test. In order to adjust for confounding variables, Cox proportional hazards models were used to estimate the simultaneous effects of prognostic factors on PFS. Frequency and percentage descriptions were used for categorical variables and chi-squared test was conducted to compare the incidence of different events. If the theoretical frequency was lower than 1, Fisher's exact test was conducted.

Results

Patient characteristics

Between February 2006 to June 2017, 97 patients from 13 medical centers were enrolled. The most common primary tumor location was small bowel. Thirty patients had GIST with unifocal progression, and 67 had multifocal progression after imatinib therapy. All patients underwent optimal cytoreductive surgery. Forty-three patients underwent R0/R1 resection, and 54 underwent R2 resection after GIST progression. Forty-three patients continued imatinib 400 mg/d therapy and thirteen patients received imatinib dose escalation to 600 mg/d, and 41 patients selected postoperative sunitinib treatment after cytoreductive surgery. Table 1 summarizes the demographic data of all the patients. There were no significant differences between the two groups in terms of clinicopathological features.

Table 1
The clinical and pathological features of imatinib and sunitinib groups.

Features	Imatinib group (n = 56)	Sunitinib group (n = 41)	P value
Median Age	56.0 (54.0–56.0)	51 (47.9–54.1)	0.105
Gender			
Male	62.5% (35/56)	68.3% (28/41)	0.668
Female	37.5% (21/56)	31.7% (13/41)	
Location of primary tumor			
Stomach	10.7% (6/56)	19.5% (8/41)	0.297
Small bowel	83.9% (47/56)	70.7% (29/41)	
Others	5.4% (3/56)	9.8% (4/41)	
Number of progression sites			
Unifocal	33.9% (19/56)	26.8% (11/41)	0.510
Multifocal	66.1% (37/56)	73.2% (30/41)	
Cytoreductive surgery			
R0/R1	41.1% (23/56)	48.8% (20/41)	0.536
R2	58.9% (33/56)	51.2% (21/41)	
Primary genotype			
Kit exon 11 mt	71.4% (40/56)	56.1% (23/41)	0.079
Kit exon 9 mt	10.7% (6/56)	31.7% (13/41)	
Other type	8.9% (5/56)	2 (4.9%)	
Unknown	8.9% (5/56)	7.3% (3/41)	
Secondary genotype			
Kit exon 13 mt	14.3% (8/56)	12.2% (5/41)	0.979
Kit exon 17 mt	10.7% (6/56)	9.8% (4/41)	
No secondary mutation	53.6% (30/56)	53.7% (22/41)	
Unknown	21.4% (12/56)	24.4% (10/41)	

Progression-free survival

As of November 2017, 52 patients had tumor progression after postoperative imatinib or sunitinib therapy. The median PFS for all the patients was 18.0 months (95%CI 13.5–22.5). The PFS of postoperative sunitinib group (30.0 months, 95% CI 23.1–36.9) was longer than that of postoperative imatinib group (12.0 months, 95% CI 9.8–14.2, $p = 0.009$, Fig. 1). Postoperative sunitinib therapy significantly reduced the risk of tumor progression in patients with GIST receiving cytoreductive surgery, according to the Cox proportional hazards regression model ($p = 0.045$, HR = 0.392; 95% CI 0.157–0.980).

PFS in subgroups

Subgroup analysis revealed postoperative sunitinib therapy significantly improved PFS compared with postoperative imatinib treatment in patients with multifocal progression GIST (25.5 months 95% CI 15.9–35.1 vs 12 months 95% CI 10.6–13.4, $p = 0.008$), but not in the unifocal progression GIST subgroup (39 months 95% CI 22.2–55.8 vs 13 months 95% CI 4.2–21.8, $p = 0.156$, Fig. 2A and B).

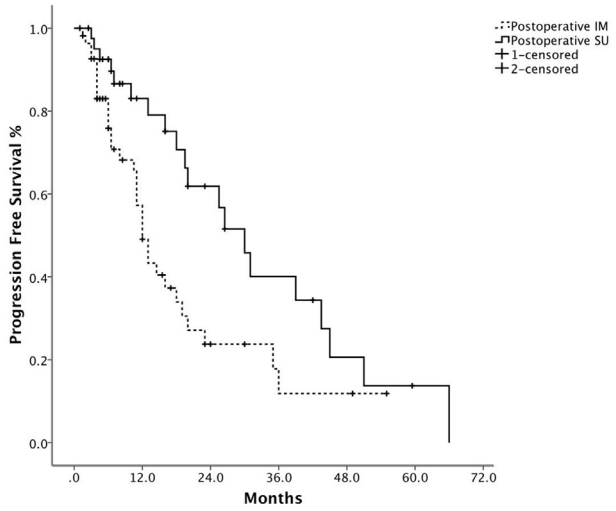

Fig. 1. The PFS of postoperative sunitinib group and imatinib group.

According to extent of cytoreductive surgery, the PFS of patients who underwent R0 or R1 resection and those who received R2 resection were 25.5 months (95% CI 13.0–38.0) and 13.0 months (95% CI 9.2–16.8), respectively ($p = 0.146$). Among the R0/R1 resection subgroups, postoperative sunitinib therapy prolonged the PFS (31 months, 95% CI 28.6–33.4) compared with postoperative imatinib (18.0 months, 95% CI 10.6–25.4, $p = 0.043$, Fig. 2C), however, there was no significant different of PFS in the R2 resection subgroup (SU 19.5 months 95%CI 13.0–26.0, IM 12.0 months 95% CI 10.6–13.4, $p = 0.171$, Fig. 2D).

In GISTs with kit exon 11 mutation, postoperative sunitinib therapy also improved RFS compared with postoperative imatinib treatment (31 months 95% CI 9.48–52.5 vs 11 months 95% CI 2.2–19.8, $p = 0.036$, Fig. 2E). For the kit exon 9 mutation and wild-type subgroups, there was a trend toward improved PFS in the sunitinib group (25.5 months 95% CI 12.5–38.5 vs 13.0 months 10.5–15.5, $p = 0.06$, Fig. 2F).

Univariate and multivariate analysis of PFS

On univariate analysis, postoperative sunitinib and R0/R1 surgery were significantly associated with good PFS. Gender, stomach as primary location, exon 11 mutation, and numbers of progression sites were not related to PFS. On multivariate analysis, postoperative sunitinib was the only independent risk factor for good prognosis (HR 0.468, $p = 0.014$, Table 2).

The secondary PFS of sunitinib after postoperative imatinib therapy

In postoperative imatinib treatment group, 17 patients continued to received sunitinib therapy after postoperative imatinib failure. The secondary PFS of sunitinib therapy was 7.5 months (95% CI 2.8–12.5). The total PFS in postoperative imatinib group (PFS of postoperative imatinib therapy plus PFS of subsequent sunitinib therapy) was 21.0 months (95% CI 15.6–27.8), and was still

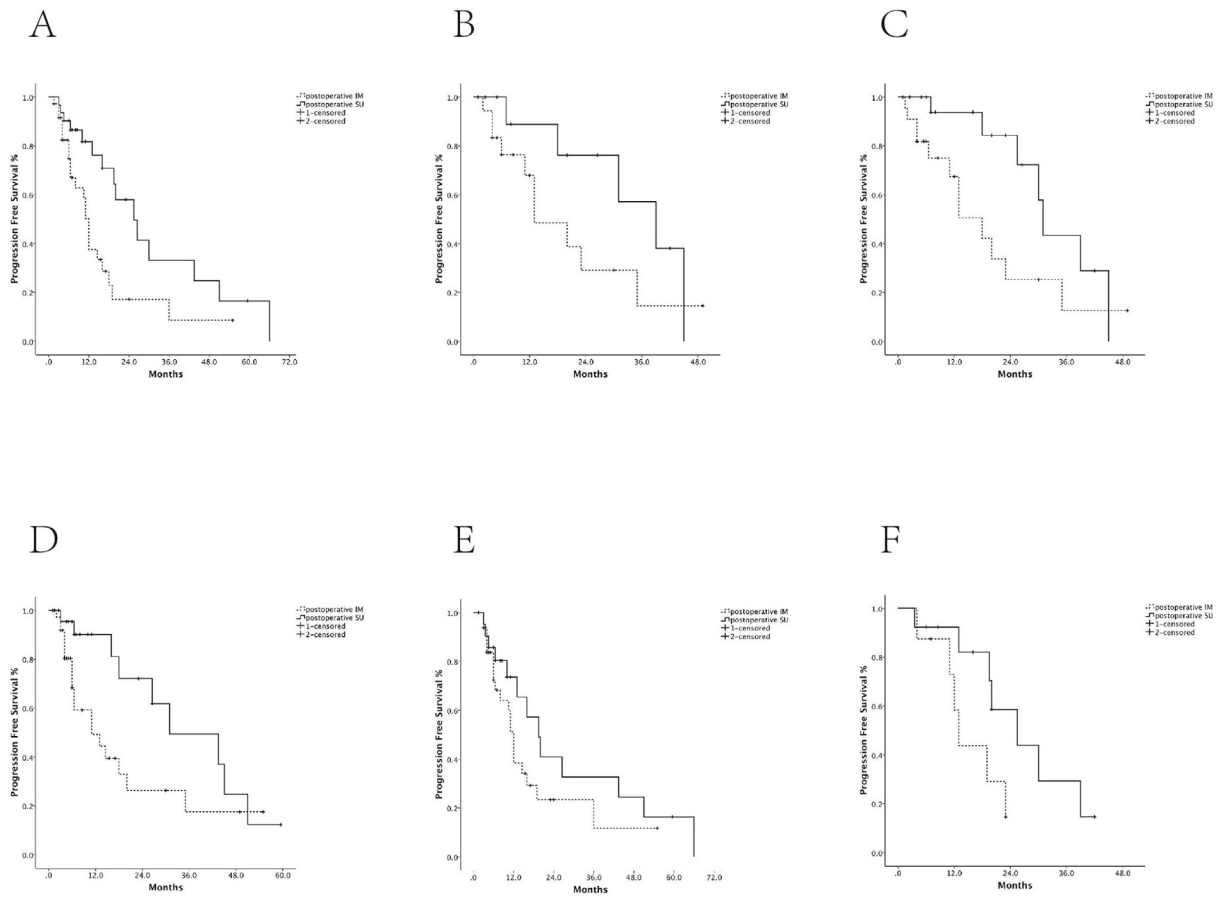

Fig. 2. The PFS of different postoperative TKI therapy in subgroups.

Table 2
Multivariate analysis by each variable in entire cohort.

Variable	HR	*P*-value
Postoperative TKI (sunitinib)	0.468	0.014
Gender (male)		0.864
Primary location (stomach)		0.206
Primary gene mutation (kit exon 11 mt)		0.589
Numbers of progressive disease (unifocal)		0.811
Extent of surgery (R0/R1)		0.545

inferior to PFS of postoperative sunitinib group (30.0 months, 95% CI 23.1–36.9) ($p = 0.012$).

Overall survival

Of the entire cohort, thirty-six patients died because of tumor progression. The median overall survival was 36.0 months (95% CI 27.4–44.6). There was no significant difference between OS in the postoperative sunitinib group (37.0 months, 95% CI 33.4–40.6) and the postoperative imatinib group (33.0 months, 95% CI 10.8–55.2, $p = 0.794$) (Fig. 3). In the patients with unifocal progression, 27.3% (3/11) died in sunitinib group and 36.9% (7/19) died in imatinib group. The OS in patients with unifocal progression in sunitinib group and imatinib group were 40.0 months (95% CI 14.7–47.2) and 42.5 months (95% CI 17.2–55.3) ($p = 0.778$), respectively.

Safety

The most common adverse events in the postoperative sunitinib group were neutropenia, fatigue, hand-foot syndrome,

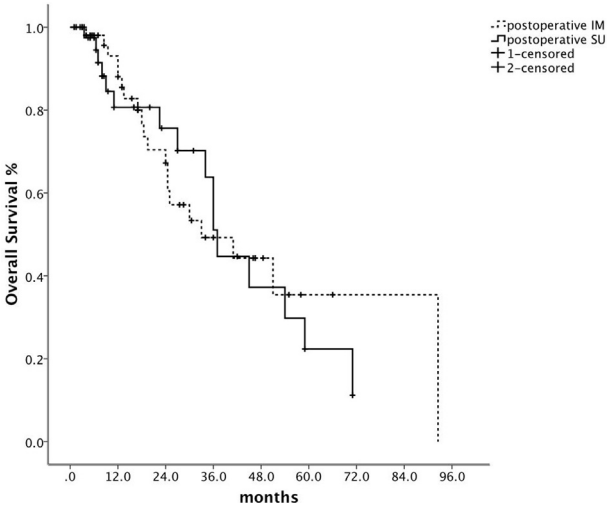

Fig. 3. The PFS of OS in postoperative sunitnib and imatinib group.

and diarrhea. In the postoperative imatinib group, most common adverse events were edema, nausea, and anemia. Grade 3 adverse events were diarrhea (4.8%) and hand-foot syndrome (2.4%), and skin rash (1.8%). No treatment related death happened.

Discussion

To our knowledge, this is the first study to evaluate the role of postoperative sunitinib therapy in GIST patients who underwent

cytoreductive surgery after imatinib resistance. Postoperative sunitinib treatment significantly improved PFS compared with postoperative imatinib therapy. According to previous studies, imatinib therapy after surgery in GIST with unifocal progression provided benefit of about 5–13 months PFS [5,9,10], and NCCN guidelines recommended continuing the same dose imatinib therapy after resection of limited progressive disease [11]. However, in theory, unifocal progression is commonly the early stage of tumor drug resistance and subsequent multifocal progression is often inevitable. Therefore, continuing the same dose imatinib maybe is not the optimal selection for this type of patient, even if progressive disease is removed.

As a multi-targeted tyrosine kinase, sunitinib has demonstrated efficacy in metastatic GIST with imatinib failure [8]. We showed that the PFS of postoperative sunitinib was superior to that of imatinib both in the entire cohort and in the multifocal progression disease subgroup, also was superior to the total PFS including postoperative imatinib and subsequent sunitinib therapy. There was also a substantial trend toward PFS improvement in the unifocal subgroup. More importantly, in multivariate analysis, postoperative sunitinib was an independent factor for good prognosis. There was no obvious selection bias because the characteristics in the two groups were well balanced, except for more patients with kit exon 9 mutation in sunitinib group. These data suggest that sunitinib is a better treatment selection than imatinib after cytoreductive surgery in patients with GIST progression.

Cytoreductive surgery in patients with metastatic GIST is feasible, with greatest benefit in PFS and OS observed in patients who were responsive, stable on TKI therapy [12–15]. However, the benefits remain uncertain for patients with multifocal progression. Although cytoreductive surgery was not routinely recommended to the patients with multifocal progression, surgery still can be performed when severe complication happened, such as bowel obstruction, uncontrollable bleeding. The response rate of sunitinib in phase III trial was only 6% [8], suggesting that sunitinib is only effective for some clones of GIST after imatinib resistance. A previous study showed that imatinib therapy provided more benefit in GIST with less tumor bulk [16]. We assumed cytoreductive surgery could reduce resistant tumor bulk so as to improve efficacy of sunitinib even further. In this study, PFS of 30 months in sunitinib group was similar to the value reported in Fairweather's study [13], and was significantly superior to the 6-month PFS in the sunitinib group without cytoreductive surgery in a phase III trial. This confirmed our hypothesis that cytoreductive surgery can prolong the effectiveness of sunitinib. However, in several studies, the survival of patients who received cytoreductive surgery was very poor [6,9,17], suggesting the selection of patients and criteria for cytoreductive surgery are very important. In this study, we adopted strict surgery criteria, according to Kang's and Dematteo's studies [4,5] to make sure there were as few residual GISTs as possible. Therefore, even patients undergoing R2 resection had good improvement of PFS. Certainly, the more appropriate patients of cytoreductive surgery remain those with stable or responsive disease with TKI therapy. One needs to be cautious to select patients with progressive disease for cytoreductive surgery.

In the present study, we showed that patients with unifocal progression disease had significantly prolonged PFS compared with those with multifocal progressive disease in the postoperative sunitinib subgroup. This finding was similar to the results previously reported [4–6]. However, there was no difference of PFS in the postoperative imatinib therapy subgroup. This could be related to the higher proportion of R0/R1 surgery and fewer kit secondary mutations in the postoperative imatinib group.

In some studies, primary genotype can predict the efficacy of sunitinib in metastatic GIST. GIST with kit exon 9 mutations and wild-type GIST had better PFS than GIST with kit exon 11 mutations [18]. We did not show a relationship of genotype and efficacy of postoperative sunitinib therapy in this study. The possible reasons may be that cytoreductive surgery eliminated the majority of tumor bulk which could be resistant to sunitinib. In addition, we did not analyze the prediction of secondary gene mutation in efficacy of TKIs because we detected only a low proportion of secondary mutations.

This was a small retrospective trial and selection bias might have been more important than the data show and patient numbers within subgroups were small.

Within these limitations we observed the following. The quality of cytoreduction is important for the outcome. Sunitinib improved outcome after surgery further, this benefit reached significance only in R0/R1. Postoperative sunitinib might be a better option than imatinib for patients who underwent surgery, particularly in multifocal progression. The underlying resistance mechanisms and the expected number of secondary mutations might explain these differences.

Conflict of interest statement

All the authors report no conflicts of interest in this work.

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