

Sunitinib Treatment in Pediatric Patients With Advanced GIST Following Failure of Imatinib

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Background. Sunitinib inhibits KIT and other members of the split-kinase-domain family of receptor tyrosine kinases. Sunitinib prolongs survival in adult patients with imatinib-resistant gastrointestinal stromal tumor (GIST). We report the experience with sunitinib in pediatric patients with advanced GIST following failure of imatinib. **Procedure.** Sunitinib therapy was provided through a treatment-use protocol. Patients were 10–17 years old at enrollment. All patients had GIST resistant to imatinib therapy. Sunitinib was administered daily for 4 weeks in 6-week treatment cycles. *KIT* and platelet-derived growth factor receptor alpha (*PDGFRA*) genotyping of tumor tissue were performed. **Results.** One patient achieved a

partial response, five patients had stable disease and one patient had progressive disease on sunitinib. The duration of disease stabilization was between 7 and 21+ months, with a mean of 15 months. Time to tumor progression was longer on sunitinib than on prior imatinib treatment for five of six patients. Two patients experienced grade 3 adverse events. All other adverse events were grade 1–2. None of the five patients tested had mutations in *KIT* or *PDGFRA*. **Conclusion.** Sunitinib treatment was associated with substantial initial antitumor activity and acceptable tolerability in this group of pediatric patients with imatinib-resistant GIST. *Pediatr Blood Cancer* 2009;52:767–771. © 2009 Wiley-Liss, Inc.

Key words: clinical trials; drug resistance; new agents; pediatric oncology; soft tissue sarcoma

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a tumor of mesenchymal origin occurring in the gastrointestinal tract. Approximately 85% of GISTs in adults harbor gain-of-function mutations in either the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) proto-oncogenes [1–3]. GIST is poorly responsive to treatment with standard chemotherapy, and median survival was 20 months prior to the advent of targeted therapies [4]. Treatment with small-molecule inhibitors of KIT and PDGFRA has prolonged survival in adult patients with GIST [5,6]. There have been no systematic studies and few published reports addressing the use of small-molecule inhibitors of KIT and PDGFRA in pediatric patients with GIST.

Pediatric GIST appears to have a different biology and clinical behavior than adult GIST. In contrast to GISTs in adults, >85% of GISTs in children are wild-type (WT), with no detectable mutations in *KIT* or *PDGFRA* [7]. Further evidence supporting a distinct biology are recently published reports of differing gene-expression profiles [8] and genetic progression mechanisms [7] in pediatric versus adult GIST. Clinical features also suggest that pediatric GIST is a distinct entity. In pediatric patients, GIST is more common in females, whereas gender distribution is equal in adults. Pediatric GIST more often has an epithelioid morphology whereas adult GIST most often has a spindle morphology [9]. These differences raise the question of whether therapies that are effective for adult GIST will be equally efficacious in pediatric patients.

Sunitinib malate is a potent small-molecule inhibitor of several members of the split-kinase-domain family of receptor tyrosine kinases (RTKs). In vitro and in vivo studies have shown that sunitinib inhibits KIT, PDGFRA, PDGFRB, vascular endothelial growth factor receptors (VEGFRs), as well as several other RTKs [10–15] (Pfizer Inc., New York, NY, data on file). Sunitinib is 10 times more potent than imatinib with regard to inhibition of WT KIT [8]. In adult patients with advanced imatinib-resistant GIST, sunitinib significantly prolongs time to tumor progression (TTP) and survival [5]. Sunitinib is approved multi-nationally for the treatment of GIST after disease progression on imatinib and is recommended for this purpose in current clinical practice guidelines

[16]. Patients with WT GIST are among those achieving the greatest clinical benefit on sunitinib [17]. While pediatric GISTs lack *KIT* mutations, KIT is expressed and activated, suggesting that inhibition of WT KIT may have clinical efficacy in these tumors [7].

We hypothesized that sunitinib may be effective in pediatric patients with advanced imatinib-resistant GIST; however, a prospective trial limited to children was determined to lack feasibility. In order to describe the response and toxicity profiles of sunitinib in pediatric GIST, we reviewed the experience of pediatric GIST patients treated with sunitinib on a treatment-use protocol.

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METHODS

Study Design

The primary objective of the treatment-use protocol was to provide access to sunitinib (SUTENT, SU11248; Pfizer Inc.) to patients with GIST who had the possibility of deriving benefit from the drug but were not eligible for other ongoing sunitinib trials. During the study period, there were no ongoing sunitinib GIST trials allowing entry of subjects aged less than 18 years, so all pediatric GIST patients were enrolled on the treatment-use protocol. Additional objectives were to evaluate safety, TTP, and objective response rates. The treatment-use protocol was approved by the institutional review boards at each of the participating institutions. The patients' legal guardians consented to treatment, and the patients assented themselves if age-appropriate.

Patients

Eligibility criteria included histopathologically confirmed diagnosis of GIST not amenable to complete surgical resection and failure of prior imatinib treatment, defined as either disease progression on imatinib or intolerable imatinib-related toxicities. Additionally, patients must have received the last dose of imatinib or other cancer-directed therapy >1-week prior to starting sunitinib and all toxicities of prior therapy had to have resolved. Adequate hepatic, renal, cardiac, and bone marrow function were required for enrollment. Symptomatic central nervous system metastases or significant cardiac disease, pregnancy or lactation, or any other significant medical condition that could result in excess risk from exposure to sunitinib were criteria for exclusion. The seven patients reported here are those <18 years of age who were enrolled prior to January 2006, which is when sunitinib was approved by the US Food and Drug Administration.

Drug Administration and Dosing

Patients received sunitinib daily for 4 weeks followed by 2 weeks off therapy, comprising 6-week treatment cycles. Sunitinib was taken orally in the morning at a dosing level of 25, 37.5, or 50 mg daily. Starting and maintenance doses were determined by the principal investigator on the basis of age, weight, and tumor response.

Doses were reduced in response to grade 3 or 4 toxicities. Sunitinib was interrupted until the toxicity grade had decreased to 2. In the case of grade 3 toxicities, sunitinib was resumed at the original dose-level or reduced by one-dose-level at the investigator's discretion. For grade 4 toxicities, a one-dose-level reduction was made prior to resumption. Grade 3 or 4 lymphopenia not complicated by an opportunistic infection was an exception in that sunitinib could be resumed at the same dose-level. Doses were not re-escalated in subsequent cycles.

Evaluation of Efficacy and Safety

On days 1, 14, and 28 of the first cycle and days 1 and 28 of subsequent cycles, a complete blood count with differential, liver transaminases, bilirubin, electrolytes, blood urea nitrogen, and creatinine were evaluated and adverse events were assessed.

Patients kept a daily journal of adverse events. For grading of adverse events, the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used [18].

Assessments of disease response were obtained at each site based on local standards of care. All patients had computed tomography (CT) scans and some patients also underwent [18] fluorodeoxyglucose positron emission tomography (FDG-PET) scanning. Objective disease restaging evaluations were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by the principal investigator per Response Evaluation Criteria in Solid Tumors [19]. Reported responses represent the best responses achieved as of the end of data collection.

Mutational Analysis

DNA was extracted and purified from paraffin-embedded tumor tissue. Exons 9, 11, and 13 of the *KIT* gene and exons 12 and 18 of the *PDGFRA* gene were amplified by polymerase chain reaction (PCR). The PCR products were screened for mutations by denaturing high-performance liquid chromatography. Primers, PCR conditions, and sequencing methods were described previously [2,20].

RESULTS

Patients

Seven patients were enrolled prior to September 2005. Duration of follow-up ranged from 18 to 23 months, with a median of 22 months. Data on treatment response to imatinib and sunitinib, as well as any sunitinib-related adverse events, were available for all seven patients. Additional clinical data were available for six of seven patients. Seventy-one percent of the patients were female. One patient had Carney Triad.

Patient age at enrollment was 10–17 years (Table I), with a mean age of 15. Data on site(s) of disease at enrollment were available for six patients. All six patients had metastatic disease. Sites of metastatic disease were liver (in five patients), peritoneum (in two patients), retroperitoneum (in one patient), and lung (in one patient). Several patients had metastases at more than one site. All patients had disease measurable by CT at the time of enrollment.

Response to prior imatinib therapy was SD in three patients and PD in three patients (Table I). The seventh patient received adjuvant imatinib following complete resection and then had recurrence of disease while still on imatinib. TTP in patients with SD on imatinib ranged from 12 to 16 months. One patient (case 5) received another investigational RTK inhibitor prior to enrollment. All patients had been off prior therapy for over 2 weeks when sunitinib was started.

KIT and *PDGFRA* Mutational Analysis

Tumor material was available for mutational analysis from five patients. None of the five patients had mutations in *KIT* or *PDGFRA* (Table I).

Tumor Response to Sunitinib

One patient achieved a PR, five patients had SD, and one patient had PD on sunitinib treatment (Table I). The PR reflected complete resolution of metastatic disease in the lungs. The duration of PR or SD was 7–21+ months, with a mean of 15 months. Two patients have continued to take sunitinib for more than 18 and 21 months

TABLE I. Baseline Characteristics and Response to Treatment in Pediatric GIST Patients

Case	Age		Gender	Morphology	Genotype		Response ^a		Time to tumor progression		
	Dx	Study entry			<i>KIT</i>	<i>PDGFRA</i>	IM	SU	IM	SU	SU versus IM
1	17	17	F	Epithelioid	WT	WT	PD	SD	<1	7	+6
2	8	10	F	Epithelioid	WT	WT	Adjuvant	PR	14	>21	+7
3	13	16	F	Epithelioid	WT	WT	SD	SD	12	8	-4
4	15	16	M	Epithelioid	WT	WT	SD	SD	16	18	+2
5	15	16	F	Spindle	WT	WT	PD	SD	<1	>18	+17
6	16	16	M	Mixed	NA	NA	PD	PD	<1	<1	0
7	NA	14	F	NA	NA	NA	SD	SD	12	18	+6

Dx, age at diagnosis; study entry, age at time of enrollment; *PDGFRA*, platelet-derived growth factor receptor alpha; IM, imatinib; SU, sunitinib; F, female; WT, wild-type; PD, progressive disease; SD, stable disease; PR, partial response; M, male; NA, not available. ^aAssessed based on RECIST.

for sustained SD/PR. In five of six patients with SD/PR, sunitinib resulted in a longer TTP than was achieved during prior imatinib therapy. The difference in TTP on sunitinib versus prior imatinib ranged from 2 to 17 months, with an average of 7.5 months. The one patient in whom imatinib resulted in a longer TTP than sunitinib received the lowest dose of sunitinib (25 mg) despite being

an average-sized 16-year-old. Although patients with SD did not have a significant reduction in tumor bulk as measured by CT scan, both patients who had imaging with FDG-PET exhibited a significant reduction in tumor glycolytic activity (Fig. 1). The patient with PD had extensive hepatic, omental, and intestinal disease prior to initiation of sunitinib.

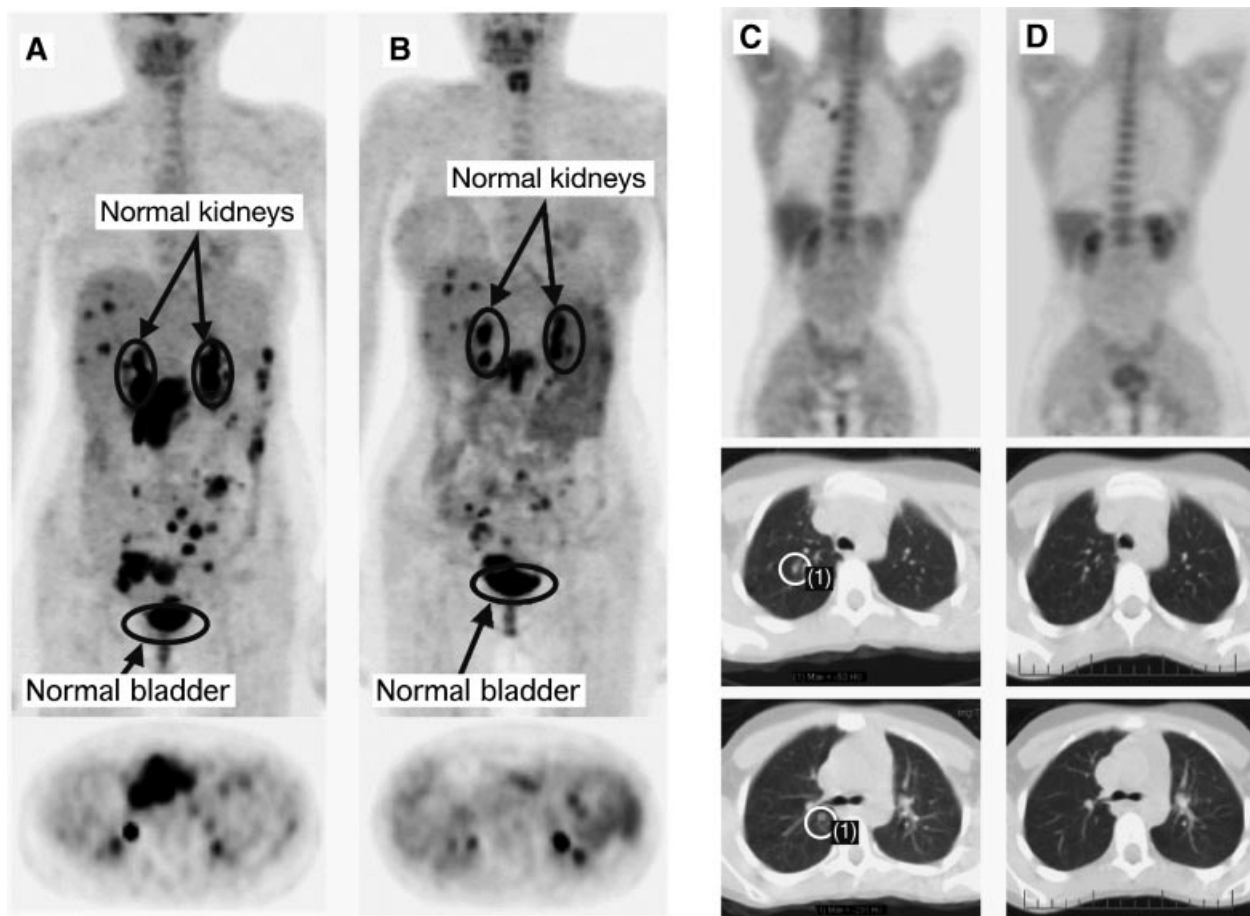


Fig. 1. Case 1 before (A) and after (B) two cycles of sunitinib treatment: FDG-PET scan maximal intensity projection view (top) and axial slices through the midline mass (bottom), showing resolution of FDG uptake in several hepatic, mesenteric, and peritoneal metastases, and decreased FDG uptake in all other masses. Case 2 before (C) and after (D) three cycles of sunitinib treatment: coronal FDG-PET scan (top) and axial CT slices of the chest (middle and bottom) showing resolution of two FDG-avid lesions and the corresponding pulmonary nodules in the right lung.

TABLE II. Treatment-Related Adverse Events in Pediatric Patients Receiving Sunitinib

Adverse event	Any grade (N = 7), n (%)	Grade 3 (N = 7), n (%)
Fatigue	4 (57%)	1 (14%)
Gastrointestinal	4 (57%)	1 (14%)
Hematologic	4 (57%)	1 (14%)
Hair hypopigmentation	4 (57%)	0
Musculoskeletal	4 (57%)	0
Headache	2 (29%)	0
Hypothyroidism	2 (29%)	0
Anorexia	1 (14%)	0
Hepatic	1 (14%)	0

Adverse Events

Treatment-related adverse events in these seven pediatric patients are summarized in Table II. No grade 4 adverse events were reported. Three grade 3 events were experienced by two patients (cases 2 and 7). There were two dose reductions due to gastrointestinal adverse events (in both of these patients) and fatigue (in one patient). Musculoskeletal events included creatinine kinase elevation in one patient, leg pain in two patients, and joint pain in one patient. Gastrointestinal events included abdominal pain, vomiting, and diarrhea.

DISCUSSION

Sunitinib treatment of pediatric patients with metastatic imatinib-resistant GIST led to SD or PR in six of seven patients. In five patients, the duration of disease stabilization was greater with sunitinib than with imatinib. In advanced GIST, disease stabilization is a clinically important measure of therapeutic efficacy. Overall survival in adult patients who continue to exhibit SD on imatinib at 6 months is similar to overall survival in patients who achieve a PR [21]. Additionally, in the patients imaged with FDG-PET, tumors exhibited decreases in glycolytic metabolism. A decrease in FDG-PET activity following imatinib therapy has been shown to be a sensitive biomarker of biochemical changes in GIST patients and model systems [22–24], and FDG-PET response to imatinib is predictive of long-term outcome [25,26]. The patients described here are similar with respect to demographics and GIST pathobiology to previously published pediatric cases [8,9,27], suggesting that other pediatric patients with GIST may respond similarly to sunitinib.

The only previously published data available on sunitinib treatment of pediatric patients with GIST is a case series reporting on four patients [8]. In that series, there was one patient with a PR, one patient with SD, one patient with PD, and one patient who was not able to tolerate sunitinib. One of the patients reported in that series was treated with sunitinib on the treatment-use protocol (case 1) and is included in this report. Duration of SD/PR in the patients who responded to sunitinib in that report was 8 months. Our results are consistent with the limited previously published data.

In this study, sunitinib appeared to have greater efficacy for pediatric GIST than imatinib. This outcome is consistent with previously reported biologic and clinical data: the GIST genotype was WT in all of the patients who had SD or PR and the potency of

sunitinib against WT KIT is 10 times higher than that of imatinib [8]. In addition, adult patients with WT GIST are among those with the greatest clinical benefit from sunitinib [17]. However, this was not a comparative trial, and conclusions about the relative efficacy of one drug versus another are speculative. Moreover, the study was restricted to patients with imatinib-resistant GIST, which could result in imatinib appearing less effective. However, the imatinib responses in the pediatric GIST patients described here were similar to those reported previously [8,28]. Nevertheless, the results of this study do not inform a recommendation about whether sunitinib or imatinib should be the first-line therapy in pediatric GIST, beyond suggesting that sunitinib has efficacy when given after imatinib. Because tumors resistant to imatinib may be sensitive to sunitinib and vice versa, sequential use of both drugs may prolong progression-free survival.

One important consideration in selecting first-line therapy for pediatric patients with GIST is toxicity. Sufficient data do not exist for a direct comparison of toxicities of imatinib and sunitinib in pediatric patients. In this study, serious adverse events to sunitinib were unusual. There were only three grade 3 events in two patients and no grade 4 toxicities. Nevertheless, all patients had at least one grade 1 or 2 adverse event. The adverse events seen in children in this study were similar to those seen in adults [5,29]. However, the small number of patients in the current study and the lack of patients less than age 10 limit the conclusions that can be drawn from these safety data. Until further data are available, patients younger than 10 years of age (the age of the youngest patient included in this study) should be treated with sunitinib only as part of a research protocol because dosing, adverse events, and drug metabolism are not well established in this age-group and because special drug formulations may be needed. A phase I study of sunitinib is currently being carried out by the Children's Oncology Group.

In conclusion, sunitinib therapy in pediatric patients with GIST following failure of imatinib resulted in PR or SD in six of seven patients for an average of 15 months without significant toxicity. In all but one patient with SD/PR, the TTP was greater with sunitinib than with imatinib.

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