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Tolerability and pharmacokinetic profile of a sunitinib powder formulation in pediatric patients with refractory solid tumors: a Children's Oncology Group study

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Abstract

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Purpose—Sunitinib is an oral tyrosine kinase inhibitor of VEGF, PDGF, c-KIT, and flt-3 receptors. A pediatric phase I study of sunitinib capsules identified the maximum tolerated dose as 15 mg/m^2/day. This study was conducted to evaluate sunitinib given as a powder formulation.

Methods—Sunitinib 15 mg/m^2 was administered orally daily for 4 weeks on/2 weeks off to patients <21 years old with refractory solid tumors. Sunitinib capsules were opened, and the powder sprinkled onto applesauce or yogurt. Plasma levels of sunitinib and an active metabolite, SU12662, were measured, and pharmacokinetic parameters were estimated.

Results—12 patients, median age 13 (range 4–21) years, were treated. The most common first-cycle toxicities were leucopenia (*n* = 6), fatigue (*n* = 5), neutropenia (*n* = 4), and hypertension (*n* = 4). Three patients had dose-limiting toxicities (DLTs) in cycle 1 (dizziness/back pain, hand–foot syndrome, and intratumoral hemorrhage/hypoxia). A median peak plasma sunitinib concentration of 21 (range 6–36) ng/ml was reached at a median of 4 (range 4–8) h after the first dose. The median exposure ($AUC_{0–48}$) was 585 (range 196–1,059) h ng/l. The median half-life was 23 (range 13–36) h. The median trough concentration measured before day 14 dosing was 32 (range 12–58) ng/ml.

Conclusions—The pharmacokinetic profile of sunitinib appears similar between a powder formulation and published data using capsules. The powder formulation allows patients unable to swallow capsules to receive sunitinib.

Keywords

Sunitinib; Pediatric; Pharmacokinetics; Formulation

Introduction

Sunitinib, an oral multi-targeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), c-KIT, Flt3, CSF-1 receptor, and RET [1–3], is approved for use in adults with advanced gastrointestinal stromal tumor (GIST) and renal cell carcinoma [4–6]. The approved adult dose is 50 mg/day for 28 days followed by a 14-day break [5, 7]. Following an initial dose of 50 mg, adults with cancer typically reach a maximum plasma concentration of 20–30 ng/ml within 5–7 h [7, 8]. This dosing leads to an exposure of approximately 350–450 h ng/l and a steady-state trough concentration of 40–80 ng/ml [7, 8]. Apparent clearance in adults has been reported to be 40–50 l/h [7, 9].

A phase I study of sunitinib capsules in children with refractory solid tumors identified a maximum tolerated dose of 15 mg/m^2/day for 28 days followed by a 14-day break in a cohort of patients without prior anthracycline or cardiac radiation exposure [10]. Adjusting for patient size and dose delivered, the pharmacokinetic profile of sunitinib was similar to the reported adult experience.

The aforementioned studies were conducted with intact sunitinib capsules. Young children and other patient groups have a limited ability to swallow capsules. The current report describes the results of a tolerability and pharmacokinetic study of a powder formulation of sunitinib in children with refractory or recurrent solid tumors. The primary aims of the study

were to describe the toxicities of sunitinib when administered as a powder sprinkled onto applesauce or yogurt and to characterize the pharmacokinetic profile of this formulation in children. Secondary endpoints included an assessment of antitumor efficacy and pharmacodynamic markers of antiangiogenesis.

Materials and methods

Patients

Patients were eligible for participation if they were 2–21 years of age, had histologic diagnosis of solid malignancy with measurable or evaluable disease, and had no known curative options. Patients were required to have a Karnofsky (age >10 years) or Lansky (age ≤10 years) performance score ≥50 and to have recovered from prior therapy. Patients were required to have adequate baseline bone marrow, renal, hepatic, pancreatic, and cardiac function according to defined protocol criteria. Patients with pre-existing hyper- or hypothyroidism were required to have stable thyroid function. Patients could not be receiving concomitant antihypertensive medications and had to have blood pressure <95th percentile for age, height, and gender.

Exclusion criteria included prior anthracycline or cardiac radiation exposure (due to cardiac toxicity observed in the pediatric phase I study); concurrent use of strong CYP3A4 inducers or inhibitors; treatment with agents that might increase the risk of bleeding complications; presence of pleural based tumors; uncontrolled infection; and allergy or intolerance to both applesauce and yogurt. Patients with known central nervous system (CNS) primary tumors or metastatic disease were excluded if they demonstrated any evidence of tumor-associated hemorrhage.

Each treating center's institutional review board approved the protocol. All patients or their legal guardians provided written informed consent before study participation.

Treatment and evaluations

Patients received sunitinib, 15 mg/m^2/day, orally once daily for 28 days followed by a 14-day break, such that the duration of one cycle of therapy was 42 days. Instructions were given to patients and caregivers for administering the drug using the powder within sunitinib capsules sprinkled onto either applesauce or yogurt. Specifically, sunitinib capsules were opened using gentle pressure applied to each end of the capsule while shaking over a level teaspoon of room temperature applesauce or yogurt until no more powder could be seen within the capsules. Patients ate the contents of the spoon without mixing within 30 min of first sprinkling the powder onto the food. These steps were repeated for each capsule required to administer the total daily prescribed dose. Patients were instructed to drink a minimum of 2 oz of water or apple juice after the full dose was administered. Drug was given without regard to other meals. Caregivers limited exposure to the sunitinib powder by using masks and gloves. No pregnant caregivers were to prepare the sunitinib doses.

The total daily sunitinib dose was rounded to the nearest 6.25 mg using a dosing nomogram. Patients were required to receive sunitinib as the powder formulation for the first dose; thereafter, patients who were able to swallow capsules had the option to change back to the

capsule formulation. Sunitinib was held on the second day of the first cycle so that the terminal half-life could be estimated. Patients without disease progression or unacceptable toxicity could receive up to 18 cycles of therapy.

Patients had routine physical examinations and surveillance laboratory testing to evaluate for toxicity. Electrocardiograms and echocardiograms were obtained during the 4 week of cycles 1, 2, 3, and then every third cycle. Thyroid-stimulating hormone (TSH) levels were obtained on day 28 of cycle 1, days 1 and 28 of cycle 2, and day 28 of every subsequent odd-numbered cycle.

Toxicities were graded according to the NCI Common Terminology Criteria, version 3.0. Dose-limiting toxicity (DLT) was defined as any of the following that were attributed as at least possibly related to sunitinib: grade 4 neutropenia; grade 4 thrombocytopenia; any grade 4 non-hematologic toxicity; grade 2 cardiac systolic dysfunction; blood pressure >25 mmHg above the 95th percentile for age, height, and gender; any grade 2 non-hematologic toxicity for ≥7 days that required drug interruption; any non-hematologic toxicity that required drug interruption for >7 days; or any grade 3 non-hematologic toxicity with the exception of nausea and vomiting of <3 days duration, ALT elevation that returned to baseline prior to the next cycle, AST elevation, fever of <5 days duration, electrolyte abnormalities responsive to oral supplementation, and asymptomatic elevations of amylase or lipase resolving to <grade 1 within 7 days of drug interruption.

Patients underwent disease re-evaluation at the end of cycle 1 and then every other cycle. For patients with measurable disease, tumor response was evaluated using RECIST [11].

Pharmacokinetic analysis

Serial plasma samples were obtained in all patients prior to sunitinib and 1, 2, 4, 6, 8–10, 24–28, and 48–52 h after the first dose. In the absence of early withdrawal from study, all patients had trough plasma samples obtained on days 7, 14, 21, and 28 of cycle 1. Plasma concentrations of sunitinib and its main active metabolite, SU12662, were measured using liquid chromatography–tandem mass spectrometry by Bioanalytical Systems, Inc (BASi; West Lafayette, IN), as previously described [12]. Sunitinib and SU12662 plasma concentration–time data were analyzed by standard non-compartmental methods using WinNonlin Pro (Pharsight Corp; Mountain View, CA).

Biomarker studies

Blood samples were obtained at baseline and day 28 of cycle 1 in consenting patients to evaluate plasma biomarkers of angiogenesis. VEGF, VEGFR2, placental growth factor (PlGF), and endoglin levels were measured by ELISA using commercially available kits (R&D Systems, Inc; Minneapolis, MN).

Statistical methods

Changes in biomarkers of angiogenesis obtained at baseline and at the end of cycle 1 were assessed using the Wilcoxon signed-rank test.

Results

Patient characteristics and dose delivery

Characteristics of the 12 patients treated with sunitinib as a powder formulation are shown in Table 1. Six patients were <12 years of age at study entry. Patients received a median of 1 cycle of therapy (range 1–9 cycles).

Nine patients received sunitinib as a powder formulation throughout the entire first cycle of therapy. Three patients changed to the capsule formulation on days 3 (n = 2) and 8 (n = 1) of the first cycle of therapy. In two of these cases, this change was made due to an aversion to the taste of the powder. For the other patient, this change was made due to the convenience of taking intact capsules. All patients treated with more than one cycle of therapy received sunitinib as intact capsules in subsequent cycles. Due to dose rounding to the nearest 6.25 mg, the 12 patients treated at a planned dose of 15 mg/m^2 received a median actual dose of 13.9 mg/m^2 (range 12.9–16.6 mg/m^2).

Toxicity of sunitinib administered as a powder formulation

Three of 12 patients experienced protocol-defined DLTs during the first cycle of therapy. These included grade 3 dizziness with back pain; grade 3 hand–foot syndrome; and grade 4 hypoxia in the setting of bleeding into a known site of a primary CNS tumor. The latter two patients had changed from powder formulation to intact capsule formulation on days 8 and 3 of cycle 1, respectively. DLTs occurred on days 22 and 17 of cycle 1, respectively. Two patients developed protocol-defined DLTs in subsequent cycles of therapy while receiving sunitinib as intact capsules: grade 3 proteinuria and grade 3 alkaline phosphatase.

Additional non-dose-limiting toxicities observed in more than 10% of patients in the first cycle of therapy are shown in Table 2. The most common first-cycle toxicities were leucopenia (n = 6), fatigue (n = 5), neutropenia (n = 4), and hypertension (n = 4). Two patients developed grade 1 increased thyroid-stimulating hormone levels during the first course of therapy.

Pharmacokinetics

Pharmacokinetic parameters for the 12 patients treated with the powder formulation are shown in Table 3. For comparative purposes, previously published parameters are also presented for pediatric patients treated with a dose of 15 mg/m^2 using the capsule formulation [10].

All 12 patients provided serial plasma samples following the first dose of the powder formulation for the determination of pharmacokinetic parameters (Table 3). The time to maximal sunitinib concentration (T_{max}) appeared to be earlier with the powder formulation compared to the capsule formulation (median 4.0 h vs. 7.0 h, respectively). Despite this difference, the peak plasma sunitinib concentration did not appear to differ between the two formulations (median 21.3 ng/ml vs. 16.8 ng/ml, respectively). Other pharmacokinetic parameters for sunitinib or its metabolite, SU12662, did not appear to differ substantially between powder and capsule formulations.

Ten patients submitted at least one sample for the evaluation of steady-state trough levels while still receiving sunitinib as the powder formulation (Fig. 1). Median trough concentrations of sunitinib, the active metabolite SU12662, and total drug (sunitinib + SU12662) were similar on days 7, 14, 21, and 28, with steady state reached by day 7. At each time point, no more than one-third of patients receiving powder formulation had total drug trough concentrations >50 ng/ml, the target concentration derived from preclinical studies [2]. Two of the three patients with DLT in the first course had day 7 total drug trough concentrations >50 ng/ml.

Antitumor activity

Six of 12 patients had disease progression in the first cycle of therapy. Two patients with high-grade glioma and ependymoma had confirmed stable disease for 3 and 9 cycles, respectively. Both patients received the capsule formulation after the first cycle of therapy and remain on study therapy.

Plasma biomarkers of angiogenesis

Five patients had paired baseline and day 28 plasma samples available for the evaluation of angiogenic factor biomarkers by ELISA. Plasma-soluble VEGFR2 levels decreased significantly over 28 days of therapy [median baseline level 10,072 ng/ml (range, 7,840–11,243) versus 6,821 (range 6,304–10,169) ng/ml at day 28; $P = 0.043$]. Similarly, plasma endoglin levels decreased over the first cycle of therapy [median baseline level 4.4 (range 3.8–5.8) pg/ml versus 3.8 (range 3.0–4.6) pg/ml at day 28; $P = 0.043$]. Plasma VEGF and placental growth factor levels did not change consistently with sunitinib therapy.

Discussion

Sunitinib is commercially available as capsules, limiting availability of this oral antiangiogenic agent to patients who are able to swallow intact capsules. The current study provides detailed clinical, pharmacokinetic, and pharmacodynamic data for the administration of sunitinib using the active drug contained within sunitinib capsules. The results of this study indicate that sunitinib administration as powder on applesauce or yogurt provides an alternative mode of administration for patients who are unable to swallow capsules. While this study was conducted in children, the results may apply to adults since the pharmacokinetics of sunitinib appear similar in these two populations, accounting for differences in dose received and patient size. Therefore, young children and older patients with swallowing dysfunction may benefit from the current findings.

Prior to the current study, two previous reports described alternative sunitinib formulations [13, 14]. In one study, a powder in bottle formulation was developed specifically for first in human clinical testing [14]. This formulation is not commercially available. In the second study, a sunitinib suspension was developed using commercially available capsules, though clinical results with this extemporaneous formulation are not available [13].

The toxicity profile of sunitinib in the current study was similar to previous evaluation of sunitinib in children [10, 15]. Although 3/12 patients in the current study had protocol-defined DLTs in the first cycle and 0/6 patients had DLTs with this same dose in the

previous phase I study of sunitinib capsules, this finding most likely reflects the small number of patients receiving these formulations since the pharmacokinetic profile of the two modes of administration was similar. Moreover, two of the patients with DLT in the current study changed from the powder to capsule formulation 14 days prior to onset of DLT.

The pharmacokinetic parameters estimated following day 1 dosing were approximately similar between children receiving either powder or capsule formulation [10] although an earlier time to maximal concentration was observed with the powder formulation. At steady state, median sunitinib, SU12662, and total drug concentrations were similar between powder and capsule formulations. However, a lower proportion of patients treated with the powder formulation had total drug concentrations that exceeded the target concentration of 50 ng/ml compared with results observed with the capsule formulation [10]. Specifically, weekly trough total drug concentrations were > 50 ng/ml in at least a third of patients treated with capsules, while less than a third of patients achieved these levels with the powder formulation in the current study. Plasma concentrations were obtained using identical blood sampling and plasma analysis methods in both studies, decreasing the likelihood that any observed differences may reflect methodological differences. Additional studies with larger numbers of patients will be necessary to determine whether the steady-state pharmacologic properties of these two formulations differ.

In previous studies, a decrease in soluble VEGFR2 has been among the most consistent pharmacodynamic markers of sunitinib activity [16–18]. This same finding was previously observed in pediatric patients treated with sunitinib capsules, along with decreases in plasma endoglin [10]. In the current study, these same biomarkers were modulated using sunitinib given as a powder formulation, indicating pharmacodynamic activity with this dose and formulation.

In conclusion, the pharmacokinetic profile of a sunitinib powder formulation appears similar to results obtained with capsules, though trough levels may be lower with the powder formulation. A similar range of toxicities was observed with the powder formulation compared to previous studies of capsules. Pharmacodynamic modulation of angiogenesis-related biomarkers was also achieved with the powder formulation at the maximum tolerated pediatric dose of 15 mg/m^2. Given these findings, administration of sunitinib as a powder formulation to patients unable to swallow capsules appears to be feasible.

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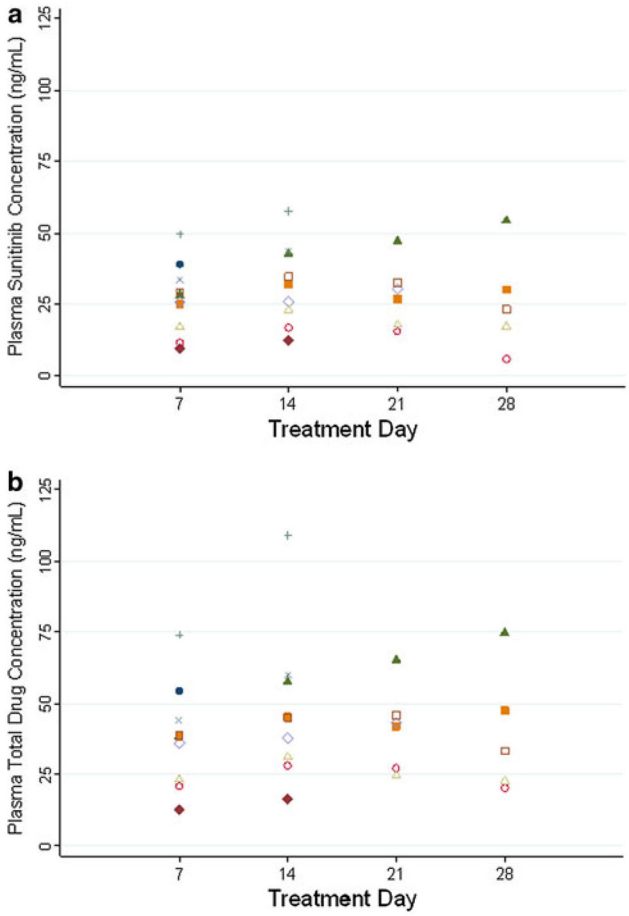

Fig. 1.

Trough plasma concentrations (ng/ml) of sunitinib (**a**) and total drug (sunitinib plus SU12662) (**b**) on days 7–28 of sunitinib therapy (15 mg/m^2) in 10 patients treated with powder formulation. Values reflect only patients who were receiving the powder formulation on the given days

Table 1

Characteristics of 12 patients treated with powder formulation of sunitinib

	***N* = 12**
Median age, years (range)	13.1 (4.2 – 21.5)
Boys : Girls	5 : 7
Diagnosis	
High-grade glioma	5
Brain stem glioma	4
Ependymoma	1
Mesothelioma	1
Undifferentiated carcinoma	1
Prior receptor tyrosine kinase inhibitor	2[a]
Median number sunitinib cycles (range)	1 (1–9)

[a] Pazopanib (*n* = 1) and erlotinib (*n* = 1)

Table 2

Hematologic and non-hematologic toxicities observed in 12 patients treated with a powder formulation of sunitinib

	Course 1 (total, 11 courses[a])			Courses 2–9 (total, 15 courses)[b]		
	Maximum grade			Maximum grade		
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Leukopenia	36	18		7	13	
Lymphopenia	18	9				7
Neutropenia		27	9	7	7	
Thrombocytopenia	18	9		7		
Hypertension	27	9				
Fatigue	27	18		7		
Dry skin	18					
Diarrhea	9	18				
Nausea	18	9				
Taste alteration	18					
Vomiting	9	18				
Epistaxis	18					
ALT elevation	27			20		
Hypocalcemia	18			7	7	
Hypermagnesemia	18			13		
Dizziness		9	9	7		
Mood alteration	9	9				
Abdominal pain	18					
Headache		18		7		

Only toxicities possibly, probably, or definitely related to sunitinib and which occurred in more than 10% of patients in cycle 1 are displayed. Values represent percent of patient cycles with listed toxicity according to grade

[a] One patient was not fully evaluable for toxicity in cycle 1 due to early disease progression

[b] At time of data cutoff, 2 patients were still on therapy in courses 5 and 10. Table reflects toxicities experienced up through and including courses 4 and 9 in these patients, respectively

Table 3

Detailed day 1 pharmacokinetic parameters for sunitinib and SU12662 in 12 pediatric patients treated with sunitinib 15 mg/m^2 given as a powder formulation, compared to previous results in 8 pediatric patients treated with sunitinib 15 mg/m^2 given as capsules [10]

Formulation	*N*	Sunitinib						SU12662			
			T_{max} (h)	C_{max} (ng/ml)	$AUC_{0–48h}$ (h ng/l)	$AUC_{0–\infty}$ (h ng/l)	Cl/F (l/hr/m^2)	Half-life (h)	T_{max} (h)	C_{max} (ng/ml)	$AUC_{0–48h}$ (h ng/l)	Half-life (h)
Powder	12	Median	4.0	21.3	585	791	18.8	22.7	6.6	3.9	163.1	54.1
		Min	4.0	6.1	196	292	11.8	12.7	4.0	0.0	0.0	24.4
		Max	8.0	35.9	1,059	1,396	44.3	36.4	25.9	12.2	307.8	357.5
Capsule	8	Median	7.0	16.8	492	747	19.5	24.1	8.0	2.3	76	88.5
		Min	2.0	9.5	247	298	6.8	17.8	4.0	1.5	38	45.8
		Max	48.0	61.4	1,111	5,365	43.3	76.4	48.7	8.5	285	127.2

T_{max} time to maximum plasma concentration, C_{max} maximum plasma concentration, $AUC_{0–\infty} = AUC_{0–48h} + C_{48h}/k_{el}$, where k_{el} (terminal elimination rate constant) was calculated by linear least squares regression of the linear terminal elimination phase of the graph of ln(plasma concentration) versus time