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ORIGINAL ARTICLE

A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period

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Abstract
Purpose Sunitinib, an oral multitargeted tyrosine kinase inhibitor that inhibits VEGFR, PDGFR, FLT3, KIT, and RET, is currently approved for the treatment of imatinib-refractory GIST and advanced renal cell carcinoma at a dose of 50 mg daily for 4 weeks followed by a 2-week off period (4/2 schedule). This trial was performed to investigate the safety, tolerability, and pharmacokinetics of sunitinib 50 mg daily for 2 weeks followed by a 1-week off period (2/1 schedule).
Experimental design Twelve patients with advanced refractory malignancies were treated with sunitinib on the 2/1 schedule. Intensive safety monitoring included serial measurements of left ventricular ejection fraction (LVEF). Extensive pharmacokinetic sampling was performed on days 1 and 14 of course 1, and on day 14 of courses 2 and 3 to evaluate sunitinib and the SU12662 metabolite.
Results Twelve patients received a total of 50 courses with an average (±SD) off-drug period of 11.5 ± 5.7 days. Two patients experienced DLT: one patient had asymptomatic grade 4 elevations in lipase and amylase, and another patient had an asymptomatic grade 2 decline in LVEF in course 1. In total, five patients demonstrated asymptomatic grade 2 declines in LVEF. Other principal effects were similar to previous experience with sunitinib, including fatigue, myelosuppression, skin discoloration, and gastrointestinal effects. Pharmacokinetic studies revealed no significant accumulation of sunitinib or SU12662. One patient with papillary thyroid cancer developed a partial response, and was on study for 16 courses, followed by an additional 18 courses on a continuation protocol.
Conclusions The 2/1 schedule of sunitinib 50 mg was tolerable, and no significant drug accumulation was demonstrated. The safety profile on this schedule was consistent with the safety profile of sunitinib when administered on a 4-week on, 2-week off schedule.

Keywords Pharmacokinetics · Phase I · Solid tumors · Sunitinib (SU11248; SUTENT®) · Tyrosine kinase inhibitors

Introduction

Sunitinib malate (SUTENT®; Pfizer Inc., New York, NY) is a small molecule tyrosine kinase inhibitor (TKI) targeting class 3 and 5 split-kinase domain receptor tyrosine kinases (RTKs) including platelet-derived growth factor receptor-α and -β, KIT, FLT3, and vascular endothelial growth factor receptor (VEGF)-1 and -2 [1, 13, 19]. In biochemical and cell-based assays, sunitinib inhibits the targeted RTKs at low nanomolar concentrations [1, 13, 19]. In vitro, sunitinib inhibits stem cell factor-induced proliferation of KIT-positive small cell lung cancer cells [1], and it inhibits proliferation of MV4;11 human leukemia cells driven by constitutively active FLT3 receptors [19]. In vivo, oral sunitinib at doses of 40 mg/kg/day causes regression or

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tumor growth inhibition in a variety of s.c. human tumor xenograft models [1, 2, 13]. Most of these xenografts do not express the RTKs targeted by sunitinib, suggesting that the antitumor activity in these models is due to antiangiogenesis. In support of this hypothesis, sunitinib reduces tumor microvessel density and vascular permeability in established tumors [12, 13]. Also, sunitinib impairs endothelial cell migration and tubule formation in vitro, and blood vessel formation in vivo [20]. Taken together, the preclinical data demonstrate that sunitinib has direct antiproliferative activity against tumors harboring the targeted RTKs, but its broad spectrum of antitumor activity is likely due to antiangiogenesis.

In the clinic, sunitinib's promising preclinical data translated into impressive anticancer activity with manageable toxicity. At the recommended dose of sunitinib 50 mg orally once daily for 4 weeks followed by a 2-week off-drug period, the most common toxicities include fatigue, diarrhea, nausea, hypertension, bleeding, mucositis, skin abnormalities, and altered taste [5, 15, 16]. In phase II trials for patients with cytokine-refractory renal cell cancer [15, 16], sunitinib produced response rates of 39–40%, stable disease rates of 23–27%, a median time to tumor progression of 8.7 months, and a median overall survival of 16.4 months [15, 16]. In a randomized phase III trial in cytokine naïve patients, patients receiving sunitinib demonstrated a clinically significant improvement in progression-free survival compared to those receiving interferon-α (11 vs. 5 months) [17]. In a randomized double-blind placebo-controlled phase III trial for patients with imatinib-refractory gastrointestinal stromal tumor (GIST) [5], sunitinib resulted in a time to tumor progression of 6.3 months for patients treated with sunitinib, compared to 1.5 months for patients in the placebo arm [5]. Sunitinib also decreased the risk of death of GIST patients by 50% compared to placebo [5]. Sunitinib is currently approved by the Food and Drug Administration in imatinib-refractory GIST and advanced renal cell carcinoma, and additional clinical trials are ongoing in a variety of malignancies.

The initial clinical trials with sunitinib employed intermittent dosing schedules with a 2-week off-drug period (schedule 2/2). This early schedule was selected based on the preclinical toxicology data available at the time clinical investigation was initiated in 2001. However, preclinical experiments have demonstrated tumor growth during the off-dosing period [2], suggesting that sunitinib may be most effective with more continuous dosing. Also, in a phase I trial for patients with acute myelogenous leukemia (AML), four of seven responding patients experienced a rise in peripheral blood blasts during the off-drug period [8]. Therefore, after initial clinical trials demonstrated favorable antitumor activity and toxicity profiles, this phase I trial was undertaken to investigate sunitinib administration in 3-week courses, to better fit the schedule used for administration of commonly used chemotherapies, and to increase the total exposure time by reducing the length of the off-drug period. In this phase I trial for patients with solid tumors, sunitinib 50 mg orally once daily was administered for 2 weeks, followed by a 1-week off period (2/1 schedule). Although dose escalation was originally planned, dose levels above 50 mg were removed through protocol amendment when emerging data from ongoing trials identified 50 mg as the recommended dose for the 4/2 and 2/2 schedules [7, 8, 21]. The objectives of this trial were to: (1) determine the safety and tolerability of the 2/1 schedule of sunitinib in subjects with solid tumors; (2) evaluate the pharmacokinetic behavior of sunitinib on the 2/1 schedule; and (3) explore the clinical antitumor activity of sunitinib.

Methods

Patient selection

Adult patients with histologically confirmed advanced solid malignancies refractory to standard therapy or for whom no effective therapy existed were candidates for this study. Other eligibility criteria included: (a) Karnofsky performance status (KPS) ≥70% (able to care for self); (b) adequate hematopoietic [absolute neutrophil count ≥1,000/μl, platelets ≥50,000/μl, hemoglobin (Hb) ≥8 g/dl], hepatic [total serum bilirubin ≤2 times the upper limit of normal (ULN), transaminases ≤2.5 times ULN or ≤5 times ULN in the presence of liver metastases], renal (serum creatinine <1.5 times ULN, or calculated creatinine clearance >40 ml/min), and adrenal [normal adrenocorticotropic hormone (ACTH) stimulation test] function; (c) adequate cardiac function [left ventricular ejection fraction (LVEF) ≥ lower limit of normal (LLN) as assessed by echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan and serum cardiac troponin T (cTnT) and/or serum cardiac troponin I (cTnI) ≤ ULN] function; (d) no cardiovascular, cerebrovascular, or thromboembolic event within the previous 12 months; (e) no symptomatic congestive heart failure within the previous 12 months; (f) no ongoing cardiac dysrhythmias of National Cancer Institute (NCI) Common Toxicity Criteria (CTC) grade ≥ 2, atrial fibrillation of any grade, or prolongation of the corrected QT interval to >450 ms for males or >470 ms for females within the previous 12 months; (g) no chemotherapy, radiotherapy, or biologic therapy within the previous 3 weeks; (h) no nitrosoureas or mitomycin C within the previous 6 weeks; (i) no investigational agents within the previous 4 weeks; and (j) no known central nervous system metastases. Females of childbearing age were required to be practicing effective contraceptive measures and to have had a negative

serum pregnancy test before study entry. Written informed consent was obtained according to federal and institutional guidelines.

Drug dosage and schedule

The first six patients were to receive sunitinib 50 mg orally once daily for 14 days followed by a 7-day off period. A dose of 50 mg was chosen because it was well tolerated when administered daily for 2 or 4 weeks followed by a 2-week off period, and it produced the preclinically-predicted target plasma concentration of ≥50 ng/ml in other phase I studies [4, 7, 21]. Once at least four patients completed course 1 without dose-limiting toxicities (DLTs), up to an additional six patients were to be enrolled at the 50 mg dose level. The original protocol allowed an additional cohort of patients to be enrolled at 75 mg. However, when the maximum tolerated dose of 50 mg was established for the 2/2 and 4/2 schedules, dose escalation to 75 mg was omitted for the 2/1 schedule.

Dose-limiting toxicity was defined as any one of the following: (a) grade 4 hematologic toxicity associated with sunitinib of at least 7 days' duration; (b) grade 4 hematologic toxicity complicated by grade ≥ 2 fever (temperature ≥ 38°C), grade 3 or documented infection, hemorrhage, or the need for blood product support; (c) grade 3 thrombocytopenia with grade 3 or 4 hemorrhage; (d) grade 3 or 4 nausea and vomiting refractory to anti-emetic therapy; (e) clinical or radiographic evidence of left ventricular dysfunction as defined by the development of congestive heart failure (new cardiomegaly by X-ray, S3 gallop, paroxysmal nocturnal dyspnea, and/or orthopnea), decline from baseline in LVEF by ≥20% and to less than the LLN, or a LVEF of ≥10% below the LLN; (f) cTnT and/or cTnI above the institutional ULN; (g) any other grade ≥ 3 nonhematologic toxicity at any time, excluding asymptomatic, uncomplicated grade 3 increase in serum lipase levels. Grade 4 increases in serum lipase levels, or grade 3 increases in serum lipase levels associated with clinical or radiographic evidence consistent with pancreatitis; however, were considered unacceptable. Toxicities were graded according to the NCI CTC, version 2.0.

Patients were permitted to continue treatment with sunitinib at the same dose and schedule after an off-drug period of no less than 7 days following the last dose of the previous course as long as there was no evidence of progressive disease or DLT and as long as: (a) any other sunitinib-associated toxicity of grade ≥ 2, or any other grade 3 toxicity had recovered to baseline levels or to grade ≤ 1; (b) pharmacokinetic evaluations (if available) suggested that the combined concentrations of the drug and active metabolite were <25 ng/ml at the end of the off-drug period; (c) there was no evidence of left ventricular dysfunction; and (d) there was no evidence of adrenal dysfunction. Patients who developed DLT were required to discontinue sunitinib immediately, and they were permitted to resume study treatment at a reduced dose if there was reasonable evidence of clinical benefit to justify continuation, once all toxicity had resolved or returned to baseline. Patients who developed cTnT or cTnI levels above the institutional ULN or had evidence of cardiac dysfunction were required to discontinue sunitinib immediately, but they could resume study treatment after discussion with a cardiologist, provided all other cardiac safety evaluations were normal, and if there was reasonable evidence of clinical benefit to justify continuation of dosing. Patients continuing treatment after the third course could have their dose adjusted in 12.5 mg increments per course (range 25–75 mg/day) based on tolerance. In the absence of DLT or progressive disease, treatment with additional courses could continue for up to 1 year. A separate continuation protocol was instituted for patients who required therapy beyond 1 year or beyond termination of the study.

Drug administration

Sunitinib was supplied by Pfizer Global Research and Development (La Jolla, CA) as hard gelatin capsules in strengths of 12.5, 25, or 50 mg. Patients swallowed sunitinib once daily in the morning, with a glass of water, and without regard to meals.

Pretreatment and follow-up studies

Prior to the first course of treatment, histories and physical examinations were performed, and the following evaluations were also obtained: complete blood count, routine chemistries and electrolytes, pancreatic lipase and amylase, clotting studies, cardiac enzymes, urinalysis, ACTH stimulation testing, 12-lead electrocardiogram (ECG) (three times at 30-min intervals), and ECHO or MUGA scan.

Intensive monitoring during this exploratory study included complete blood count, routine chemistries and electrolytes, and pancreatic lipase and amylase on days 1 and 14 of every course. Cardiac enzymes (cTnI) were obtained weekly throughout the study, and LVEF was assessed by either ECHO or MUGA scan on day 14 of odd-numbered courses. An ACTH stimulation test was performed on day 14 of odd-numbered courses.

Computed tomography and/or magnetic resonance imaging to document disease status and to image the adrenal glands was performed pretreatment and after every three courses. Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Pharmacokinetic sampling and assay

To determine the pharmacokinetic (PK) behavior of the parent compound sunitinib and the primary, active, metabolite SU12662 on the 2/1 schedule, full PK blood sampling (pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 20, and 24 h post-dose) was performed on days 1 and 14 of course 1, and on day 14 of courses 2 and 3. Trough plasma drug samples were drawn on day 7 of course 1, days 1 and 7 of courses 2 and 3, and days 1 and 14 of subsequent courses. Samples (4 ml) were collected in tubes containing ethylenediaminetetraacetic acid, placed on wet ice, and centrifuged at 3,500 rpm at 4°C for 10 min. Plasma was separated and divided between two 1.5-ml Nalgene cryovials (Nalgene, Rochester, NY), and stored at −80°C protected from light until analysis.

Sunitinib and SU12662 concentrations were measured by liquid chromatography–tandem mass spectrometry. Briefly, the plasma samples were extracted by protein precipitation with methanol in a 96 well plate. The analytes were detected by positive ionization Turbo-Ionspray™ ionization in multiple reaction-monitoring mode. Weighted [1/(concentration^2)] linear regression analysis was used to generate data for calibration curves and to calculate the sample results. The calibration curve was linear over the concentration range of 0.100–100.0 ng/ml for sunitinib and SU12662.

Pharmacokinetic analysis

Individual sunitinib and SU12662 plasma concentration-time data sets were analyzed by model-independent methods using the software program WinNonlin, version 3.2 (PharSight Corp, Mountain View, CA). Area under the concentration-time curve from time 0 to 24 h ($AUC_{0–24}$), maximum concentration (C_{max}), trough concentration (C_{trough}), time to C_{max}, and half-life were calculated for both sunitinib and SU12662. Totals for sunitinib plus SU12662 were calculated without adjusting for modest differences in molecular weight. Summary statistics were calculated using Statistical Analysis System, version 8.2 (SAS Institute, Cary, NC).

Fatigue assessment

Patients completed the Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) before receiving sunitinib on day 1 (as the baseline assessment) and weekly during the first six courses (18 weeks). The scale is a validated questionnaire that contains 13 questions measuring fatigue in cancer patients [23]. The FACIT-Fatigue score may range from 0 (most fatigue) to 52 (no fatigue). Data were analyzed for all patients and for subgroups based on baseline characteristics; these subgroups include less versus more fatigue (FACIT-Fatigue score >43.5 vs. <43.5), good versus relatively poor performance status (KPS score >80% vs. =80%), and normal Hb versus anemia (Hb > LLN vs. <LLN). Post-baseline scores were also summarized for the assessments during and right after the treatment (days 7 and 14) versus after the 7-day off-drug period (day 1 or next course). Due to the small sample size, only the descriptive statistics (medians and means) were used.

Results

General

Twelve patients, whose characteristics are detailed in Table 1, were treated with 50 (48 complete) courses of sunitinib on the 2/1 schedule. The median number of courses per patient was three (range 1–16), and one patient who received 16 courses subsequently received an additional 18 courses through a continuation protocol.

No patient underwent dose escalation, and four patients required dose reduction to 37.5 mg. The first patient, reduced on course 2 day 1 for grade 2 fatigue and neutropenia, received 15 courses at 37.5 mg. The second patient, reduced on course 2 day 1 for dose-limiting elevations in amylase and lipase, received two courses at 37.5 mg before developing progressive disease. The third patient, reduced on course 3 day 1 for grade 3 neutropenia, was ultimately withdrawn from study after course 3

Table 1 Patient's characteristics

Characteristic		No. of patients
Total no. of patients		12
Gender (male:female)		9:3
Median age in years (range)	57 (28–75)	
Karnofsky performance status		
100%		1
90%		5
80%		6
Tumor type		
Colorectal		2
Gastrointestinal stromal tumor		2
Neuroendocrine		2
Thyroid		2
Other (angiosarcoma, larynx, hepatocellular, pancreas)		1 Each
Prior treatment		
Radiation		8
Systemic therapy		10

due to persistent grade 2 neutropenia. The fourth patient, reduced on course 2 day 1 due to grade 3 thrombocytopenia, withdrew from study during course 2 with grade 2 foot pain.

Dose delay, defined as prolongation of the off-drug period, was required by four patients due to drug-related toxicities, and by an additional two patients due to disease-related complications. Overall, the average (±SD) duration of the off-drug period was 11.5 ± 5.7 days. The cumulative number of patients receiving sunitinib on schedule per course is listed in Table 2.

In addition to dose reduction and dose delay, four patients experienced dose interruption, defined as a break in the continuous dosing period: one patient experienced disease-related complications; one patient developed progressive disease before completing course 2; one patient withdrew due to foot pain; and one patient forgot one dose during each of courses 9, 12, 14, and 15. Among the ten patients who received multiple courses of sunitinib on the 2/1 schedule, only two patients received 50 mg daily without dose reduction, delay, or interruption.

Two patients experienced DLT as pre-defined by protocol. A 65-year-old woman with colorectal cancer developed asymptomatic grade 4 elevations in lipase and amylase on course 1 day 14. These laboratory abnormalities recovered to normal within 7 days, and subsequent courses were administered at a dose of 37.5 mg orally once daily without further abnormalities. The patient was subsequently taken off study after course 3 for progressive disease. The second patient with DLT, a 75-year-old man with squamous cell cancer of the larynx, a history of smoking, and no prior history of cardiac disease, developed an asymptomatic decline in his LVEF as measured by ECHO from 50–55% at baseline to 40–45% on course 1 day 14. A confirmatory MUGA on course 1 day 17 revealed an LVEF of 45%, and no further assessment of LVEF was performed. He was withdrawn from study due to the decline in LVEF, and he died as a result of his underlying malignancy 27 days after his last dose of sunitinib.

Safety and tolerability

Overall, sunitinib was well tolerated and toxicities were manageable. The most common sunitinib-related toxicities are listed by maximum CTC grade in Table 3.

Table 3 Most common sunitinib-related toxicities by maximum CTC grade

Toxicity	No. of patients with toxicity by maximum CTC grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Fatigue	7	3	0	0	10
Neutropenia	2	3	3	0	8
Skin discoloration	7	0	0	0	7
Elevated lipase	4	1	0	1	6
Thrombocytopenia	3	0	3	0	6
Anemia	4	1	1	0	6
Decreased appetite	4	1	0	0	5
Decreased LVEF	0	5	0	0	5
Diarrhea	5	0	0	0	5
Nausea/vomiting	3	2	0	0	5
Hypertension	2	1	1	0	4
Dyspepsia	2	1	0	0	3
Urine discoloration	3	0	0	0	3

CTC common toxicity criteria, *LVEF* left ventricular ejection fraction

Table 2 Number of patients treated per course

Course	No. of patients who began course on time	No. of patients who began course after delay for			Total (completed)
		Myelosuppression	Other toxicity	Disease complication	
1	12	N/A	N/A	N/A	12 (12)
2	6	1	2[a]	1	10 (8)[b]
3	6	1	0	0	7 (7)
4	2	0	0	2	4 (4)
5	4	0	0	0	4 (4)
6	2	0	0	1	3 (3)
7+	1[c]	1[c]	1[c]	0	1 (1)

N/A not applicable

[a] One patient was delayed for the combination of grade 2 fatigue and neutropenia. Another was delayed for grade 2 decline in left ventricular ejection fraction

[b] One patient withdrew from study on course 2 day 13 due to foot pain. Another withdrew on course 2 day 6 due to progressive disease

[c] One patient received more than six courses. Her 7th and 9th courses were delayed due to grade 2 neutropenia. Her 13th course was delayed for treatment of grade 3 pulmonary embolus

Fatigue

Ten patients experienced grade 1–2 fatigue and/or exacerbation of fatigue. Fatigue was systematically evaluated using the FACIT-Fatigue scale [23]. Patients completed the questionnaire with good compliance: 100% of FACIT-Fatigue questionnaires were completed at days 1, 7, and 14 of each course for all courses, except 80% completed at course 2 day 14. Mean and median baseline FACIT-Fatigue scores for all patients were 41.5 and 43.5, respectively, which are similar to the scores of patients with metastatic renal cell carcinoma (40.4 and 44.0, respectively) [16], and to the scores of a non-anemic cancer population (40.0 and 42.0, respectively), but lower than the scores of a general US population (43.6 and 47.0, respectively) [3]. Mean and median post baseline FACIT-Fatigue scores through 18 weeks (six courses) of treatment were 42.3 and 43.0, respectively, which were similar to the baseline scores. There was no clear effect of the 7-day rest period on the fatigue score: post-baseline scores were the same between the assessments during/after the treatment and the assessments after the 7-day rest period. Sub-set analysis suggested that baseline fatigue was related to baseline performance status and Hb level (mean fatigue scores were 42.3 for KPS > 80% vs. 40.6 for KPS = 80%, and 43.2 for Hb > LLN vs. 40.2 for Hb < LLN), and baseline fatigue level and performance status were associated with fatigue level during treatment (mean post-baseline fatigue scores were 43.7 vs. 40.8 for high vs. low baseline fatigue scores, 44.0 vs. 40.9 for high vs. low KPS scores); however, baseline Hb level did not seem to be associated with fatigue level during treatment.

Cardiovascular effects

In this exploratory study, cardiac monitoring included ECGs, measurement of the cardiac-specific enzyme cTnI, and assessment of LVEF by ECHO and/or MUGA. There were no clinically significant ECG abnormalities. One patient developed a borderline cTnI while in hospital for bacteremia and gastrointestinal bleeding, but no other patients developed an abnormal cTnI.

In this study in which frequent measurements of LVEF were performed, five patients had LVEF measurements that were below the LLN (50%). Circumstances surrounding the grade 2 asymptomatic decreases in LVEF are outlined in Table 4. No patient experienced symptoms of cardiac dysfunction. Four patients were withdrawn from study in the setting of decreased LVEF: one had DLT; two had stable disease after six courses; and one had progressive disease after two courses. A fifth patient, a 37-year-old man with GIST, developed a transient grade 2 decrease in LVEF from 65% at baseline to 43% on course 1 day 14, measured by MUGA. A comprehensive evaluation of cardiac function by stress echocardiogram 13 days later revealed a normal resting LVEF of 50%, with an appropriate increase to 70–75% with exercise. This was not considered a DLT because the course 1 day 14 MUGA results could not be corroborated. The patient was allowed to continue sunitinib with the approval of the sponsor and the institutional review board. He received an additional four courses, and during the remainder of his treatment, his LVEF was 60% or greater by MUGA.

Four patients developed hypertension, likely related to sunitinib, including one patient who required antihypertensive treatment. The event of grade 3 hypertension occurred on course 1 day 14, but it was not considered a DLT because it responded to treatment immediately.

Pancreatic enzyme abnormalities

One patient developed asymptomatic grade 4 elevated lipase and amylase on course 1 day 14, constituting a DLT. Three patients experienced sunitinib-related asymptomatic transient grade 1–2 elevations of lipase, as outlined in

Table 4 Characteristics of patients with grade 2 cardiac toxicity

Age	Cancer diagnosis	Cardiac risk factors	Prior anthracycline	LVEF[a]			Disposition
				Baseline (%)	Lowest	Follow-up[b]	
75	Larynx	Smoker	No	50–55	40–45% (C1D14)	45%* (3 days)	Off study for DLT
28	Neuroendocrine	None	Yes	55–60	45–50% (C6D14)	50% (20 days)	Off study for decreased LVEF
66	Neuroendocrine	IDDM	No	50–55	45% (11 d after C6D14)	50% (6 days)	Off study for decreased LVEF
55	Pancreas	None	No	50–55	48–50% (C2D14)	50% (14 days)	Off study for clinical PD
37	GIST	None	Yes	65*	43%* (C1D14)	50% (13 days)	Received an additional 4 courses

LVEF left ventricular ejection fraction, *DLT* dose-limiting toxicity, *IDDM* insulin-dependent diabetes mellitus, *PD* progressive disease, *GIST* gastrointestinal stromal tumor, *ECHO* echocardiogram

[a] All LVEF assessments performed using ECHO, except where marked by an asterisk

[b] Time interval between lowest LVEF and follow-up LVEF is noted in parentheses

Table 3. Two other patients experienced elevated lipase and/or amylase more than 3 weeks after their last dose of sunitinib, and these laboratory abnormalities were attributed to disease. No pancreatitis was observed.

Effects on the adrenal gland

Frequent monitoring of adrenal gland anatomy and function failed to reveal any clinically-significant toxicity. All adrenal imaging scans were normal, without evidence of adrenal hemorrhage. Among the three patients who developed abnormal cosyntropin stimulation tests during sunitinib treatment, none required hormone replacement therapy, and one returned to normal after discontinuation of sunitinib. An additional patient with panhypopituitarism was permitted to participate despite an abnormal test at baseline, and he did not require any change in his hormone replacement therapy while on study.

Pharmacologic studies

Individual and median C_{trough} plots showed that steady state concentrations were generally achieved by days 7–14 for sunitinib and by day 14 for SU12662. Median concentration-time profiles are depicted in Fig. 1, and pertinent pharmacokinetic parameters are outlined in Table 5. Once daily dosing for 14 days resulted in an approximately 4.5-fold accumulation of sunitinib, tenfold accumulation of SU12662, and fivefold accumulation of total drug (sunitinib plus SU12662) on day 14 compared with day 1. Sunitinib and SU12662 were both detectable before dosing on day 1 of courses 2 and beyond, indicating incomplete washout during the off-drug period. However, the mean and/or median intrapatient accumulation ratios for C_{max} and AUC_{0-24} between courses 1 and 2 (day 14) were close to one for all analytes, demonstrating no significant further accumulation in subsequent courses compared to course 1. The interpatient variability accounted for the difference observed in median sunitinib and SU12662 concentrations during courses 1, 2, and 3; individual AUC_{0-24} values on day 14 were comparable between courses.

Efficacy

There was one confirmed partial response in a 73-year-old woman with radiation-associated papillary thyroid cancer metastatic to lung and bone. This patient was on study for 16 courses, and completed an additional 18 courses on a continuation protocol before developing progressive disease. Two patients with neuroendocrine malignanices, removed from study due to asymptomatic declines in LVEF, had stable disease after six courses.

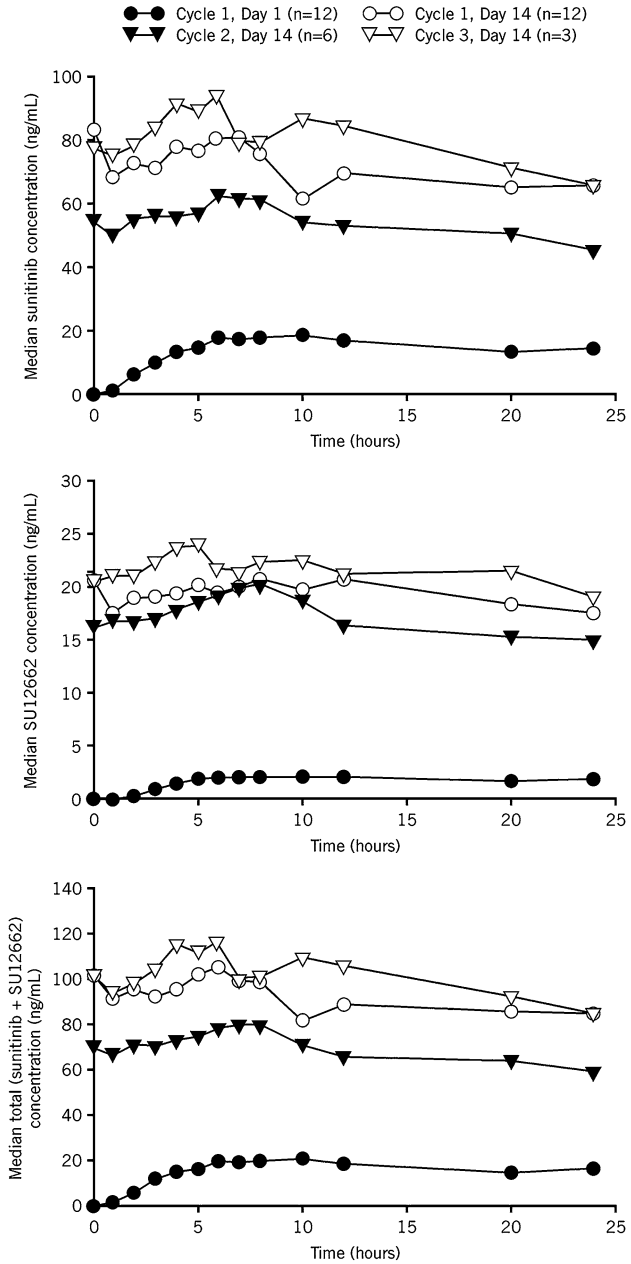

Fig. 1 Linear plots of median plasma sunitinib, SU12662, and total drug (sunitinib + SU12662) concentration-time profiles

Discussion

This phase I trial was designed to evaluate the feasibility of administering sunitinib 50 mg orally once daily for 2 weeks followed by a 1-week off period. Using common phase I definitions, there were two DLTs among the 12 patients studied. In addition, one half of those patients (five out of ten) who received more than one course developed drug-related toxicities resulting in dose and/or schedule modifications. This reflects a limitation in the application of

Table 5 Pharmacokinetic behavior of sunitinib, SU12662, and total drug (sunitinib + SU12662)

Pharmacokinetic parameters	Arithmetic mean (CV %) [median]		
	Sunitinib	SU12662	Total
Course 1, day 1 (n = 12)			
C_{max} (ng/ml)	22.2 (41) [20.8]	2.90 (45) [2.87]	24.9 (41) [23.3]
AUC_{0-24} (ng h/ml)	355 (40) [341]	48.3 (44) [49.4]	430 (40) [376]
T_{max} (h)[a]	7.0 (4.0, 12.1)	7.0 (3.0, 24.0)	7.0 (4.0, 12.1)
Course 1, day 14 (n = 12)			
C_{max} (ng/ml)	91.9 (46) [92.9]	25.1 (44) [24.9]	117 (43) [123]
AUC_{0-24} (ng h/ml)	1,592 (41) [1,717]	477 (45) [445]	2,069 (39) [2204]
C_{trough} (ng/ml)	79.9 (54) [83.4]	21.3 (50) [21.4]	101 (51) [102]
T_{max} (h)[a]	6.0 (0.0, 8.3)	6.0 (0.0, 24.0)	6.0 (0.0, 12.0)
Course 1 ratios, day 14/day 1 (n = 12)			
AR (AUC_{0-24})	4.56 (32) [4.42]	10.3 (38) [9.27]	5.24 (32) [4.93]
AR (C_{max})	4.44 (62) [3.90]	9.41 (55) [8.67]	5.01 (59) [4.39]
Day 14 ratios, course 2/course 1 (n = 6)			
AR (AUC_{0-24})	1.01 (40) [0.93]	1.22 (53) [1.09]	1.06 (44) [0.94]
AR (C_{max})	0.94 (39) [0.96]	1.20 (58) [1.06]	1.00 (43) [0.95]

CV coefficient of variance, C_{max} maximum concentration, AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h, t_{max} time to C_{max}, C_{trough}, trough concentration, *AR* accumulation ratio, *N/A* not applicable

[a] Median (minimum, maximum)

traditional phase I design to the development of targeted agents administered continuously and/or chronically. Specifically, dosing recommendations based on course 1 experience may not be applicable over multiple courses, and adjustments may be required based on individual safety and tolerability over time. Data from this trial suggest that heavily pre-treated patients with advanced malignancies may not adhere to a strict 2/1 schedule. Nonetheless, with minor dose and/or schedule modifications, patients may achieve prolonged drug exposure without major sequelae.

Intense cardiac monitoring was implemented in this study as a result of congestive heart failure observed in patients with AML [8]. Grade 2 asymptomatic declines in LVEF were observed in 42% (5/12) of patients on the 2/1 schedule, whereas large clinical trials employing the 4/2 schedule reported that 15% of patients with metastatic renal cell cancer and 11% of patients with GIST developed sunitinib-related grade ≥ 2 declines in LVEF [5, 15, 16, 22]. The incidence of cardiac dysfunction observed in this phase I trial may be due to the prolonged drug exposure time provided by the 2/1 schedule. Also, two of the affected patients on the 2/1 schedule had previously received an anthracycline, and results from clinical trials with bevacizumab in metastatic breast cancer suggest that prior anthracycline exposure may predispose patients treated with an anti-angiogenesis agent to cardiac dysfunction [14]. Of course, the small sample size of this phase I trial cannot accurately reflect the true rate of cardiac dysfunction. Therefore, the incidence of cardiac dysfunction reported in this study must be interpreted with caution.

The clinical significance of an asymptomatic decline in LVEF is unknown, and this exploratory phase I trial did not adequately address the feasibility of continued treatment with sunitinib in the setting of left ventricular dysfunction. LVEF measurements were interpreted within their clinical context, and decisions to discontinue sunitinib were made conservatively. One patient was successfully retreated, but four other affected patients were withdrawn from study because the risk of further treatment appeared to outweigh any potential benefit. Four of the affected patients in this phase I trial demonstrated an improvement in LVEF to within normal limits following either a prolonged off-drug period or withdrawal from study. This is consistent with other clinical trials with sunitinib, in which some patients with decreased LVEF recovered without intervention, and others improved with dose reduction and/or standard medical therapy [5, 15, 16, 22]. Although none of the patients in this study experienced congestive heart failure, life-threatening cardiac dysfunction has been observed in other studies with sunitinib [5, 15, 16, 22]. The current recommendation is to interrupt or reduce the dose of sunitinib in patients with significant asymptomatic declines in LVEF, and to discontinue sunitinib in the presence of symptoms of congestive heart failure [22].

The other principal adverse effects on the 2/1 schedule were similar to those previously observed with sunitinib. Fatigue and asymptomatic elevations in lipase and amylase have been associated with the multitargeted TKI sorafenib, and may represent class effects [6]. Likewise, controllable hypertension has been associated with anti-angiogenesis agents targeting either VEGF or VEGFR [6, 9, 18]. Altogether, the toxicities observed in this phase I trial were acceptable, and consistent with previous experience.

Pharmacokinetic data demonstrated that the 2/1 schedule provided prolonged drug exposure compared to the 4/2

schedule with repeated courses. In a phase I study of sunitinib in refractory AML, a 2-week off-drug period resulted in almost complete elimination of sunitinib and its metabolite SU12662 prior to dosing on course 2 day 1 [8]. In contrast, with the 2/1 schedule, the parent compound and its metabolite were detectable prior to dosing on course 2 day 1. However, there was no significant accumulation of sunitinib between courses on the 2/1 schedule, although the mean dosing interruption was 11.5 days rather than the planned 7 days.

In this phase I trial, one patient with radiation-associated papillary thyroid cancer achieved a durable partial response, reflective of either a direct antitumor effect or an indirect anti-angiogenesis effect. While it is unknown whether this patient's malignancy harbored a *RET* gene rearrangement, such rearrangements have been identified in 60–70% of radiation-associated papillary thyroid cancers [11]. Sunitinib inhibits *RET* with an IC_{50} of 224 nM in cell-based assays [10], and responses in thyroid cancer patients were observed in a previous phase I study [21]. Alternatively, the antitumor activity observed in thyroid cancer patients may have been due to an anti-angiogenesis effect. Other multitargeted TKIs, including AMG706 and ZD6474, are currently in phase II clinical trials for patients with *RET*-activated thyroid cancers, and the results of these studies may define the utility of this class of agents for the treatment of thyroid cancer.

Sunitinib is among the first small molecule anti-angiogenic TKIs to be approved for the treatment of patients with advanced malignancies. Unlike sorafenib, which is administered twice daily, sunitinib achieves clinically-relevant concentrations when administered once daily. The 4/2 schedule of sunitinib was initially developed based on the preclinical data available at the time testing in humans began. Large clinical trials employing the 4/2 schedule revealed that sunitinib is well tolerated and produces significant antitumor activity in metastatic renal cell cancer, and in imatinib-refractory GIST. This phase I trial demonstrates that the 2/1 schedule is tolerable, though patients may require minor dose adjustments and/or modifications. In addition, the absence of significant drug accumulation between courses suggests that prolonged sunitnib exposure is feasible over multiple courses. Based on these results, the 2/1 schedule is currently being evaluated in combination with several chemotherapy regimens administered in 3-week courses, including gemcitabine plus cisplatin, carboplatin plus paclitaxel, and capecitabine.

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