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Alternative Formulations of Sorafenib for Use in Children

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Abstract

Background—Sorafenib is an oral multikinase inhibitor with antiangiogenic and antitumor activity. In most cases, the commercially available 200 mg tablet is not suitable for administration to children. We studied the chemical and physical stability of extemporaneously prepared formulations and evaluated the pharmacokinetic profile of cut tablets and smaller-dosage capsules of sorafenib in children.

Procedure—Commercially available 200 mg tablets of sorafenib tosylate were used to prepare liquid suspensions of sorafenib in oil and Ora-Plus®:Ora-Sweet® solution, and to prepare 5, 10, 20, 50 and 100 mg capsules. Plasma concentrations of sorafenib were measured in patients receiving capsules and cut tablets, using a validated HPLC-based method with tandem mass spectrometric detection.

Results—At room temperature and under refrigeration, sorafenib concentrations in Ora Plus®:Ora Sweet® were highly variable (means ranging from 75% to 131% of the intended concentration of 50 mg/mL). In oil suspension, sorafenib concentrations were inconsistent during compounding. In contrast, all smaller-dosage capsules, except the 5 mg capsule, were within 91%–99% of the intended content and were stable at room temperature for at least 8 months. Sorafenib pharmacokinetic parameters in patients receiving capsules or cut tablets were consistent with those reported previously in adults and children receiving intact tablets.

Conclusions—Sorafenib is not stable in an oral suspension prepared from commercially available tablets, but compounded capsules in smaller-dosage forms that can be sprinkled on food or cut tablets are alternatives for administration to children who need smaller doses based on body surface area or cannot swallow tablets.

Keywords

Sorafenib; formulation; suspension; compounded capsule

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INTRODUCTION

Sorafenib is an orally bioavailable, potent ATP-competitive inhibitor of a group of closely related tyrosine kinases consisting of the platelet-derived growth factor receptor, vascular endothelial growth factor receptor (types 1–3), stem cell factor receptor (c-Kit), Fms-like tyrosine kinase-3 receptor (FLT-3), RET, Raf-1 (c-Raf), and BRAF. In preclinical and clinical testing, sorafenib has demonstrated significant antitumor activity by inhibiting tumor cell proliferation and angiogenesis in several tumor types.[1–6] A 400 mg twice daily dose of sorafenib has been approved by the US Food and Drug Administration for the treatment of adult patients with advanced renal cell carcinoma and unresectable hepatocellular carcinoma. Phase I testing of single-agent sorafenib in children has recently been completed[7] and we and others have shown that the drug in combination with chemotherapy and biological agents has promising antitumor activity in pediatric patients with leukemia and solid tumors.[8–10]

Testing of sorafenib in children for whom drug dosages are determined on the basis of body mass or body surface area has been limited by the available dosing formulation of the drug. Sorafenib tosylate is commercially available as a 200 mg tablet only. In the phase I study of sorafenib in children, only patients who could swallow intact tablets and 50 mg tablets (supplied by the Cancer Therapy Evaluation Program) were eligible for the study.[7] As no liquid formulations or small-dosage forms of sorafenib are commercially available for clinical use, it is not possible to accurately and safely titrate the dose of sorafenib on the basis of body size with the commercially available 200 mg tablets. Further, the drug is not accessible to patients who cannot swallow pills.

To overcome these limitations, we extemporaneously prepared an oral liquid formulation of sorafenib tosylate in commercially available vehicle and oil suspensions as well as smaller dosages in capsules. We assessed the chemical and physical stability of the drug in suspension at room temperature and under refrigeration at 4°C and of the capsules at room temperature. We also performed pharmacokinetic studies in children and young adults receiving extemporaneously compounded capsules and/or cut tablets.

METHODS

Patients

Children, adolescents, and young adults 21 years old or younger were treated with sorafenib on 2 phase I trials, one for recurrent or refractory leukemia and the other for recurrent or refractory solid tumors. In the leukemia trial, participants received 200 mg/m² sorafenib twice daily. Eligibility criteria, treatment plan, and frequency of patient monitoring have been described previously.[8] Sorafenib was administered as sorafenib tosylate tablets whole (200 mg), halved (100 mg), or quartered (50 mg), with the dose rounded to the nearest 50 mg; as extemporaneously compounded capsules in strengths of 10, 20, 50, and 100 mg; or as a combination of tablets and capsules. In the solid tumor trial, participants received 90 mg/m² sorafenib twice daily in combination with bevacizumab and low-dose oral cyclophosphamide.[9] Sorafenib was administered as a combination of capsules compounded in strengths of 10, 20, 50, and 100 mg. The dose had to be within 10% of the calculated dose based on patients' body surface area and was rounded to the nearest 10 mg. Capsules were opened and sprinkled on low-to moderate-fat-containing soft foods for administration to children who could not swallow capsules.

The clinical protocols were approved by the St. Jude Children's Research Hospital institutional review board. Informed consent was obtained from all patients or their legal guardians.

Preparations of sorafenib tosylate

Each preparation described below was made with commercially available sorafenib tosylate (molecular weight 637.0 g/mol; Nexavar®, Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ). Each tablet was equivalent to 200 mg of sorafenib (274 mg sorafenib tosylate).

Ora-Sweet®:Ora-Plus® suspension—Ora-Plus® and Ora-Sweet® solutions (Paddock Laboratories, Inc., Minneapolis, MN; now owned by Perrigo Co. Allergan, MI) were purchased from the manufacturer. On the basis of the approved daily adult dose of 400 mg (235 mg/m² for an average body surface area of 1.7 m²), a 50 mg/mL sorafenib suspension was selected for the study to ensure that the volume of the suspension calculated over the wide range of body surface areas in children would not be too low to measure accurately and not too high to ingest. The suspensions were prepared under nonsterile conditions. Six independent samples were prepared by mixing 4 sorafenib 200 mg tablets in a mortar and pestle to a final volume of 16 mL in a 1:1 mixture of Ora-Plus®:Ora-Sweet® to yield a final concentration of 50 mg/mL. Suspensions were transferred to amber plastic (polyethylene terephthalate) prescription ovals with child-resistant caps. Three samples were refrigerated (0°C to 12°C; median, 4°C). and three were stored at room temperature (22 ± 1°C). Sorafenib concentration from each bottle was measured within 1 h of compounding and on days 3, 8, 14, 22, and 29.

Oil suspension of sorafenib tosylate—Silica Gel powder and Almond Oil (Base G) (Professional Compounding Centers of America, Houston, TX) were purchased from the manufacturer. The suspension was prepared under nonsterile conditions. The coating of each tablet was peeled off after an application of acetone. The number amount of tablets required for each batch was calculated based on the required strength of the suspension. The tablets with the coating removed were then crushed to a fine powder using a mortar and pestle. The Silica Gel powder was then weighed using a Ohaus Explorer Pro digital balance (Ohaus, Parsippany, NJ). The crushed tablets were combined with Silica Gel by using the geometric dilution technique. After thorough mixing, Almond Oil was added by using geometric dilution up to the volume required. The suspension was then homogenized using an IKA T 25 digital ULTRA-TURRAX® homogenizer (Daigger, Vernon Hills, IL) with a dispersing element at a setting of 2 for 2 min. The suspension was then dispensed in a standard liquid prescription bottle. Sorafenib concentration from each bottle was measured in quadruplicate at the time of compounding and on days 7, 10, 14, 22, and 30 if the variability between the intended and the measured concentration was less than 10% at the time of compounding (day 1).

Extemporaneously compounded capsules of sorafenib tosylate—

Microcrystalline cellulose powder (Professional Compounding Centers of America, Houston, TX) was purchased from the manufacturer. The doses of 5 mg, 10 mg, 20 mg, 50 mg, and 100 mg were chosen to meet the specific dosage requirements for the study. The capsules were prepared under nonsterile conditions. The coating of each tablet was peeled off after an application of acetone, and the tablet was crushed to a fine powder using a mortar and pestle. The crushed sorafenib tablets were combined with microcrystalline cellulose powder by using a geometric dilution technique. For each strength of capsule, a specific amount of the commercially available sorafenib tablet and microcrystalline cellulose was required: 5 mg capsule, 8.65 mg sorafenib tablet and 120 mg microcrystalline cellulose; 10 mg capsule, 17.3 mg sorafenib tablet and 118.5 mg microcrystalline cellulose; 20 mg capsule, 34.6 mg sorafenib tablet and 116.22 mg microcrystalline cellulose; 50 mg capsule, 86.5 mg sorafenib tablet and 76 mg microcrystalline cellulose; and 100 mg capsule, 173 mg sorafenib tablet and 8.33 mg microcrystalline cellulose. After thorough mixing, the Jaansun® capsule machine (Professional Compounding Centers of America, Houston, TX)

was assembled by using a #3 size capsule. A specific color combination was given for each capsule strength. Then, the powder was packed into capsules. The capsules were capped and dispensed into an amber plastic prescription bottle. Each batch was assigned a specific lot number that was mentioned on the label of the bottle.

Pharmacokinetic Studies

Pharmacokinetic studies were performed during course 1 of therapy. For the leukemia trial, sampling was done after the first oral dose on day 1 at the following times: pretreatment and then at 0.5, 1, 2, 4, 6, 8, and 24 h. On day 7, sampling was done pretreatment and then after the dose at 2, 4.5, and 7.5 h. For the solid tumor trial, sampling was done on day 1 at the following times: pretreatment and then at 0.5, 1, 2, 4.5, 6, 7.5, 24, and 48 h; samples were also obtained pretreatment on days 7, 13, and 21. Peripheral blood samples (3 mL) were collected in a heparinized tube, centrifuged for 10 min at 3000×g, and plasma was stored at –80°C until analysis. Sorafenib concentrations were measured in the plasma by using a validated high performance liquid chromatography (HPLC)–based method with tandem mass spectrometric detection.[11] Maximum plasma concentrations ($C_{\max}$) and time to $C_{\max}$ ($T_{\max}$) were the observed values. Area under the concentration-time curve (AUC) was estimated using noncompartmental methods as implemented in Phoenix WinNonlin (Pharsight, Cary, NC). The sorafenib AUC from time 0 to 8 h (AUC_{0-8h}) was estimated to compare with previously published sorafenib pharmacokinetic studies in adults,[12] and the AUC from time 0 to 24 h (AUC_{0-24h}) was estimated to compare with pharmacokinetic parameters in the pediatric phase I study.[7] For the leukemia trial, sorafenib steady-state plasma concentration (C_{ss}) was calculated as the mean concentration of the 4 samples collected on day 7, because negligible fluctuations from maximum to minimum plasma concentrations were observed during this time period. For the solid tumor trial, C_{ss} values were the observed pretreatment concentrations on days 7, 13, and 21.

Analytical Assays for Sorafenib Dosing Formulations

A method based on HPLC with ultraviolet detection was used to measure sorafenib in the Ora-Sweet®:Ora-Plus® and oil suspensions. The HPLC system consisted of a Shimadzu SCL-10AVP System equipped with a Shimadzu SPD-M10AVP Diode Array Detector (Shimadzu Scientific, Columbia, MD). A Waters X-Terra MS Column (C18 3.5 μ m, 50 $\times$ 2.1 mm) with a Waters X-Terra RP18 guard column (3.5 μ m, 20 $\times$ 2.1 mm) was used. The isocratic mobile phase was 0.1% formic acid in 50% acetonitrile. Sorafenib was measured at a wavelength of 254 nm. The sample was prepared by transferring 10 μ L of the sorafenib suspension to a 1.5 mL polypropylene tube containing 990 μ L of tetrahydrofuran. The sample was vortexed for 1 min and centrifuged for 5 min at 16 $\times$ g. Five microliters of the supernatant was mixed with 995 μ L of internal standard solution (2.0 μ g/mL clozapine in 70% acetonitrile). The mixture was vortexed, and 5 μ L was used for analysis.

A method based on HPLC with tandem mass spectrometric detection was used to measure sorafenib in extemporaneously compounded capsules. The HPLC consisted of a Waters 2692 separation system (Milford, MA) and Micromass Quattro LC triple-quadrupole system (Beverly, MA). Samples were separated on a Waters X-Terra MS C18 column (3.5 μ m, 50 $\times$ 2.1 mm), using a column heater operating at 30°C with a Waters X-Terra RP18 guard column (3.5 μ m, 10 $\times$ 2.1 mm). The mobile phase was 10 mM ammonium acetate (pH 3.8 adjusted with formic acid) – 0.1% formic acid in acetonitrile (35:65 vol/vol). The flow rate was 0.3 mL/min, and isocratic separation was completed within 4 min. The analysis was performed in the MRM mode: m/z 465.1 > 252.0 for sorafenib and m/z 469.0 > 256 for the internal standard. The sample was prepared by weighing the entire contents of the capsule before transferring to a glass bottle. Tetrahydrofuran was used to extract sorafenib (50 mL tetrahydrofuran for 50 mg of content). The sample was rotated at room temperature for 24 h.

One milliliter of the extraction solution was centrifuged at 10,000 rpm for 3 min. Ten microliters of the supernatant was diluted with 5 mL of methanol and acetonitrile (1:1 vol/vol). Fifty microliters of the sample was mixed with 250 μ L of internal standard solution (100 μ g/mL [$^{13}\text{C}, ^2\text{H}_3$] – sorafenib in methanol, AlsaCHIM, Strasbourg, France), and 5 μ L of the mixture was used for analysis. A variability of 10% between the intended and measured sorafenib concentrations in the suspensions was considered clinically acceptable for administration.

RESULTS

Initial Concentration and Stability of Sorafenib in Compounded Suspensions

The tablets were crushed to a fine powder with flakes of red film coat remaining in the white sorafenib powder. The resulting suspension in Ora Plus®:Ora Sweet® was slightly pink and homogeneous looking. At room temperature and under refrigeration, the mean percentage of sorafenib concentration remaining of the initial concentration in Ora Plus®:Ora Sweet® was highly variable, ranging from $75.2\% \pm 7.9\%$ at 4°C to $131.0\% \pm 12.1\%$ at room temperature. Under these experimental conditions, the color, consistency, and odor of all 6 preparations remained unchanged throughout the study. Visual inspection revealed no evidence of mold or bacterial growth.

Table I shows the intended sorafenib concentration of 50 mg/mL in oil suspension and the initial sorafenib concentration measured by HPLC. There was high variability in the measured initial sorafenib concentration among prepared suspensions, ranging from 29.1 mg/mL to 64.2 mg/mL. Stability testing was performed on suspension 1 only, because suspensions 2–5 did not meet the criteria for further testing (>10% variability between the intended and measured concentrations of the suspension at the time of initial compounding).

Content and Stability of Sorafenib in Compounded Capsules

Table II shows the sorafenib content in extemporaneously compounded capsules of sorafenib tosylate at different capsule strengths on various days since compounding for capsules stored at room temperature. There was less than 10% variability in the intended and measured sorafenib content of the 10 mg and 50 mg capsules after 11 months of storage and the 20 mg and 100 mg capsules after 8.5 months of storage. Although the 5 mg capsules appeared to be stable in the first 3 months of storage, the content of the capsule after 8 months dropped below the 10% variability cutoff that we considered acceptable for clinical administration. Therefore, we did not use the 5 mg capsules in our clinical trials.

Sorafenib Pharmacokinetic Studies

Pharmacokinetic studies were completed in 12 patients. Six patients received sorafenib at 90 mg/m² and 6 patients received sorafenib at 200 mg/m². Table III summarizes patient characteristics, sorafenib formulation and administration, and individual sorafenib pharmacokinetic parameters after the first dose and steady-state concentrations. Figure 1 gives individual sorafenib concentration–time profiles after the first dose. The mean ($\pm$ SD) T_{max} value at 90 mg/m² sorafenib was 4.3 (1.3) h and at 200 mg/m² sorafenib was 6.7 (2.4) h. There was higher sorafenib exposure at 200 mg/m² than at 90 mg/m² both after the first dose and at steady state. After the first dose of 90 mg/m², mean values for C_{max} and $\text{AUC}_{0-24\text{h}}$ were 1.56 (0.98) mg/L and 19.2 (8.7) mg/L*h, respectively, and at 200 mg/m² mean values ($\pm$ SD) for C_{max} and $\text{AUC}_{0-24\text{h}}$ were 2.32 (1.37) mg/L and 33.2 (14.9) mg/L*h, respectively. At a dose of 90 mg/m², mean values ($\pm$ SD) for C_{ss} on days 7, 13, and 21 were 3.65 (2.06) mg/L, 3.26 (1.86) mg/L, and 2.52 (1.70) mg/L, respectively. At a dose of 200 mg/m², the mean values ($\pm$ SD) for C_{ss} on day 7 was 5.43 (1.46) mg/L.

DISCUSSION

One of the challenges in developing drugs for pediatric use is that commercially available oral formulations, such as those for sorafenib, are not suitable for accurate dosing based on body surface area or for administration to children who cannot swallow intact pills. We have previously shown that sunitinib, another orally bioavailable multitargeted tyrosine kinase inhibitor, is stable in oral suspensions prepared from commercially available capsules.[13] In the present study, we took the same approach with sorafenib and found that sorafenib cannot be reliably (with 10% variability) compounded extemporaneously at a concentration of 50 mg/mL in a 1:1 mixture of commonly chosen commercially available vehicles of Ora-Sweet[®] and Ora-Plus[®]. Similarly, we found high variability in measured concentrations of sorafenib prepared in an oil-based suspension. Therefore, we compounded small-dosage capsules, and found that dosages of 10 mg sorafenib or higher are stable at room temperature for at least 8 months. The benefit of these small-dosage capsules is that they can be opened and sprinkled on low- to moderate-fat-containing soft foods and easily ingested.

The pharmacokinetics of sorafenib in patients 12 years old or younger receiving capsules (solid tumor patients) or a combination of capsules and cut/whole tablets (leukemia patients) showed marked interpatient variability, as has been previously shown in adult and pediatric patients.[7, 12] The mean sorafenib AUC_{0–8h} values after the first dose and steady-state concentrations in our study are consistent with exposures observed in adults receiving 100 mg or 200 mg sorafenib twice daily or 400 mg twice daily.[12] The mean sorafenib AUC_{0–24h} values after the first dose and steady-state concentrations at 90 mg/m² and 200 mg/m² are also similar to the exposures observed in pediatric patients receiving 105 mg/m² twice daily (mean AUC_{0–24h} 11.8 ± 8.7) and 200 mg/m² twice daily (mean AUC_{0–24h} 27.3 ± 17.0), respectively.[7] These results suggest that similar plasma concentrations of sorafenib can be achieved by cutting the 200 mg commercially available tablets or by compounding smaller-dosage capsules from commercially available tablets, thereby allowing for more precise dosing in children.

In our study, sorafenib was given to 2 patients (leukemia patients 1 and 3) by dissolving half of a tablet in 30 mL of water, to 1 patient (leukemia patient 2) by dissolving the contents of capsules in apple juice, to 1 patient (solid tumor patient 1) by sprinkling the capsule contents on food and to 1 patient (solid tumor patient 2) by dissolving the capsule contents in water and then administering the solution through a nasogastric tube. Because of the interpatient variability of the drug and the small number of patients in our study, we cannot confirm whether the dissolution of tablets or capsule contents, sprinkling capsule contents on food, or administration of the drug through a nasogastric tube can alter the pharmacokinetic profile of sorafenib; however, the values obtained in these 4 patients are still within the exposures observed in the other patients. These findings are comparable with results of a study performed in healthy adult male volunteers who had similar sorafenib plasma concentrations when they received two 200 mg intact tablets with 8 oz of water or two 200 mg tablets disintegrated over 10 min in 2 oz of water.[14]

Sorafenib is currently being tested in pediatric phase II trials of leukemia, rhabdomyosarcoma, Wilms tumor, low-grade astrocytoma, papillary thyroid carcinoma, and hepatocellular carcinoma. A large international, multiinstitutional study of sorafenib is being considered for patients with hepatoblastoma. Our study on various formulations of sorafenib will be useful to expand the access of these studies to younger pediatric patients (i.e. those less than 24 months of age) and those unable to swallow tablets, allow more accurate dosing based on milligrams per body surface area, and expand options for dose reductions.

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Figure 1.

Individual sorafenib plasma concentration–time profiles after the first sorafenib oral dose on day 1 of course 1 in patients enrolled in the solid tumor trial (A) and leukemia trial (B).

Initial concentration and stability of sorafenib (intended concentration 50 mg/mL) in an oil suspension of sorafenib tosylate

Table 1

Suspension number ^a	Intended sorafenib concentration (mg/mL)	Initial sorafenib concentration (mg/mL) ^b	% Nominal initial of intended concentration	Storage condition	% Initial concentration remaining				
					Day 7	Day 10	Day 14	Day 22	Day 30
1	50	49.3	98.7	RT	106.6	105.5	104.4	107.7	119.2
2	50	64.2	128.4	-	-	-	-	-	-
3	50	29.1	58.2	-	-	-	-	-	-
4	50	55.7	111.4	-	-	-	-	-	-
5	50	42.6	85.2	-	-	-	-	-	-
	Mean	48.2	96.4						
	SD	13.3	26.6						

RT, room temperature; Dash (-), not done.
^aIndependent suspensions were prepared.
^bValue is the average of quadruplicate measurements.

Table II

Sorafenib content and stability in capsules extemporaneously compounded from sorafenib tosylate

Sorafenib capsule strength (mg)	Days since capsule compounded ^a	Sorafenib content in capsule (mg) ^b	% Nominal of intended content ^b
5	66	4.76	95.1
5	87	4.92	98.4
5	332	4.09	81.8
10	66	9.79	98.0
10	87	9.18	91.8
10	332	9.12	91.2
20	87	19.9	99.5
20	260	19.0	95.2
50	66	49.6	99.2
50	87	48.9	97.9
50	332	45.9	91.7
100	87	97.8	97.8
100	260	93.0	93.0

^aCapsules were stored at room temperature.^bValues are the mean of 1 to 3 capsules tested in triplicate.

Table III

Patient characteristics and sorafenib pharmacokinetic parameters

Study	Patient No.	Age	Sex	BSA	Dose (mg/m ²)	Dose and administration ^d	First dose PK parameters				C _{ss} (mg/L)		
							T _{max} (h)	C _{max} (mg/L)	AUC _{0-8h} (mg* ^a h/L)	AUC _{0-24h} (mg* ^a h/L)	Day 7	Day 13	Day 21
Solid tumor	1	14 mo	M	0.47	90	50 mg (cap) bid ^b	4.5	3.35	14.2	31.1	5.94	6.58	ND
	2	22 mo	F	0.49	90	50 mg (cap) bid ^c	4.5	1.87	10.7	28.8	3.18	2.53	ND
	3	8 y	M	1.11	90	100 mg (cap) bid	2.0	1.32	6.1	14.0	2.30	2.39	1.47
	4	11 y	M	1.47	90	100 mg (cap) + 2×20 (cap) bid	6.0	0.69	2.0	10.8	2.96	2.38	2.68
	5	12 y	F	1.49	90	100 mg (cap) + 2×20 mg (cap) bid	4.5	0.72	3.7	12.8	6.34	-	4.86
	6	12 y	F	1.35	90	100 mg + 20 mg (cap) bid	4.5	1.45	6.5	17.6	1.17 ^d	2.40	1.07
						Mean	4.33	1.56	7.2	19.2	3.65	3.26	2.52
						SD	1.29	0.98	4.5	8.7	2.06	1.86	1.70
Leukemia	1	14 mo	M	0.48	200	100 mg (tab) bid ^e	2.0	4.77	23.6	44.8	3.13	-	-
	2	3 y	F	0.68	200	100 mg (cap) + 2×20 (cap) bid ^f	8.0	2.57	11.5	48.3	7.47	-	-
	3	5 y	F	0.75	200	150 mg (tab) bid ^e	8.0	1.67	9.0	28.2	5.17	-	-
	4	6 y	F	0.89	200	200 mg (tab) AM + 150 mg (tab) PM	8.0	1.79	8.4	27.0	4.94	-	-
	5	6 y	M	0.85	200	150 mg (tab) + 20 mg (cap) bid	8.0	0.72	1.1	8.7	6.37	-	-
	6	12 y	F	1.41	200	300 mg (tab)AM + 250 mg (tab) PM	6.0	2.43	14.0	42.3	5.52	-	-
						Mean	6.67	2.32	11.3	33.2	5.43		
						SD	2.42	1.37	7.4	14.9	1.46		

AM, morning; AUC, area under the concentration time curve; bid, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{ss}, steady-state concentration; h, hours; mo, months; PK, pharmacokinetic; PM, evening; y, years; tab, tablet; cap, capsule.

^aSorafenib was administered as compounded capsules (10 mg, 20 mg, 50 mg, 100 mg) in all solid tumor patients; as sorafenib tosylate 200 mg tablets whole or quartered or halved; or as a combination of compounded capsules and tablets (whole or cut).

^bCapsule content was sprinkled on food and ingested.

^c On day 1, capsule content was dissolved in water and the dose administered by a nasogastric tube. For subsequent doses, capsule content was sprinkled on a small amount of yogurt and ingested by mouth.

^d Patient mistakenly took prescribed dose of sorafenib once daily instead of twice daily for days 3 through 7.

^e Tablets were dissolved in 30 mL water before administration.

^f Capsules were opened and contents put in apple juice before administration.