The Pharmacokinetics and Safety of ABT-751, a Novel, Orally Bioavailable Sulfonamide Antimitotic Agent: Results of a Phase 1 Study

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Abstract

Purpose: Microtubules play a critical role in many cellular functions, including cell division and mitosis. ABT-751 is a novel sulfonamide antimitotic that binds to the colchicine site on β-tubulin that leads to a block in the cell cycle at the G_2M phase, resulting in cellular apoptosis. ABT-751 was investigated in this phase 1 trial designed to assess its maximum tolerated dose (MTD), dose-limiting toxicity (DLT), tolerability, and pharmacokinetics.

Experimental Design: ABT-751 was administered on a daily (q.d.) or twice daily (b.i.d.) oral schedule for 7 days every 3 weeks to 39 patients with refractory solid tumors. Toxicity was monitored weekly. Plasma and urine ABT-751 and metabolite pharmacokinetics were determined.

Results: The MTD for the q.d. schedule was 250 mg/d. DLTs during cycle 1 were abdominal pain, constipation, and fatigue. The MTD on the b.i.d. schedule was 150 mg. Cycle 1 of therapy with the 175 mg b.i.d. schedule was tolerated without DLT. However, six of seven patients reported grade 3 toxicity (ileus, constipation, abdominal pain, or fatigue), which occurred in cycle 2 or 3. ABT-751 was absorbed after oral administration with an overall mean T_{max} of about 2 hours. The pharmacokinetics of ABT-751 were dose-proportional and time-independent. There was minimal accumulation of ABT-751 after multiple q.d. and b.i.d. doses. Efficacious concentrations, as determined from preclinical models (0.5-1.5 μg/mL), were achieved in all subjects. ABT-751 metabolism occurred primarily by glucuronidation and sulfation. No complete or partial tumor responses were noted, but one patient had a minor response, and four patients had stable disease lasting at least 6 months.

Conclusions: The MTD and recommended phase 2 doses for ABT-751 were 250 mg q.d. and 150 mg b.i.d. on a 7-day schedule given every 3 weeks, due to subsequent cycle toxicities at 175 mg b.i.d. dosing. Toxicities were abdominal pain, constipation, and neuropathy.

Microtubules play a critical role in determining cell shape and polarity, facilitating cellular movement and intracellular transport, and segregating chromosomes during mitosis. In mitosis, interphase microtubules disappear and are replaced with a new network of microtubules that interact with the mitotic spindle to distribute chromatids equally between the two daughter cells (1). Disruption of microtubules arrests the cell division cycle at the G_2M checkpoint, preventing cell division and triggering apoptosis. Thus, these important and highly labile microtubules are a principal target of several effective anticancer agents.

Known antimitotic agents fall into three classes, *Vinca* alkaloids (vincristine, vinblastine, and vinorelbine), taxanes (paclitaxel and docetaxel), and colchicine site binders or colchicines. The *Vinca* alkaloids and colchicines are potent inhibitors of microtubule polymerization that block cell proliferation at metaphase during mitosis (2). The taxanes stabilize microtubules and block microtubulin depolymerization (3). Each antimitotic class has a distinct binding site on tubulin β-subunits (4, 5). The consequences of disruption of tubulin and microtubule dynamics with these three drug classes seems to be the same: a block in the cell cycle that ultimately induces cellular apoptosis. The *Vinca* alkaloids and the taxanes have shown antineoplastic activity in a wide variety of human cancers. No colchicine-site binders are currently approved for cancer chemotherapy.

ABT-751 is a novel sulfonamide molecule (Fig. 1), that has shown significant preclinical tumor activity in a variety of syngeneic and human xenograft models (colon, lung, stomach, breast, pancreas, prostate, nasopharyngeal; refs. 6–10). ABT-751 binds to the colchicine binding site on β-tubulin (11) and is distinct from the current clinically approved tubulin binding agents, the *Vinca* alkaloids and the taxanes. ABT-751 is not a substrate for the multiple drug resistance (MDR) transporter

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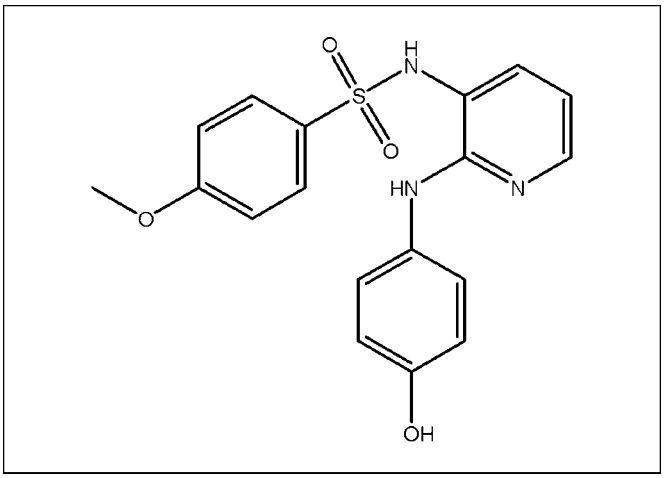

Fig. 1. The structure of ABT-751 [*N*-(2-[(4-hydroxyphenyl)amino]-3-pyridinyl)-4-methoxybenzenesulfonamide].

and is active against cell lines resistant to vincristine, doxorubicin, and cisplatin (11).

ABT-751 has been previously evaluated in a phase 1 study in Japan using both a single dose (80-480 mg/m^2) and a 5-day repeated dose (30-240 mg/m^2 q.d.) oral administration. The study design was unconventional in that no additional subjects were added to confirm the maximum allowable dose, nor were additional cycles of drug administered after the first cycle. The estimated maximal allowable dose in this study, based on Japanese toxicity criteria (12), was 480 mg/m^2 for the single dose and 240 mg/m^2 for the 5-day dose schedule. The toxicities reported included peripheral neuropathy and intestinal paralysis. Antitumor activity was noted in 3 of 41 patients studied in this clinical trial.

Because of the novel site of tubulin binding of this antimitotic agent and the preclinical and clinical activity shown in other studies, this phase 1 trial was designed to determine the maximum tolerated dose, toxicities, and pharmacokinetics of ABT-751 given to cancer patients with solid tumors on a fixed (i.e., non–body surface area adjusted) q.d. and b.i.d. oral dosing schedule for 7 days every 3 weeks.

Patients and Methods

Eligibility criteria. Study eligibility included the following criteria: (*a*) patients with a solid tumor malignancy (leukemias and lymphomas excluded) documented by radiographic and histologic evaluation, refractory to standard therapy or for which no effective therapy is available, (*b*) age ≥18 years, (*c*) estimated life expectancy ≥3 months, (*d*) Eastern Cooperative Oncology Group performance status 0 to 2, (*e*) no chemotherapy, radiation therapy, immunotherapy, or hormonal therapy within 4 weeks of study start, (*f*) body weight ≥45 kg, (*g*) adequate bone marrow, renal, and hepatic function defined by WBC ≥3,000/mm^3, absolute neutrophil count ≥1,500/mm^3, platelets ≥100,000/mm^3, hemoglobin ≥9 g/dL, creatinine clearance ≥50 mL/min, aspartate aminotransferase and alanine aminotransferase ≤2.5× upper limit of the laboratory normal, bilirubin <1.5× upper limit of normal, and (*h*) a willingness to participate in this investigational study as indicated by signing an Institutional Review Board–approved informed consent. Patients were ineligible for study if any of the following exclusion criteria were present: (*a*) pregnant or lactating females, (*b*) >grade 1 neurologic abnormality, (*c*) HIV-positive status, (*d*) known allergy to sulfa medications, and (*e*) New York Heart Association class 3 to 4 cardiovascular disability status.

This was an open-label, phase 1 dose escalation study of ABT-751 administered on a q.d. or b.i.d. oral administration schedule. Patients self-administered the appropriate dose of ABT-751 for 7 consecutive days at ~8 a.m. for the q.d. regimen and 8 a.m. and 8 p.m. for the b.i.d. regimen. ABT-751 morning doses (8 a.m.) were administered with breakfast. Additional cycles of drug were administered every 3 weeks until dose-limiting toxicity (DLT) or disease progression was noted. DLT was defined as any of the following if the event was considered possibly or probably related to the study drug during the first cycle of therapy: (*a*) National Cancer Institute Common Toxicity Criteria (CTC), version 2.0 (13), grade 4 absolute neutrophil count >7 days, (*b*) CTC grade 4 platelet count, (*c*) CTC ≥grade 3 absolute neutrophil count with fever, (*d*) any other CTC ≥grade 3 toxicity that represents a two-grade increase from baseline (excluding inadequately treated nausea and vomiting), (*e*) CTC ≥grade 2 neurotoxicity (excluding neuropathy) persisting through the entire cycle (day 21), (*f*) a toxicity that represents at least a two-grade increase from baseline, which required a delay of more than 1 additional week of recovery before starting the next cycle of study drug administration. The initial dose tested was 300 mg/d on the q.d. schedule that was calculated using ~75% of the maximum tolerated dose (240 mg/m^2) from the Japanese repeated-dose regimen (12) based on an estimated body surface area of 1.7 m^2. B.i.d. dosing began at 125 mg once the 250 mg q.d. dose was cleared.

Table 1. Patient characteristics

	q.d. Administration	b.i.d. Administration
Entered	15	24
Male/Female	10/5	13/11
Age (y)		
Median	55	54
Range	30-75	22-75
Eastern Cooperative Oncology Group performance status		
0	3	0
1	9	18
2	3	6
Tumor type		
Colorectal	6	7
Glioma		3
Pancreatic		2
Hepatocellular	1	1
Renal	3	4
Melanoma	2	
Chondrosarcoma	1	
Adrenocortical carcinoma	1	
Adenoid squamous	1	
NSCLC		1
Cervical		1
Prostate		1
Bladder		1
Thymic carcinoid		1
Insulin-secreting		1
Leiomyosarcoma		1

Table 2. Drug-related (probable or possible) toxicities

Dose level	Number of patients				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cycle 1 only					
200 mg q.d. ($n = 3$)	1	0	1	1	0
250 mg q.d. ($n = 6$)	0	3	2	1	0
300 mg q.d. ($n = 6$)	1	0	3	2	0
125 mg b.i.d. ($n = 6$)	3	2	0	1	0
150 mg b.i.d. ($n = 10$)	4	2	2	1	1
175 mg b.i.d. ($n = 8$)	2	1	4	1	0
Any cycle					
200 mg q.d. ($n = 3$)	1	0	1	1	0
250 mg q.d. ($n = 6$)	0	1	2	3	0
300 mg q.d. ($n = 6$)	0	1	3	2	0
125 mg b.i.d. ($n = 6$)	2	3	0	1	0
150 mg b.i.d. ($n = 10$)	1	0	6	2	1
175 mg b.i.d. ($n = 8$)	0	1	0	7	0

A minimum of three patients was entered into each dosing cohort. Dose escalation, dose reduction, or expansion of a cohort took place when all three patients completed 21 days of therapy. Patients were evaluated weekly for symptoms with measurement of laboratory variables. Toxicity was graded weekly according to National Cancer Institute CTC. If none of three patients experienced DLT, the dose of ABT-751 was increased by a total of 50 mg/d in both the q.d. and b.i.d. schedules for the next treatment cohort. If 2 patients developed DLT, dose escalation was stopped and additional patients were studied at lower doses. If one of three patients experienced DLT, up to three additional patients were entered in that dose cohort. The maximum tolerated dose was defined as the highest dose that produced DLT in fewer than one-third of treated patients over the first three cycles of therapy. An expanded cohort of at least six patients was required at the dose recommended for phase 2 studies.

Clinical and laboratory evaluations. Patients were screened with a complete medical history, physical examination, prothrombin time, partial thromboplastin time, complete blood count, comprehensive metabolic panel, chest X-ray, urinalysis, echocardiogram or multiple gated acquisition scans, ECG, pregnancy test, and tumor assessment by computed tomography scans <4 weeks before starting the study. A similar evaluation was done prior to the initiation of each 21-day treatment cycle, with the exception of computed tomography scans which were done after every 2 cycles, or at any time disease progression was clinically suspected. On days 8 and 15 of each cycle, patients were examined, symptoms and vital signs monitored, and laboratory samples obtained, including a comprehensive metabolic panel, prothrombin time, partial thromboplastin time, and complete blood count.

Pharmacokinetic evaluations. Blood samples were drawn on day 7, cycle 1. Samples (5 mL) were collected into evacuated collection tubes containing EDTA. For patients on q.d. regimens, blood samples were collected predose, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing. Trough blood samples were collected on day 8 of cycles 2 and 3, ~24 hours after the last dose. For patients on b.i.d. regimens, blood samples were collected predose, 0.5, 1, 2, 4, 6, and 8 hours after the morning dose and immediately before the evening dose. In addition, blood samples were collected at 0.5, 1, 2, 4, 6, 8, and 12 hours after the evening dose in patients of the first cohort receiving the b.i.d. regimen. Trough blood samples were collected on day 8 of cycles 2 and 3, ~12 hours after the evening dose. After collection, blood samples were immediately placed on ice and centrifuged within 1 hour of collection and stored at −20°C until analysis at Abbott Laboratories (Abbott Park, IL).

Urine samples were collected prior to the study initiation and over a dosing interval on day 7, cycle 1. A single cumulative urine sample was collected without preservatives from 0 to 24 hours after drug administration for the q.d. regimen and from 0 to 12 and from 12 to 24 hours for the b.i.d. regimen. The urine volume of each collection on day 7, cycle 1 was recorded. Two 5-mL aliquots of each urine sample collected were frozen at −20°C until analysis.

Plasma and urine concentrations of ABT-751 and its metabolites (glucuronide and sulfate) were measured using validated liquid chromatography with tandem mass spectrometry detection assay methodology. Plasma method accuracy, expressed as the percentage of mean bias, ranged from 0.7% to 10.0%; and precision, expressed as the percentage of coefficient of variation, was within 11.4% for all analytes. Urine method accuracy ranged from −8.7% to −1.7% mean bias, and precision within 11.8% coefficients of variation for the three analytes. Overall procedural recovery was determined, taking into account sample preparation efficiency and matrix effect on ionization for both plasma and urine. Mean recovery was 76.9%, 47.3%, and 30.3% of theory for plasma; and 114.2%, 80.5%, and 93.7% of theory for urine for ABT-751, glucuronide and sulfate, respectively. Plasma and urine samples were prepared by the addition of an internal standard, a structural analogue of ABT-751 used for quantitation of all analytes, to an aliquot of the matrix. The analytes were isolated from plasma matrix by solid phase extraction with SPEC C18 AR 96-well format plates (Varian, Walnut Creek, CA). Chromatographic separation was done by reversed phase high-pressure liquid chromatography on a Nucleosil 100-5 C18 Nautilus 125 × 2.0 mm column (Macherey-Nagel, Easton, PA) with a mobile phase of acetonitrile (pH 5) aqueous ammonium acetate (55:45, v/v), delivered at an isocratic flow rate of 400 μL/min. Injection volume was 10 to 20 μL. The parent drug, glucuronide, sulfate, and internal standard peaks were chromatographically resolved. Detection was by tandem mass spectrometry with the API 365 (Applied Biosystems/MDS Sciex, Foster City, CA). The lower limit of quantitation in plasma was ~0.015 μg/mL with the linear range from ~0.015 to 40 μg/mL for the three analytes. Urine matrix cleanup was done with an online trapping column, YMC Basic S5 20 × 2.0 mm (YMC, Inc., Wilmington, NC). The liquid chromatography separation and tandem mass spectrometry analysis for urine were as described for plasma with injection volume of 15 μL. The urine assay analyte peaks were chromatographically resolved as

well. The lower limit of quantitation for urine was ~0.06 μg/mL for all analytes, with the linear range from ~0.06 to 40 μg/mL. Quantitation was by internal standardization using $1/x^2$ weighted linear regression with Watson LIMS (Thermo Electron Corp., Wayne, PA). All reported results were within the calibration ranges for each analyte and matrix, and dilutions were done as necessary to yield calculated concentrations within range. The stability of the analytes in both matrices was established to cover the duration of sample analysis, with the exception of some reassays. The affected reassay results were flagged as suspect for this reason. Plasma samples which exceeded stability were subject 1002, day 7, 1 and 2 hours; subject 1403, cycle 2, day 8, 0 hours; subject 1501, day 7; 2, 4, and 6 hours; subject 1503, cycle 3, day 8, 0 hours; and subject 5703, day 7, 1 hour for all analytes; subject 5701 final visit, 0 hour only for ABT-751; and subject 1503 day 7, 8 hours for the two metabolites only. The urine samples which exceeded stability were all from day 7, subject 1001, 0 and 24 hours; subject 1002, 24 hours; subject 1004, 0 and 24 hours; and subject 1006, 0 and 24 hour collections for all three analytes. These represent 2.3% and 7.6% of plasma and urine determinations, respectively, exceeding established stability.

The following pharmacokinetic variables were determined using WinNonlin program (Pharsight Corporation, Cary, NC) with standard noncompartmental methods for ABT-751 and its metabolites: the maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), trough plasma concentration (C_{trough}), and area under the plasma concentration-time curve (AUC) over a dosing interval (AUC_τ). Oral clearance (CL/F) of ABT-751 was calculated by dividing the dose by AUC_τ. The amount of ABT-751 or its metabolites excreted in urine (A_u) over a dosing interval was estimated by calculating the product of urine concentration and volume. The percentage of the dose recovered in urine as parent drug and metabolites was calculated as the total amount recovered in urine divided by the dose multiplied by 100, with the adjustment of metabolites to ABT-751 equivalents. Renal clearance (CL_r) of ABT-751 was computed as A_u/AUC_τ.

Analysis of covariance (ANCOVA) was done for q.d. and b.i.d. regimens separately on T_{max} and natural logarithms of dose-normalized C_{max}, C_{trough}, and AUC_τ for ABT-751 and its metabolites. The sources of variation included in the model were dose and gender, with age and body weight as the covariates. Linear trend in dose was done within the ANCOVA framework to assess dose proportionality. A paired t test was done on T_{max} and natural logarithms of C_{max}, C_{trough} and AUC_τ for ABT-751 and its metabolites after morning and evening doses of 125 mg b.i.d.

Tumor assessments. Repeat evaluation of tumor size was made by physical examination and radiographic evaluation after every two treatment cycles. The Response Evaluation Criteria in Solid Tumors guideline was used to assess radiographic response (14). Responses required verification by a repeat evaluation at least 1 month later.

Results

Patient characteristics. Thirty-nine patients were enrolled in the study and treated between September 2001 and June 2004. Patient characteristics are summarized in Table 1. The median age was 54. The majority of patients had a pretreatment Eastern Cooperative Oncology Group performance status of 1 (range 0-2). The average number of previous chemotherapy regimens prior to study entry was 2.6. The 39 patients received 117 treatment cycles (median, 2; mean, 3; range, 0.5-13). Ten patients received at least four treatment cycles.

Toxicity. Toxicity was evaluated for all 39 patients using National Cancer Institute CTC, version 2. All drug-related toxicities seemed to be reversible. With q.d. administration, DLTs (grade 3 peripheral neuropathy and ileus) occurred in two of six patients at the initial dose tested (300 mg). Because DLT was encountered at the initial dose, the tolerability of lower doses (200 and 250 mg) was subsequently investigated. At a dose of 200 mg q.d., no DLT was observed in any of the three patients studied. At a dose of 250 mg q.d., five of six patients were entered without DLTs during the first treatment cycle. Therefore, 250 mg was chosen as the recommended phase 2 dose for q.d. ABT-751 administration for 7 consecutive days every 3 weeks. Table 2 summarizes the number of patients having no toxicity (grade 0) or grades 1, 2, 3, or 4 toxicity at each dose studied. The highest grade toxicity for each patient during cycle 1 only as well as for any time during the study is presented in Table 2. At 300 mg q.d., grade 3 toxicity was dose-limiting in two patients, and five of six patients treated at this dose had grade 2 or greater toxicity during cycle 1. At 250 mg

Table 3. Grade 3 or 4 toxicities possibly or probably related to ABT-751 during all cycles

Toxicity	Number of patients per dose level					
	q.d. regimen (mg)			b.i.d. regimen (mg)		
	200 (n = 3)	250 (n = 6)	300 (n = 6)	125 (n = 6)	150 (n = 10)	175 (n = 8)
Asthenia	0	1	0	1	2	5
Constipation	0	1	1	0	2	3
Abdominal pain	0	0	0	0	0	1
Ileus	0	1	1*	0	1*	0
Nausea	0	0	0	0	0	1
Neuropathy	0	0	2*	0	0	0
Paresthesia	0	0	0	0	1	1
Anemia	1	0	0	0	0	0
Prothrombin time elongation	1	0	0	0	0	0
Arthralgia	0	0	0	0	0	1
Myalgia	0	0	0	0	0	1
Fecal impaction	0	0	0	0	0	1

*Indicates DLT.

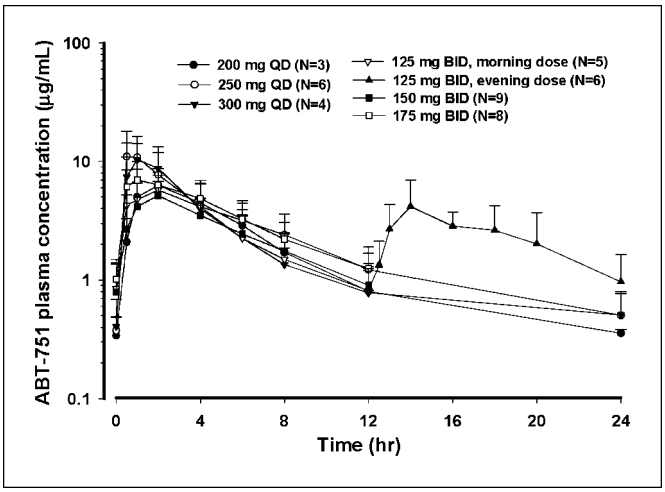

Fig. 2. ABT-751 plasma concentration-time profiles on cycle 1, day 7 (mean ± SD).

q.d., three of six patients were noted to have grade 2 or greater toxicity during cycle 1. During the entire treatment period, three of six patients at the 250 mg q.d. dose developed grade 3 or greater toxicity (Tables 2 and 3).

The toxicity grade of adverse events noted in each of the b.i.d. dosing cohort groups (125, 150, and 175 mg × 7 days) is summarized in Table 2. Of patients receiving b.i.d. administration, a DLT of grade 4 ileus occurred following cycle 1 in 1 of 10 patients at the second cohort studied (150 mg b.i.d.). Grade 2 or greater toxicities (ileus, constipation, and fatigue) were noted more frequently in cycles 2 and 3. Because late developing constipation and fatigue were seen in the 150 mg b.i.d. cohort (during cycles 2 and 3), patients with underlying constipation or Eastern Cooperative Oncology Group performance status >1 were excluded from enrollment into the 175 mg b.i.d. dosing regimen.

In the 175 mg b.i.d. dosing schedule, no DLTs were noted during cycle 1. However, seven of eight subjects had grade 3 drug-related toxicities during cycles 2 and 3 (Table 2). Dose reduction was frequently needed at this dose after the first 2 treatment cycles. One subject's dose was reduced to 150 mg b.i.d. in cycle 2, and two subjects' doses were reduced to 150 mg b.i.d. in cycle 3. Four patients did not continue therapy beyond cycle 2 due to progressive disease. As no patient was able to continue the drug at 175 mg b.i.d. for over 9 weeks, chronic therapy with ABT-751 at 175 mg b.i.d. was not considered feasible. Hence, the recommended phase 2 dose of ABT-751 for a b.i.d. schedule is 150 mg twice daily for 7 days given every 3 weeks. This dose was tolerated by one subject for eight cycles.

All drug-related grade 2 or 3 toxicities seen in patients on the b.i.d. dosing schedule are noted in Table 3. Fatigue (asthenia), constipation or ileus, anorexia, myalgia, neuropathy, and paresthesia were the most frequent toxicities noted.

One patient died during the first treatment cycle at the 150 mg b.i.d. dose. This death was suspected to be due to a pulmonary embolism, and considered unlikely to be related to study treatment. No other deaths during therapy were noted. No myelosuppression, renal toxicity, or hepatic toxicity was seen in any patient.

Antitumor effect. All 39 patients were assessed for tumor response. One minor response (21% decrease, cycle 4) was observed in a patient with recurrent anaplastic astrocytoma given 175 mg b.i.d. as ninth-line therapy. Her disease subsequently stabilized through 13 cycles. Stable disease was observed in three additional patients for longer than 6 months. One patient with renal cell cancer was given 150 mg b.i.d. as fourth-line therapy with stable disease through eight treatment

Table 4. Pharmacokinetic variables of ABT-751 and its metabolites on cycle 1, day 7 (mean ± SD)

Analyte	Variable	q.d. Regimens			b.i.d. Regimens			
		200 mg (n = 3)	250 mg (n = 6)	300 mg (n = 4)	125 mg Morning (n = 5)	125 mg Evening (n = 6)	150 mg (n = 9)	175 mg (n = 8)
ABT-751	C_{max} (μg/mL)	6.6 ± 1.7	12.7 ± 5.8	13.0 ± 2.6	9.0 ± 1.8*	5.4 ± 1.8	5.8 ± 2.0	9.0 ± 3.3
	T_{max} (h)	1.7 ± 0.6	2.0 ± 3.0	0.8 ± 0.3	1.9 ± 1.3	3.3 ± 2.9	1.8 ± 1.0	1.3 ± 1.2
	C_{trough} (μg/mL)	0.4 ± 0.0	0.5 ± 0.3	0.5 ± 0.3	0.8 ± 0.5	1.0 ± 0.7	0.9 ± 0.5	1.3 ± 0.4
	AUC_τ (μg·h/mL) †	42.8 ± 1.9	60.5 ± 21.6	50.2 ± 21.3*	33.5 ± 8.6	28.1 ± 9.5	31.4 ± 9.0	43.5 ± 8.1
	CL/F (L/h) ‡	4.7 ± 0.2	4.6 ± 1.8	6.6 ± 2.0	4.0 ± 1.2	4.9 ± 1.6	5.1 ± 1.2	4.1 ± 0.8
ABT-751 Glucuronide	C_{max} (μg/mL)	4.3 ± 1.4	6.1 ± 0.6	8.9 ± 1.8	8.7 ± 5.5	7.6 ± 3.5	9.5 ± 5.3	8.8 ± 2.9
	T_{max} (h)	4.7 ± 1.2	3.7 ± 2.3	3.5 ± 1.9	4.4 ± 2.2	4.7 ± 2.1	5.8 ± 1.6	4.0 ± 2.6
	C_{trough} (μg/mL)	1.1 ± 0.4	1.5 ± 1.2	2.7 ± 2.4	5.1 ± 4.2	4.7 ± 3.4	6.5 ± 4.4	4.8 ± 3.0
	AUC_τ (μg·h/mL)	60.2 ± 19.8	83.7 ± 19.1	128.9 ± 49.3	81.6 ± 56.5	69.4 ± 38.9	92.4 ± 50.5	78.3 ± 29.2
ABT-751 Sulfate	C_{max} (μg/mL)	6.9 ± 3.3	7.8 ± 1.2	14.7 ± 6.8	8.1 ± 3.2	7.1 ± 2.9	9.0 ± 4.1	7.8 ± 3.1
	T_{max} (h)	5.3 ± 1.2	3.2 ± 2.6	2.5 ± 1.0	3.6 ± 2.2	4.7 ± 2.1	4.9 ± 2.3	3.1 ± 2.2
	C_{trough} (μg/mL)	2.0 ± 1.6	1.9 ± 2.0	3.3 ± 3.1	4.0 ± 2.1	3.9 ± 2.0	5.5 ± 3.8	4.0 ± 3.2
	AUC_τ (μg·h/mL)	102.9 ± 67.4	94.6 ± 40.1	179.2 ± 82.7	71.1 ± 31.9	61.8 ± 30.2	86.6 ± 44.7	65.9 ± 32.2

*Dose-normalized pharmacokinetic variables were statistically significantly different from those in other groups in the same regimen ($P < 0.05$).
†AUC_{0-24} for q.d. regimens: AUC_{0-12} for b.i.d. regimens.
‡The statistical test for this variable was equivalent to that for AUC_τ.

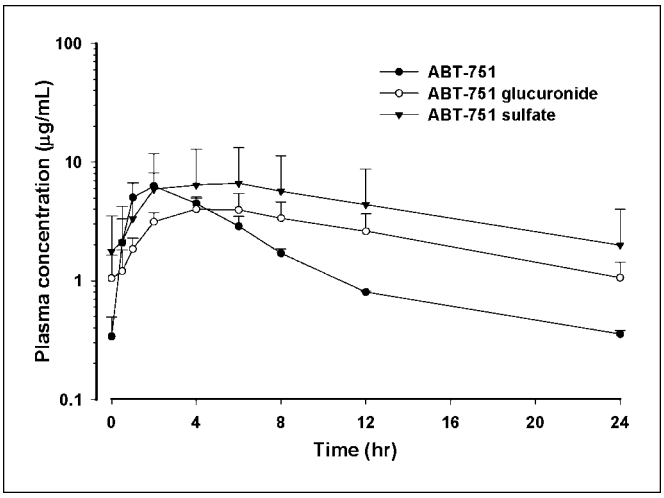

Fig. 3. Plasma concentration-time profiles of ABT-751 and its metabolites on cycle 1, day 7, 200 mg q.d. (mean ± SD).

cycles. A patient with thymic carcinoid tumor was given 175 mg b.i.d. as the third-line therapy with stable disease through 10 cycles.

Pharmacokinetics. After oral administration, ABT-751 plasma concentrations increased rapidly with an overall mean T_{max} of ~2 hours and declined multiexponentially (Fig. 2; Table 4). ABT-751 C_{max} and AUC_{τ} increased approximately dose proportionally across the dose range studied. With the exception of ABT-751 C_{max} in 125 mg b.i.d. after the morning dose and AUC_{τ} at 300 mg q.d., there was no statistically significant difference in dose-normalized C_{max} and AUC_{τ} across the regimens studied. ABT-751 C_{trough} were minimal after a 7-day dosing on cycle 1, and there was no statistically significant difference in dose-normalized C_{trough} across the dose and regimens studied. There was no significant difference in ABT-751 C_{trough}, AUC_{τ}, and T_{max} after morning and evening doses of 125 mg b.i.d. Similar C_{trough} of ABT-751 and its conjugated metabolites were observed on day 8 of cycles 2 and 3 with those on cycle 1, indicating time-independent pharmacokinetics (data not shown). Variability in ABT-751 C_{max} and AUC_{τ} was relatively low, overall mean coefficients of variation were ~30% and 25%, respectively, across the doses and regimens studied. No significant correlation between body weight, gender and ABT-751 dose-normalized AUC_{τ} was observed.

Two major metabolites of ABT-751, pharmacologically inactive, were identified in plasma, glucuronide, and sulfate conjugates. Plasma concentrations of these two metabolites increased after oral dosing and reached peak plasma concentrations at ~4 hours (overall T_{max}; Fig. 3). Dose-normalized AUC_{τ} AUC_{τ} of each ABT-751 metabolite were approximately double that of the parent drug. There were no statistically significant differences in T_{max} and dose-normalized C_{trough}, AUC_{τ}, and C_{max} for ABT-751 metabolites across the doses and regimens studied ($P > 0.22$).

Nearly 55% of the dose administered was excreted into the urine as ABT-751 (0.5%), ABT-751 sulfate (32%), and ABT-751 glucuronide (22%) during a dosing interval on cycle 1 day 7. ABT-751 CL_r (<30 mL/h) was negligible across the dose and regimens studied compared with CL/F.

Discussion

Drugs that bind to tubulin are among the most effective antineoplastic agents currently available. The *Vinca* alkaloids have shown effectiveness in the treatment of lung cancer, lymphomas, testicular cancer, breast cancer, bladder cancer, selected sarcomas, and germ cell tumors. The taxanes are active against breast cancer, ovarian cancer, lung cancer, head and neck cancer, prostate cancer, and esophageal cancer. ABT-751 uniquely targets the colchicine site on β-tubulin, which distinguishes it from the *Vincas* and taxanes. With its distinctive binding site, oral delivery, and demonstration of preclinical activity, ABT-751 warrants further evaluation against a variety of human tumors.

This study identified 250 mg orally q.d. for 7 days and 150 mg b.i.d. for 7 days given every 21 days as the recommended doses to carry forward into phase 2. The most frequent toxicities seen with ABT-751 were fatigue, asthenia, constipation (ileus), anorexia, peripheral neuropathy and myalgias. Ileus and neuropathy are recognized colchicine toxicities (15, 16). Although diarrhea is the most common manifestation of colchicine toxicity, constipation was noted with ABT-751. Toxicities of ABT-751 seem to be reversible. At a dose of 250 mg q.d. for 7 days, no DLTs were reported. In the 150 mg b.i.d. for 7 days group, 1 of 10 patients reported grade 3 toxicities related to the study drug. A dose of 250 mg q.d. or 150 mg b.i.d. for 7 days can be given to a majority of patients with manageable toxicity for three or more treatment cycles.

Consistent with previous studies (12, 17), dose-proportional and time-independent pharmacokinetics of ABT-751 were shown in the current study, supported by the approximately linear increase in ABT-751 exposure (AUC_{τ} and C_{max}) with dose, and similar pharmacokinetics after morning and evening doses and trough concentrations at different cycles. Similar to preclinical and clinical observations, ABT-751 clearance is mediated by direct glucuronidation and sulfation, with minimal involvement of CYP450.

The antiproliferative activity of ABT-751 is due to reversible binding to tubulin and inhibition of mitotic division. *In vitro* studies have shown that ABT-751 exhibits antiproliferative activity when tumor cells are exposed to ABT-751 for ≥12 hours. The efficacious concentrations of ABT-751 determined in preclinical tumor models were 0.5 to 1.5 μg/mL. These efficacious concentrations were achieved in all of the subjects in the current study.

In this phase 1 study, fixed doses of ABT-751 were administered to all subjects. The variability in ABT-751 C_{max} and AUC was relatively low and similar to that reported in the Japanese phase 1 study, in which ABT-751 was dosed by body surface area (12). There was no significant correlation between gender or body weight and ABT-751 AUC. The study results support fixed dosing (i.e., non–body surface area–based dosing) of ABT-751 in patients with solid tumors.

No complete or partial responses were seen in our phase 1 trials of extensively pretreated patients; however, one minor response (21% decrease) was observed and stable disease was noted in four patients for >6 months. Clinical responses have been noted in other phase 1 trials with ABT-751 (12, 17).[3]

[3] Unpublished data.

Due to its tolerable toxicity profile, unique binding site on tubulin, favorable pharmacokinetics, and suggestions of antineoplastic activity from *in vitro*, *in vivo*, and clinical studies, ABT-751 warrants investigation in phase 2 studies to further assess its antineoplastic activity. Four phase 2 studies are exploring the activity of ABT-751 in subjects with taxane-refractory breast cancer and lung cancer, renal cell carcinoma, and refractory colon cancer.

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