Phase I Study of Pazopanib in Combination with Weekly Paclitaxel in Patients with Advanced Solid Tumors

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This manuscript describes the use of pazopanib in combination with paclitaxel, which is investigational.

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ABSTRACT

Purpose. To evaluate the maximum tolerated regimen (MTR), dose-limiting toxicities, and pharmacokinetics of pazopanib, an oral small-molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit, in combination with paclitaxel.

Patients and Methods. Pazopanib was given daily with weekly paclitaxel on days 1, 8, and 15 every 28 days. Dose levels of pazopanib (mg/day)/paclitaxel (mg/m²) were 400/15, 800/15, 800/50, and 800/80. An expanded cohort was enrolled at the MTR. Plasma samples were collected to evaluate the effect of pazopanib, an inhibitor of cytochrome P450 (CYP)3A4, on the pharmacokinetics of paclitaxel, a CYP3A4 and CYP2C8 substrate.

Results. Of 26 enrolled patients, 17 were treated at the MTR of 800 mg pazopanib and 80 mg/m² paclitaxel. Dose-limiting toxicities included a grade 3 abscess and grade 2 hyperbilirubinemia. Other toxicities included elevated liver transaminases and diarrhea. Six patients (23%) had partial responses and 15 patients (58%) had stable disease. Administration of 800 mg pazopanib resulted in a 14% lower paclitaxel clearance and a 31% higher paclitaxel maximal concentration than with administration of paclitaxel alone at 15, 50, and 80 mg/m². At the MTR, coadministration of 800 mg pazopanib and 80 mg/m² paclitaxel resulted in a 26% higher geometric mean paclitaxel area under the curve.

Conclusion. Pazopanib, at a dose of 800 mg daily, can

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be safely combined with a therapeutic dose of paclitaxel at 80 mg/m² when administered on days 1, 8, and 15, every 28 days. The observed greater plasma concentra-

tions of paclitaxel given concurrently with pazopanib suggest that pazopanib is a weak inhibitor of CYP3A4 and CYP2C8. *The Oncologist* 2010;15:1253–1261

INTRODUCTION

Angiogenesis plays an essential role in the growth and progression of cancer [1]. Small-molecule tyrosine kinase inhibitors represent a novel approach to targeting angiogenesis. These multitargeted compounds may overcome redundancies in signaling pathways and result in more effective inhibition of tumor growth than with single targeted agents. Pazopanib (Votrient®; GlaxoSmithKline, Research Triangle Park, NC) was approved by the U.S. Food and Drug Administration (FDA) in October 2009 for the treatment of patients with advanced renal cell carcinoma [2]. It is an oral, small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)- α , PDGFR- β , and c-Kit tyrosine kinases [3]. In preclinical experiments, pazopanib has shown significant inhibition of VEGF-induced VEGFR-2 phosphorylation with a half-maximal inhibition concentration (IC₅₀) of 30 nM, and is three- to 400-fold selective for VEGFRs compared with other kinases. It also inhibits VEGF-induced proliferation of human umbilical vein endothelial cells with an IC₅₀ of 8 nM. Studies in mice also showed that a plasma concentration ≥ 40 μ M (17.5 μ g/ml) is required for optimal inhibition of VEGF-induced VEGFR-2 phosphorylation in mice. Additionally, pazopanib shows growth inhibition in a variety of human tumor xenografts in mice including breast, renal, lung, colon, and prostate tumors, and melanoma, and also inhibits angiogenesis in vivo [4]. In a phase I study, single-agent pazopanib was administered to 63 patients with advanced solid tumors at doses of 50 mg three times weekly to 2,000 mg once daily. Steady-state plasma pazopanib concentrations appeared to plateau at doses ≥ 800 mg daily [5]. At a daily dose of 800 mg pazopanib, the majority of patients achieved a target trough concentration of ≥ 15 μ g/ml, which is similar to that required to inhibit VEGFR-2 phosphorylation in vivo. Of the 14 patients treated with pazopanib at a dose of 800 mg once daily, one patient had dose-limiting toxicities of grade 3 hypertension and grade 3 proteinuria. Based on these observations, the recommended phase II dose of single-agent pazopanib is 800 mg orally once daily.

The combination of an angiogenesis inhibitor with chemotherapy is a common treatment approach for several solid tumor types. Bevacizumab (Avastin®; Genentech, South San Francisco, CA), a humanized monoclonal anti-

body directed against VEGF, combined with chemotherapy has indications for the treatment of patients with metastatic colon cancer and non-small cell lung cancer (NSCLC) as first-line therapy [6, 7]. Cytotoxic agents, such as paclitaxel, when administered at low doses and frequent intervals, may exert antiangiogenic effects, thereby enhancing anticancer activity [8, 9]. Patients with metastatic human epidermal growth factor receptor (HER)-2–negative breast cancer who received treatment with weekly paclitaxel on days 1, 8, and 15 every 28 days in combination with bevacizumab on days 1 and 15 experienced a longer progression-free survival interval and higher response rate than patients treated with paclitaxel alone, which led to the FDA approval of this combination in the first-line setting [10].

On the basis of preclinical evidence of the antiangiogenic activity of pazopanib, the activity of paclitaxel in the treatment of solid tumors, and the observation that weekly paclitaxel has antiangiogenic effects, we investigated the combination of once-daily pazopanib with paclitaxel given once weekly for three consecutive weeks every 28 days. Paclitaxel is metabolized by cytochrome P450 (CYP)3A4 and CYP2C8 [11, 12]. In vitro data suggest that pazopanib is a potential inhibitor of the CYP3A4 and CYP2C8 isoenzymes and may decrease the clearance of paclitaxel [4]. Therefore, this study also was designed to determine the potential effect of pazopanib on the pharmacokinetics of paclitaxel. The specific objectives of this phase I study were to determine the maximum-tolerated regimen (MTR) and dose-limiting toxicities of pazopanib in combination with weekly paclitaxel, assess the effect of pazopanib on the pharmacokinetic profile of paclitaxel, and evaluate antitumor activity.

PATIENTS AND METHODS

Trial Design

This was a three-center, open-label, dose-escalation study (clinicalTrials.gov identifier, NCT00388076) to assess the safety and pharmacokinetics of once-daily pazopanib in combination with paclitaxel on a weekly schedule for three consecutive weeks of a 28-day cycle. The starting dose level was 400 mg pazopanib and 15 mg/m² paclitaxel. Dose escalation of paclitaxel was guided both by prespecified pharmacokinetic considerations and by safety data from each cohort. Dose escalation of paclitaxel could be halted

Table 1. Dose levels and dose-limiting toxicities (DLTs)

Cohort	Dose level	No. of patients	No. of patients with DLTs (event)
1	400 mg pazopanib + 15 mg/m ² paclitaxel	3	0
2	800 mg pazopanib + 15 mg/m ² paclitaxel	3	0
3	800 mg pazopanib + 50 mg/m ² paclitaxel	3	0
4	800 mg pazopanib + 80 mg/m ² paclitaxel	17	2 (grade 3 groin abscess and grade 2 hyperbilirubinemia)

based on the pharmacokinetic results. The pharmacokinetic analysis was performed to determine the ratio of paclitaxel exposure on day 15 to exposure on day 1 to help select the appropriate dose of paclitaxel for escalation. The dose levels are shown in Table 1. At least three patients were enrolled at each dose level. If none of the three patients experienced a dose-limiting toxicity, dose escalation continued. If one patient developed a dose-limiting toxicity, three additional patients were enrolled at the same dose level. The MTR was defined as the highest dose at which no more than one in six patients evaluable for toxicity experienced a dose-limiting toxicity. Inpatient dose escalation was not permitted. Up to nine additional patients were treated at the MTR to further explore the pharmacokinetics and toxicity of the combination. Additionally, the MTR definition also took into consideration a dose of paclitaxel in which the median systemic exposure of paclitaxel at the selected dose level could not exceed 115% of the predicted exposure at 100 mg/m² and the maximum predicted exposure did not exceed 200% of the predicted exposure at 100 mg/m².

Adverse events were evaluated and graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. A dose-limiting toxicity was defined as one of the following events occurring during cycle 1: grade 4 neutropenia >5 days, grade 3 or 4 febrile neutropenia, grade 4 thrombocytopenia, grade ≥2 nonhematologic toxicity that persisted beyond cycle 1, inability to begin the next course of treatment within 2 weeks because of unresolved toxicity, or any grade 3 or 4 clinically significant nonhematologic toxicity. For hepatotoxicity, the protocol specified discontinuation of pazopanib if the alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels were >2.5× the upper limit of normal (ULN) with a concomitant elevation in total bilirubin >1.5× ULN that was at least 35% direct bilirubin, the presence of hypersensitivity symptoms such as fever and rash, or if the ALT and/or AST levels were >8× ULN. Retreatment was considered if the ALT and/or AST level decreased to grade

1, the patient was experiencing benefit, and the total bilirubin was ≤1.5× ULN or the direct bilirubin was ≤35%.

Eligibility Criteria

Eligible patients were required to have a histologic or cytologic diagnosis of metastatic carcinoma, an Eastern Cooperative Oncology Group performance status score ≤1, and age ≥18 years. Requirements for adequate organ function included an absolute neutrophil count ≥2,000/mm³; platelet count ≥100,000/mm³; hemoglobin ≥9.0 g/dl; prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) ≤1.2× ULN; measured creatinine clearance ≥60 ml/minute by 24-hour urine collection; urine protein:urine creatinine (UPC) ratio ≤1; total bilirubin ≤1.5× ULN; and ALT and AST ≤2× ULN. Chemotherapy, radiotherapy, investigational agents, or surgery within 28 days of study treatment were not permitted. Patients were excluded if they had more than three prior cytotoxic regimens for metastatic disease, grade ≥2 neuropathy, poorly controlled hypertension (≥140/90 mm Hg), corrected QTc interval ≥470 msec, arterial or venous thrombi within 3 months of study entry, a history of bleeding within 1 month of study entry, brain metastases or leptomeningeal disease, concurrent therapeutic warfarin (low-molecular-weight heparin and prophylactic low-dose warfarin were permitted), or hypersensitivity to paclitaxel or other angiogenesis inhibitors. Patients were not permitted to use medications metabolized by CYP3A4 that had the potential to cause serious and/or life-threatening adverse events, because in vitro data indicated that pazopanib is a potential inhibitor of CYP3A4 [4]. The following medications were prohibited: warfarin, oral hypoglycemics (tolbutamide, chlorpropamide), ergot derivatives, pimozide, erectile dysfunction agents (sildenafil, tadalafil, vardenafil), antiarrhythmics (bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone), immune modulators (cyclosporine, tacrolimus, sirolimus), theophylline, quetiapine, risperidone, tacrine, clozapine, and atomoxetine. The protocol was approved by the institutional re-

view board at each participating institution. All patients gave written informed consent before treatment.

Treatment

Pazopanib was supplied by GlaxoSmithKline as 200-mg and 400-mg tablets. Pazopanib was administered orally once daily at least 1 hour before or 2 hours after a meal based on data showing that administration of food results in a twofold greater area under the curve (AUC) and maximal concentration (C_{max}) of pazopanib [13]. Pazopanib was started on day 2 during cycle 1 to allow assessment of paclitaxel pharmacokinetics alone on day 1, then pazopanib was continued throughout the duration of the study. Paclitaxel was administered i.v. as a 1-hour infusion on days 1, 8, and 15 of a 28-day cycle after oral ingestion of pazopanib. Premedication consisted of 10 mg dexamethasone, 25 mg diphenhydramine, and 50 mg ranitidine given i.v. 1 hour before paclitaxel.

Assessments

A history, physical examination, and laboratory tests, including hematology, PT, PTT, and INR (before cycle 1 only), clinical chemistry, and UPC ratio, were done before each cycle. Hematology and clinical chemistry studies were done on days 8 and 15 of each cycle. An electrocardiogram was done at baseline and 4 hours after pazopanib dosing on day 15 of cycle 1 for QTc interval measurement. Amylase, lipase, and thyroid function tests were obtained every two cycles. At each visit, blood pressure was measured three times at 2-minute intervals. The second and third values were averaged to determine whether dose modification of pazopanib was necessary. Imaging of involved cancer sites was performed within 4 weeks before the first dose then every 8 weeks. Response was assessed using the Response Evaluation Criteria in Solid Tumors [14].

Pharmacokinetic Sampling, Assay, and Analysis

During cycle 1, blood samples for analysis of plasma paclitaxel concentrations were collected before treatment and at 0.5, 1 (end of infusion), 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after the start of infusion on days 1 and 15. During cycle 1, samples were also obtained for pazopanib pharmacokinetics before treatment and at 1, 2, 3, 4, 6, 8, 12, and 24 hours after administration on day 15. Blood samples were collected for analysis of both plasma pazopanib and paclitaxel concentrations before treatment and 1, 4, and 6 hours after the start of the paclitaxel infusion on day 8 of cycle 1.

High-performance liquid chromatography tandem mass spectrometry was used to quantify the plasma concentrations of pazopanib and paclitaxel. Pazopanib was extracted from 50 μ l of plasma by protein precipitation. This vali-

Table 2. Patient characteristics

Characteristic	Patients (n = 26)
Age, median yrs (range)	56 (34–78)
Sex, n (%)	
Male	13 (50)
Female	13 (50)
Race, n (%)	
White	24 (92)
Black	2 (8)
ECOG performance status score, n (%)	
0	15 (85)
1	11 (42)
Primary tumor type, n (%)	
Breast	5 (19)
Colon/rectum	3 (12)
Esophagus	3 (12)
NSCLC	3 (12)
Bladder	2 (8)
Pancreas	2 (8)
Other	7 (27)
Unknown	1 (4)
No. of prior lines of chemotherapy, n (%)	
0	5 (19)
1	12 (46)
2	6 (23)
3	3 (12)
Patients with prior taxane therapy, n (%)	12 (46)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.	

dated analytic method has a lower limit of quantification of 100 ng/ml with a higher limit of quantification of 50,000 ng/ml of pazopanib. Paclitaxel was isolated from 0.1 ml of plasma using a liquid–liquid extraction procedure. This method has a lower limit of quantification of 2 ng/ml for paclitaxel.

Pharmacokinetic parameters were calculated by standard noncompartmental methods using WinNonlin Professional®, version 4.1 (Pharsight Corporation, Mountain View, CA).

RESULTS

Patient Characteristics

Between May 2006 and August 2007, 26 patients were enrolled. Patient characteristics are shown in Table 2. The most common tumor types were breast cancer (19%), colorectal cancer (12%), esophageal cancer (12%), and NSCLC

(12%). Most patients (81%) had received one or more prior lines of chemotherapy. Twelve patients had prior taxane exposure either in the adjuvant or metastatic setting (50% received paclitaxel, 50% received docetaxel). No patients remain on study.

Dose Escalation and Dose-Limiting Toxicity

The starting doses were 400 mg/day pazopanib and 15 mg/m² paclitaxel. The regimen was escalated to the 800/15, 800/50, and 800/80 doses (Table 1). No dose-limiting toxicities were observed during the first cycle in the nine patients treated in the first three cohorts. For each of the first three cohorts, specific pharmacokinetic criteria (the median ratio of the paclitaxel AUC on day 15 to the AUC on day 1 had to be ≤ 3) were met. The fourth cohort of patients was treated with 800 mg/day pazopanib and 80 mg/m² paclitaxel. One of the first three patients experienced a grade 3 groin abscess during cycle 1 that constituted a dose-limiting toxicity. An additional three patients were enrolled and none had dose-limiting toxicities, so that among the six patients treated in cohort 4 there was one dose-limiting toxicity. Dose escalation was guided by pharmacokinetic data, and at the 800 mg/day pazopanib and 80 mg/m² paclitaxel level, the ratio of the paclitaxel AUC on day 15 to the AUC on day 1 was 126%. Therefore, the expected exposure of the combination at the next proposed paclitaxel dose of 100 mg/m² would exceed 115% of the predicted single-agent paclitaxel exposure at the same dose that was predefined, prohibiting further dose escalation. The protocol allowed an expanded cohort of nine additional patients at the MTR; however, two patients needed replacing (one was not evaluable for dose-limiting toxicity and another did not complete the pharmacokinetic assessments), which resulted in an actual enrollment of 11 patients. In this expanded cohort, one patient developed a dose-limiting toxicity of grade 2 hyperbilirubinemia as three separate occurrences during cycle 1 that resolved upon interruption of pazopanib dosing. The MTR in this study based on pharmacokinetic data was determined to be 800 mg pazopanib daily and 80 mg/m² paclitaxel on days 1, 8, and 15 of a 28-day cycle.

Toxicities

The most frequently occurring treatment-related adverse events were fatigue (69%), nausea (58%), diarrhea (54%), alopecia (35%), vomiting (35%), and rash (31%) (Table 3). Most toxicities (92%) were grade 1 or 2. Elevations in hepatic enzymes, including AST, ALT, bilirubin, and alkaline phosphatase, were observed (Table 4). In total, four of 10 patients who experienced a hepatobiliary event across the four cohorts required a pazopanib dose reduction because of elevated transaminases, whereas the remaining six pa-

tients continued at the same dose. Among the four patients who required a dose reduction, for three patients it occurred during cycle 3 and for one patient it occurred during cycle 1. In some instances, when therapy was interrupted, recurrent elevations were observed upon rechallenge. There was one case of grade 3 acute nonviral hepatitis considered to be possibly drug related. In this instance, a breast cancer patient with metastatic disease to the liver was hospitalized for complaints of fever, nausea, vomiting, mild right upper quadrant pain, and grade 3 thrombocytopenia 2 weeks after the last dose of pazopanib. She was also being treated with levofloxacin for a urinary tract infection 4 days prior to admission. She had grade 4 AST, grade 3 ALT, and grade 3 bilirubin. She was treated with i.v. steroids and the event resolved with the return of her AST and ALT values to baseline. Given the known association of hepatotoxicity with pazopanib, it could not be ruled out that there was a possible relationship to the study drug. Hypertension was the most common cardiovascular adverse event. Ten patients had baseline hypertension. Six of these patients required either modification of their existing antihypertensive regimen or initiation of additional antihypertensive medications. The only case of grade 3 hypertension was observed in cohort 2. Hemorrhagic events consisted of one gastrointestinal hemorrhage in a patient with portal hypertension and esophageal varices, which resulted in death and was considered possibly related to the study drug. This occurred in a 64-year-old male with hepatocellular carcinoma who experienced hematemesis after 5 months of treatment. His hemoglobin was 6.5 mg/dl. An endoscopy did not reveal any obvious source of bleeding. Esophageal varices were present. No further diagnostic testing could be done because the patient rapidly deteriorated. Grade 1 asymptomatic elevations in amylase and/or lipase occurred in five patients (19%). At the MTR, there was one case of grade 2 hypothyroidism (6%) and one case of grade 2 thyroid-stimulating hormone elevation (6%). There were no episodes of QTc prolongation (>480 msec).

Pharmacokinetics

Plasma samples for analysis of pazopanib pharmacokinetics were obtained from 25 patients. The median plasma pazopanib $C_{\max}$ values were similar on day 8 and day 15, and were consistent with steady-state plasma pazopanib concentrations reached by day 8 in cohorts 1–3 (data not shown). In cohort 4 (paclitaxel, 80 mg/m²; pazopanib, 800 mg once daily), the geometric mean pazopanib $C_{\max}$ values on day 8 and day 15 were similar to the geometric mean $C_{\max}$ value of 40 μ g/ml observed on day 22 after 800 mg once-daily dosing in the phase I study [5]. These concentrations were at least 3.5-fold greater than the in vitro IC₅₀

Table 3. Drug-related adverse events occurring in $\geq 10\%$ of patients

	Maximum CTCAE grade, <i>n</i> (%)								Any grade, <i>n</i> (%)
	15 mg/m ² paclitaxel + 400 mg pazopanib (<i>n</i> = 3)		15 mg/m ² paclitaxel + 800 mg pazopanib (<i>n</i> = 3)		50 mg/m ² paclitaxel + 800 mg pazopanib (<i>n</i> = 3)		80 mg/m ² paclitaxel + 800 mg pazopanib (<i>n</i> = 17)		Total (<i>n</i> = 26)
	1 or 2	3 or 4	1 or 2	3 or 4	1 or 2	3 or 4	1 or 2	3 or 4	
Fatigue	1 (33)	0	0	0	3 (100)	0	14 (82)	0	18 (69)
Nausea	2 (67)	0	2 (67)	0	2 (67)	0	9 (53)	0	15 (58)
Diarrhea	1 (33)	0	2 (67)	1 (33)	1 (33)	1 (33)	8 (47)	0	14 (54)
Alopecia	0	0	0	0	0	0	9 (53)	0	9 (35)
Vomiting	0	0	1 (33)	0	1 (33)	0	7 (41)	0	9 (35)
Rash	0	0	0	0	0	0	8 (47)	0	8 (31)
AST elevation	0	0	1 (33)	0	1 (33)	0	3 (18)	2 (12)	7 (27)
ALT elevation	0	0	0	0	1 (33)	0	3 (18)	2 (12)	6 (23)
Anorexia	0	0	1 (33)	0	1 (33)	0	4 (24)	0	6 (23)
Dysgeusia	0	0	1 (33)	0	1 (33)	0	4 (24)	0	6 (23)
Hypertension	0	0	0	1 (33)	1 (33)	0	4 (24)	0	6 (23)
Neutropenia	0	0	0	0	0	0	3 (18)	3 (18)	6 (23)
Epistaxis	0	0	2 (67)	0	0	0	3 (18)	0	5 (19)
Dizziness	0	0	1 (33)	0	1 (33)	0	2 (12)	0	4 (15)
Hair depigmentation	0	0	1 (33)	0	0	0	3 (18)	0	4 (15)
Flushing	0	0	0	0	0	0	3 (18)	0	3 (12)
Peripheral neuropathy	0	0	0	0	0	0	2 (12)	1 (6)	3 (12)
Skin hypopigmentation	0	0	2 (67)	0	1 (33)	0	0	0	3 (12)
Visual disturbance	0	0	1 (33)	0	1 (33)	0	1 (6)	0	3 (12)

At the 80 mg/m² paclitaxel + 800 mg pazopanib dose level, one case of grade 4 lymphopenia and one case of grade 5 gastrointestinal hemorrhage were reported.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

Table 4. Hepatic enzyme shifts from baseline to maximum toxicity grade at the maximum tolerated regimen

	Patients, <i>n</i> (%) (<i>n</i> = 17)			
	Grade 1	Grade 2	Grade 3	Grade 4
Aspartate aminotransferase	7 (41)	2 (12)	1 (6)	0
Alanine aminotransferase	7 (41)	4 (24)	1 (6)	0
Total bilirubin	0	1 (6) ^a	0	0
Alkaline phosphatase	2 (12)	1 (6)	0	0

^aThis patient had a uridine-diphosphoglucuronosyl transferase 1A1 (UGT1A1)*28 (TA7/TA7) genotype, predisposing the patient to hyperbilirubinemia.

for inhibition of CYP3A4 and CYP2C8 by pazopanib [4], indicating that plasma pazopanib concentrations that could

potentially inhibit CYP3A4 (and/or CYP2C8) were achieved by day 8.

Coadministration of 800 mg pazopanib once daily and 80 mg/m² paclitaxel weekly resulted in a 36% higher geometric mean $C_{\max}$ of paclitaxel than with administration of paclitaxel alone (Fig. 1). The geometric mean paclitaxel $C_{\max}$ was greater on day 15 than on day 8, but the difference was $<20\%$, suggesting that there were no time-dependent changes in the effect of pazopanib on the pharmacokinetics of paclitaxel between day 8 and day 15. At the MTR, the geometric mean paclitaxel AUC extrapolated to infinity ($AUC_{0-\infty}$) was 26% higher and the geometric mean clearance of paclitaxel was 20% lower (Table 5).

Efficacy

In this phase I study, confirmed partial responses were observed in five patients treated with 80 mg/m² paclitaxel and

Figure 1. Median paclitaxel concentration on day 1 and day 15 after administration of 80 mg/m² paclitaxel with 800 mg pazopanib once daily.

Table 5. Geometric mean pharmacokinetic parameters of paclitaxel at the maximum tolerated regimen		
	Day 1	Day 15
AUC _{0-∞} , μg · h/ml	3.88	4.89
Clearance, l/h/m ²	20.6	16.4
C _{max} , μg/ml	2.38	3.23
V _{ss} , l/m ²	123	95.7
t _{1/2} , hours	10.3	11.1

Abbreviations: AUC_{0-∞}, area under the curve extrapolated to infinity; C_{max}, maximal drug concentration; t_{1/2}, terminal phase half-life; V_{ss}, steady-state volume of distribution.

800 mg/day pazopanib (two breast cancer, one NSCLC, one ovarian cancer, and one esophageal cancer). All these patients had previously received docetaxel or paclitaxel. There was one unconfirmed partial response in a patient with bladder cancer. The patient with NSCLC received prior docetaxel, cisplatin with vinorelbine, pemetrexed, gefitinib, and erlotinib. The patient with ovarian cancer received prior adjuvant carboplatin with paclitaxel, followed by topotecan and liposomal doxorubicin for recurrent disease. The patient with esophageal cancer had been treated with adjuvant oxaliplatin, docetaxel, and capecitabine. Interestingly, among the five breast cancer patients, two patients with triple-negative (estrogen receptor–negative, progesterone receptor–negative, HER-2–negative) tumors achieved partial responses as their best response and each received nine cycles of treatment. One of those patients had received prior bevacizumab for metastatic disease. The other three patients with breast cancer had estrogen receptor–positive tumors and experienced disease stabilization for four to 10 cycles. Fifteen patients with a variety of tumor

types had stable disease for three or more cycles after treatment with paclitaxel and pazopanib spanning all cohorts.

DISCUSSION

The primary objective of this phase I study was to determine the safety and tolerability of the combination of pazopanib, an oral, small-molecule tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and c-Kit, with paclitaxel. The study showed that 800 mg pazopanib daily can be safely combined with a clinically acceptable dose of single-agent weekly paclitaxel on a 28-day cycle. The recommended dose for weekly paclitaxel and daily pazopanib in this study met the prespecified criteria in the protocol for the MTR based on pharmacokinetic considerations of paclitaxel exposure. Specifically, the recommended dose level did not exceed the prohibitive dose-limiting frequency and did satisfy the pharmacokinetic requirements for paclitaxel exposure. While 80 mg/m² per week is the generally accepted dose for paclitaxel, doses much higher than this have been evaluated in patients with metastatic breast cancer [10, 15]. These experiences have demonstrated that doses up to 90-110 mg/m² per week are generally tolerated, whereas doses above this threshold are associated with an increasing frequency of myelosuppression and/or neurotoxicity. Additionally, systemic exposure to paclitaxel after administration of 80 mg/m² with 800 mg pazopanib once daily was similar to that reported by Mross et al. [16] after administration of single-agent paclitaxel at a dose of 100 mg/m². After administration of 80 mg/m² paclitaxel with 800 mg pazopanib in the present study, the mean AUC(0-∞) and C_{max} values were 4.89 μg · h/ml and 2.38 μg/ml, respectively. Mross et al. reported mean AUC(0-∞) and C_{max} values of 5.43 μg · h/ml and 2.85 μg/ml, respectively, after the administration of 100 mg/m² of paclitaxel alone [16]. This combination includes a dose of weekly paclitaxel that is often used in clinical practice, and achieves the systemic exposure of a paclitaxel dose of 100 mg/m².

As expected, based on the toxicity profile of each agent alone, the most common toxicities of the combination were fatigue, nausea, diarrhea, alopecia, vomiting, and rash. The most common reasons for dose interruption or dose reduction were elevations in ALT, AST, and bilirubin related to pazopanib or paclitaxel. At the MTR, 24% and 35% of patients required at least one dose reduction of paclitaxel and pazopanib, respectively. In general, liver enzyme elevations were reversible after interruption of pazopanib and did not re-elevate after pazopanib was restarted at a reduced dose. Hand–foot skin reaction, a toxicity observed with other small-molecule tyrosine kinase inhibitors, was not reported.

After the administration of 800 mg daily pazopanib with 80 mg/m² weekly paclitaxel, the geometric mean AUC and C_{max} of paclitaxel were 26% and 36% greater, respectively, on day 15 compared with day 1 than when paclitaxel was given alone. These results are consistent with *in vitro* inhibition of the metabolism of paclitaxel by CYP3A4 and/or CYP2C8 by pazopanib. However, coadministration of 80 mg/m² paclitaxel and 800 mg pazopanib once daily resulted in a less than twofold greater geometric mean paclitaxel exposure than with administration of paclitaxel alone, which characterizes pazopanib as a weak inhibitor of CYP3A4 and/or CYP2C8.

Of major interest is the potential use of this combination in breast cancer patients, given the clinical activity demonstrated in the five patients with this tumor type. The best response in two patients with triple-negative breast tumors was a partial response. One patient had received adjuvant doxorubicin and cyclophosphamide (AC) followed by paclitaxel, and upon relapse was treated with capecitabine, vinorelbine with bevacizumab, and then gemcitabine with imatinib before study treatment. The other patient had only received adjuvant AC followed by docetaxel. These data may suggest that, even with prior exposure to a taxane or antibody to VEGF, there may be a role for treatment with an alternate antiangiogenic agent in the form of a small-molecule VEGFR tyrosine kinase inhibitor.

Further evaluation of the combination of pazopanib and weekly paclitaxel is being conducted by the National Surgical Adjuvant Breast and Bowel Project, wherein patients with locally advanced breast cancer are treated with four cycles of AC every 3 weeks followed by four cycles of

weekly paclitaxel administered on days 1, 8, and 15 of a 28-day cycle with daily pazopanib as neoadjuvant therapy, and then 6 months of adjuvant pazopanib postoperatively (clinicalTrials.gov identifier, NCT00849472).

In summary, 800 mg of pazopanib administered daily with 80 mg/m² of paclitaxel weekly, administered on days 1, 8, and 15 every 28 days, resulted in 26% and 36% higher geometric mean plasma paclitaxel AUC and C_{max} values, respectively, compared with administration of paclitaxel alone. However, this regimen can be given safely and has several applications for the treatment of solid tumors. Further evaluation is proceeding in breast cancer, and further studies assessing the antitumor activity and tolerability of pazopanib with other chemotherapy agents are ongoing.

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REFERENCES

- Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 1990;82:4–6.
- Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. *J Clin Oncol* 28:1061–1068.
- Kumar R, Knick VB, Rudolph SK et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther* 2007;6:2012–2021.
- Harris PA, Bloor A, Cheung M et al. Discovery of 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzene-sulfonamide (pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. *J Med Chem* 2008;51:4632–4640.
- Hurwitz HI, Dowlati A, Saini S et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res* 2009;15:4220–4227.
- Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–2342.
- Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
- Shaked Y, Henke E, Roodhart JM et al. Rapid chemotherapy-induced acute endothelial progenitor cell mobilization: Implications for antiangiogenic drugs as chemosensitizing agents. *Cancer Cell* 2008;14:263–273.
- Lau D, Guo L, Gandara D et al. Is inhibition of cancer angiogenesis and growth by paclitaxel schedule dependent? *Anticancer Drugs* 2004;15:871–875.
- Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;357:2666–2676.
- Monsarrat B, Royer I, Wright M et al. Biotransformation of taxoids by human cytochromes P450: Structure-activity relationship. *Bull Cancer* 1997;84:125–133.
- Desai PB, Duan JZ, Zhu YW et al. Human liver microsomal metabolism of paclitaxel and drug interactions. *Eur J Drug Metab Pharmacokinet* 1998;23:417–424.
- Heath EI, Chiorean EG, Sweeney CJ et al. A phase I study of the pharmacokinetic and safety profiles of oral pazopanib with a high-fat or low-fat

- meal in patients with advanced solid tumors. *Clin Pharmacol Ther* 2010 Oct 27 [Epub ahead of print].
- 14 Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
- 15 Marchetti P, Urien S, Cappellini GA et al. Weekly administration of paclitaxel: Theoretical and clinical basis. *Crit Rev Oncol Hematol* 2002; 44(suppl):S3–S13.
- 16 Mross K, Häring B, Holländer N et al. Comparison of 1-hour and 3-hours paclitaxel infusion pharmacokinetics: Results from a randomized trial. *Onkologie* 2002;25:503–508.