Phase I Study of Pazopanib in Combination with Paclitaxel and Carboplatin Given Every 21 Days in Patients with Advanced Solid Tumors

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Abstract
Several phase III trials have shown that the addition of an antiangiogenic agent to conventional chemotherapy can improve clinical benefit in patients with advanced solid tumors. This study examined the feasibility of combining pazopanib (Votrient), an oral antiangiogenic agent, with paclitaxel and carboplatin. This 3 + 3 dose-escalation phase I study evaluated the maximum-tolerated regimen (MTR) of daily pazopanib in combination with paclitaxel 175 mg/m² and carboplatin [dosed at area under the curve (AUC) 5 or 6] given every 21 days in patients with advanced solid tumors. Plasma samples were collected to evaluate the effect of pazopanib on the pharmacokinetics of paclitaxel and carboplatin. Thirty-four patients were enrolled. The MTR was paclitaxel 175 mg/m² and carboplatin AUC5 with pazopanib 200 mg. The most common dose-limiting toxicities were neutropenia and thrombocytopenia. Two patients with esophageal cancer had a complete response and four patients, one each with breast, small-cell lung, pancreatic, and gastroesophageal junction cancer, had partial responses. Pazopanib at 200 mg increased paclitaxel maximal concentration (Cmax) by 43% and carboplatin (AUC5 or AUC6) Cmax by 54%. Paclitaxel and carboplatin given every 21 days at standard doses was not feasible in combination with the monotherapy pazopanib dose of 800 mg daily because of dose-limiting myelosuppression. Coadministration of pazopanib increased exposure to paclitaxel and carboplatin and likely contributed to this effect. Given the antitumor activity of this regimen, further studies are underway to determine a clinically tolerable schedule of pazopanib with paclitaxel and carboplatin. Mol Cancer Ther; 11(8); 1820–8. ©2012 AACR.

Introduction
Angiogenesis is an important process for tumor growth (1, 2). Therefore, the addition of angiogenesis inhibitors to chemotherapy is a potential approach to enhance antitumor activity. In addition to inhibiting tumor-mediated angiogenesis, antiangiogenic agents may normalize “leaky” tumor vasculature and increase the delivery of chemotherapy agents to the tumor site and enhance their efficacy (3). The addition of bevacizumab (Avastin), an anti-VEGF antibody, to chemotherapy has been shown to improve clinical benefit in several tumor types, including metastatic colon cancer (4, 5), non–small-cell lung cancer (NSCLC; ref. 6), and breast cancer (7, 8).

Pazopanib (Votrient) is an oral agent that inhibits the tyrosine kinases of the VEGF receptor (VEGFR), platelet-derived growth factor receptor, and c-Kit (9). Pazopanib given at 800 mg once daily has shown single-agent activity in multiple tumor types (10–15) and is approved for the treatment of advanced renal cell carcinoma in the United States and other countries. The multitarget activity of pazopanib may potentially improve tumor control compared with other angiogenesis inhibitors such as bevacizumab, which targets a single component of the angiogenesis pathway. Paclitaxel combined with carboplatin is a common chemotherapy backbone for the treatment of NSCLC and ovarian cancer (16, 17). This phase I study explored the feasibility and efficacy of adding daily pazopanib to the combination of paclitaxel and carboplatin given every 21 days in patients with advanced solid tumors.

Patients and Methods
Eligible patients had a confirmed histologic or cytologic diagnosis of cancer, an Eastern Cooperative Oncology
Group (ECOG) performance status of 0 or 1, adequate bone marrow, renal, and hepatic function as well as peripheral neuropathy of grade 1 or less. Patients with more than 3 lines of prior chemotherapy for metastatic disease, poorly controlled hypertension, prolonged QTc interval (≥ 470 msec), heart failure, a history of bleeding within 6 weeks of study entry, current use of warfarin at therapeutic doses, or central nervous system metastases were excluded. The study protocol was approved by the Institutional Review Board at each site and was conducted according to the Declaration of Helsinki. All patients gave written informed consent.

**Study design**

This was a phase I, multicenter, open-label, dose-finding study (VEGF105427, clinical trial registration identifier NCT00388076) with a 3 + 3 design that was expanded at the maximum-tolerated regimen (MTR). Cohorts of patients were treated with paclitaxel in combination with carboplatin and daily pazopanib (Fig. 1A). The MTR was defined as the maximum dose level at which no more than one of 6 patients experienced a dose-limiting toxicity (DLT) during cycle 1. A DLT was defined as grade 3 or 4 clinically significant nonhematologic toxicity (excluding alopecia or grade 3 nausea/vomiting in the absence of supportive therapy), hypertension (grade 3 not adequately controlled with medication), proteinuria (grade 3 persisting >3 weeks with no improvement to below grade 2 after discontinuation of pazopanib), febrile neutropenia, grade 4 thrombocytopenia, or granulocytopenia lasting beyond 5 days with or without fever, and any grade 2 toxicity considered a DLT in the judgment of the investigator and sponsor. In addition, the inability to begin the next course of treatment within 2 weeks of scheduled dosing because of unresolved toxicity was considered a DLT.

Secondary endpoints included the effect of pazopanib on the pharmacokinetics of paclitaxel and carboplatin [clearance and maximal concentration (C_max) for paclitaxel; area under the curve (AUC) from 0 to 23 hours (AUC(0–23)) and C_max for carboplatin] and the clinical activity of the combination therapy. The pharmacokinetic parameters for pazopanib included C_max.

**Treatment**

A phase I trial had previously shown that administration of pazopanib at 800 mg once daily reduced paclitaxel systemic exposure to paclitaxel similar to that following administration of paclitaxel 200 mg/m² and carboplatin in the absence of pazopanib. Paclitaxel 175 mg/m² was administered as a 1-hour infusion, and carboplatin AUC5 or AUC6 was given as a half-hour infusion on day 1 of a 21-day cycle. Pazopanib was started on day 2 of cycle 1 to permit assessment of paclitaxel and carboplatin pharmacokinetics individually on day 1, after which pazopanib was dosed continuously. Pazopanib was taken at least 1 hour before or 2 hours after a meal.

**Assessments**

On day 1 of each cycle, patients received a physical examination and hematology, clinical chemistry, and urine protein:creatinine ratio assessments. Hematology and clinical chemistry were also assessed on days 8 and 15 of each cycle. An electrocardiogram, ECOG performance status evaluation, amylase, lipase, and thyroid function tests were obtained on day 1 of cycle 2 and all subsequent cycles.

Blood samples for pharmacokinetic analysis of paclitaxel and carboplatin were obtained on day 1 of cycle 1, and blood samples for pharmacokinetic analysis of all 3
agents were obtained on day 1 of cycle 2. Samples for paclitaxel pharmacokinetics were collected predose (within 60 minutes before administration) and 0.5, 1 (end of infusion), 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after the start of the infusion. Samples for carboplatin pharmacokinetics were collected predose and 1.5 (end of carboplatin infusion), 4, 8, and 24 hours after the start of the paclitaxel infusion. Samples for pazopanib pharmacokinetics were collected predose and 1, 2, 3, 4, 6, 8, 12, and 24 hours after administration.

Disease assessments were carried out at baseline, after 6 weeks, and then every 9 weeks. Responses were recorded using Response Evaluation Criteria in Solid Tumors (19).

**Statistical assessments**
Pharmacokinetic parameters were calculated by standard noncompartmental analysis using WinNonlin Pro version 4.1 or higher (Pharsight Corporation). An ANOVA on logarithmic transformed data was used to assess the interaction effect of pazopanib on the pharmacokinetics of paclitaxel (C<sub>max</sub> and clearance) and carboplatin (AUC<sub>(0-23)</sub> and C<sub>max</sub>). The ANOVA used a mixed effects model with patient as a random effect. Fixed-effect terms included dose cohort, treatment, and the dose cohort treatment interaction term. The test treatment was defined as pazopanib plus paclitaxel and carboplatin (cycle 2, day 1), and the reference treatment was defined as paclitaxel and carboplatin (cycle 1, day 1). The antilogs of the confidence limits of the 90% confidence intervals (CI) for the difference in treatment means of the logarithmic transformed data were a 90% CI for the ratio of geometric means between the test and reference treatment for data were a 90% CI for the ratio of geometric means of the logarithmic transformed treatment means. The antilogs of the confidence limits were provided after transformation of the results from the logarithmic transformed analysis back to the original scale. There was no adjustment for the multiple comparisons of endpoints. The Statistical Analysis Software system (SAS version 8.2 or higher; SAS Institute, Inc.) was used to analyze the data.

**Results**
Between November 2006 and March 2009, 34 patients were enrolled (Table 1). All patients were evaluable for pharmacokinetic analyses and safety, except one patient who was not evaluable for DLT because of withdrawal from study without a DLT before completion of cycle 1 (day 19). The most common tumor types were breast (29%) and esophageal (12%) cancers. Less common tumor types (‘other’ in Table 1) included mesothelioma, NSCLC, neuroendocrine, prostate cancer, small-cell lung cancer, sarcoma, pleura, and thyroid cancer (one of each). All but 2 patients received prior anticancer therapy, which included chemotherapy (88%), radiotherapy (53%), biologic therapy (29%), and endocrine therapy (24%). Approximately 85% of patients previously received either antitubulin or platinum therapy.

**Maximum-tolerated regimen**
The starting dose level in cohort 1 was paclitaxel 175 mg/m<sup>2</sup>, carboplatin AUC6, and pazopanib 800 mg. Three of 4 patients experienced DLTs during the first cycle, including grade 4 thrombocytopenia, grade 3 hypertension, and grade 4 neutropenia (Table 2). Given these events, the dose of pazopanib was decreased to 400 mg in cohort 2. Four of 5 patients experienced dose-limiting thrombocytopenia, which in some instances resulted in a delay of cycle 2 by more than 2 weeks. In an effort to reduce myelotoxicity in cohort 3, carboplatin was decreased from AUC6 to AUC5 and pazopanib was decreased from 400 to 200 mg, whereas paclitaxel was maintained at 175 mg/m<sup>2</sup>. The first 3 patients enrolled did not experience a DLT. Accordingly, in cohort 4, pazopanib was increased to 400 mg with paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC5, and one of the initial 3 patients experienced dose-limiting neutropenia during the first cycle. This cohort was subsequently expanded.
and 2 of the next 3 patients also experienced dose-limiting neutropenia.

To determine whether maximal doses of chemotherapy could still be administered with pazopanib, a fifth cohort was treated with paclitaxel 175 mg/m², carboplatin AUC6, and pazopanib 200 mg; cohort 3 was also expanded in parallel. In cohort 5, one of the initial 3 patients experienced dose-limiting neutropenia during the first cycle. An additional 3 patients were enrolled, among whom one patient experienced dose-limiting neutropenia.

Given these findings, the MTR was determined to be paclitaxel 175 mg/m² and carboplatin AUC5 every 21 days, with pazopanib 200 mg once daily. Ten additional patients were enrolled in this cohort for further study, with 2 patients experiencing DLTs (i.e., neutropenia, hematologic toxicity, and infection resulting in treatment delay). One patient in this cohort withdrew consent at day 19 and was therefore excluded for DLT analysis. Overall, 2 of the 12 patients evaluable for DLT at this dose level experienced DLTs, confirming the MTR.

### Adverse events

Neutropenia, anemia, fatigue, nausea, thrombocytopenia, vomiting, diarrhea, peripheral neuropathy, and alopecia were the most commonly reported drug-related adverse events, with myelotoxicity being the most common grade 3 or 4 event (Table 3).

Hypertension was the most common cardiovascular event reported during the study. In addition, 9 patients experienced hemorrhagic (e.g., epistaxis, hemoptysis, melena, hematochezia, hemorrhoids, ecchymosis/petechiae, and vaginal hemorrhage) adverse events [grade 1 (n = 7) and grade 2 (n = 2)]. No cases of proteinuria were reported. Elevations in hepatobiliary parameters were considered adverse events in 7 patients, most of which were grade 2 (n = 2) or 3 (n = 3); however, one patient experienced grade 4 alanineaminotransferase increase associated with grade 4 liver abscess and grade 3 bilirubin increase that was not considered related to study drug.

One patient, treated at the MTR, withdrew during the study because of an adverse event (grade 4 sepsis) that

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### Table 2. Dose levels and dose-limiting toxicities

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dosing regimen</th>
<th>Patients enrolled, n</th>
<th>Patients with DLTs, n</th>
<th>Dose-limiting toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC6 + Pazopanib 800 mg</td>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>Grade 4 thrombocytopenia&lt;br&gt;Grade 3 hypertension&lt;br&gt;Grade 3 infection with grade 4 neutropenia&lt;br&gt;Grade 4 thrombocytopenia</td>
</tr>
<tr>
<td>2</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC6 + Pazopanib 400 mg</td>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
<td>Grade 1 thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 1 thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 4 thrombocytopenia&lt;br&gt;Grade 3 thrombocytopenia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC5 + Pazopanib 200 mg</td>
<td>3</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC5 + Pazopanib 400 mg</td>
<td>6</td>
<td>3</td>
<td>Grade 3 neutropenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 4 neutropenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 3 neutropenia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC6 + Pazopanib 200 mg</td>
<td>6</td>
<td>2</td>
<td>Grade 4 neutropenia&lt;br&gt;Grade 3 neutropenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 3 thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 2 neutropenia&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Expansion cohort&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Paclitaxel 175 mg/m² + Carboplatin AUC5 + Pazopanib 200 mg</td>
<td>10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>Grade 4 neutropenia&lt;br&gt;Grade 3 oral cavity infection&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 3 thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Grade 2 neutropenia&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The study protocol permitted 3 to 6 patients per cohort and depending on the number screened and the number eligible, some cohorts contained more than 3 patients each.

<sup>b</sup>Start of cycle 2 delayed by more than 2 weeks.

<sup>c</sup>Grade 3 thrombocytopenia was considered to be a DLT by investigator because of grade 2 or greater toxicity that occurred beyond day 28.

<sup>d</sup>Cohort 3 was expanded.

<sup>e</sup>Although 10 patients were enrolled, only 9 were evaluable for DLTs and one patient, who did not have a DLT, withdrew before completing cycle 1.
<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Pacl 175 mg/m² + Carbo AUC6+</th>
<th>Pacl 175 mg/m² + Carbo AUC5+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hematologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (75)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (50)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Nonhematologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (75)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (75)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (75)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: Carbo, carboplatin; Pacl, paclitaxel; Paz, pazopanib.

*This was determined to be the maximum-tolerated regimen.
was considered serious and required hospitalization. In addition, a patient with metastatic esophageal cancer, also receiving treatment at the MTR, who remained on study for more than 57 weeks, died within 4 weeks of the last dose of study drug in the setting of rapid disease progression, esophageal stricture, and biliary obstruction.

Among all 34 patients who received at least one dose of study drug, 12 (35%) experienced 37 serious adverse events during the study. There was no clear association between frequency of serious adverse events and cohort treatment.

A dose interruption of at least one study drug because of adverse events was reported in 30 patients (88%). Most patients (including those at the MTR) experienced interruptions in pazopanib dosing (79%) or delays in the scheduled administration of paclitaxel (68%) and carboplatin (62%). The most common toxicities leading to treatment interruption, delay, or dose reductions were neutropenia and thrombocytopenia. The frequencies of dose reductions were as follows: pazopanib (26% overall; 0% MTR), paclitaxel (24% overall; 23% MTR), and carboplatin (35% overall; 38% MTR).

**Pharmacokinetics**
Concurrent administration of pazopanib 200 mg resulted in an approximately 43% increase in paclitaxel \( C_{\text{max}} \) (Table 4) and a 54% increase in carboplatin \( C_{\text{max}} \) (AUC5 or AUC6; Table 5) compared with paclitaxel and carboplatin without pazopanib (Fig. 1B and C). Pazopanib 400 mg resulted in similar increases in paclitaxel and carboplatin \( C_{\text{max}} \) (40% and 68%, respectively) as that of pazopanib 200 mg. Pazopanib at 200 and 400 mg was found to decrease paclitaxel clearance by 30% and 17%, respectively. However, because of the wide variability of individual results, there was no statistically significant difference in paclitaxel clearance between the pazopanib 200- and 400-mg dose.

Median plasma pazopanib \( C_{\text{max}} \) on cycle 2 day 1 was 15.8 \( \mu \)g/mL in the cohort receiving paclitaxel 175 mg/m\(^2\), carboplatin AUC5, and pazopanib 200 mg, and median pazopanib \( C_{\text{max}} \) was 27.5 \( \mu \)g/mL in the cohort receiving paclitaxel 175 mg/m\(^2\), carboplatin AUC5, and pazopanib 400 mg.

**Efficacy**
In this phase I trial, there were 2 complete responses and 4 partial responses. Objective responses were observed at the MTR (paclitaxel 175 mg/m\(^2\), carboplatin AUC5, and pazopanib 200 mg) and included complete responses in 2 patients with esophageal cancer, one of whom had prior treatment with combination docetaxel and oxaliplatin, and one who was chemotherapy naive, and a partial response in a patient with small-cell lung cancer who had received one prior line of therapy.

The other 3 partial responses occurred in previously treated patients with pancreatic (paclitaxel 175 mg/m\(^2\), carboplatin AUC6, and pazopanib 400 mg), gastroesophageal junction, and breast cancer (both at paclitaxel 175 mg/m\(^2\), carboplatin AUC5, and pazopanib 400 mg). Overall, 7 patients (21%) experienced disease stabilization, and

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### Table 4. Statistical analysis of paclitaxel pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib 200 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance, L/h/m(^2)</td>
<td>14</td>
<td>11.6</td>
<td>8.16</td>
<td>0.70 (0.61–0.80)</td>
</tr>
<tr>
<td>( C_{\text{max}}, \mu g/mL )</td>
<td>14</td>
<td>26.9</td>
<td>38.5</td>
<td>1.43 (1.19–1.72)</td>
</tr>
<tr>
<td>Pazopanib 400 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance, L/h/m(^2)</td>
<td>8</td>
<td>11.2</td>
<td>9.23</td>
<td>0.83 (0.68–1.01)</td>
</tr>
<tr>
<td>( C_{\text{max}}, \mu g/mL )</td>
<td>8</td>
<td>31.2</td>
<td>43.6</td>
<td>1.40 (1.16–1.66)</td>
</tr>
</tbody>
</table>

### Table 5. Statistical analysis of ultrafilterable platinum pharmacokinetic parameters normalized to the carboplatin AUC6 dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib 200 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{0–23h}), \mu g/h/mL</td>
<td>11</td>
<td>55.5</td>
<td>78.3</td>
<td>1.41 (1.25–1.59)</td>
</tr>
<tr>
<td>( C_{\text{max}}, \mu g/mL )</td>
<td>13</td>
<td>18.2</td>
<td>28.0</td>
<td>1.54 (1.12–2.10)</td>
</tr>
<tr>
<td>Pazopanib 400 mg once daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{0–23h}), \mu g/h/mL</td>
<td>6</td>
<td>54.1</td>
<td>70.8</td>
<td>1.31 (0.89–1.93)</td>
</tr>
<tr>
<td>( C_{\text{max}}, \mu g/mL )</td>
<td>6</td>
<td>20.8</td>
<td>35.0</td>
<td>1.68 (0.91–3.10)</td>
</tr>
</tbody>
</table>
the duration of stable disease ranged from 24 to 77 weeks in a variety of tumor types.

Discussion

Taxanes such as paclitaxel in combination with platinum-based agents are the standard-of-care as first-line treatment in several solid tumor types (16, 17). In the treatment of NSCLC and ovarian cancer, the standard paclitaxel dose is 175 to 200 mg/m² every 3 weeks, and the standard carboplatin dose is AUC5 to AUC7.5 (16, 17). Previous studies have shown the feasibility of combining antiangiogenic agents with chemotherapy in patients with colorectal, NSCLC, and breast cancer (4–8, 20). Bevacizumab is approved in combination with paclitaxel and carboplatin in patients with stage IV, nonsquamous NSCLC, although an increase in the incidence of treatment-related deaths has been reported with this regimen (6). In patients with colorectal cancer, the addition of bevacizumab to chemotherapy improved progression-free and overall survival by 2 to 5 months, but increased the incidence of hypertension and bleeding (4, 20).

Several small studies have evaluated the addition of small-molecule tyrosine kinase inhibitors such as sorafenib (Nexavar) and cediranib (Recentin) to chemotherapy. In patients with advanced ovarian cancer, paclitaxel 175 mg/m² and carboplatin AUC5 with a standard sorafenib dose of 400 mg twice daily was not feasible because of increased incidence of death (21). Similar results were reported with paclitaxel 200 mg/m², carboplatin AUC6, and cediranib 30 mg daily in advanced NSCLC (22). In this study, the recommended phase II monotherapy dose of pazopanib, 800 mg once daily, was not feasible with paclitaxel 175 mg/m² and carboplatin AUC5 or AUC6 every 21 days in patients with advanced solid tumors, because of myelosuppression.

The safety profile of pazopanib in combination with paclitaxel and carboplatin reflected established adverse events for each agent. In addition to defining the MTR by reported toxicities, tolerability was assessed by comparing the actual doses of each agent received versus the assigned cohort dose. Among the cohorts, more cycles were administered at the assigned dose for cohorts receiving low daily doses of pazopanib (200 mg) than for cohorts receiving higher daily doses of pazopanib (400 or 800 mg). These results further support the identified MTR. In addition, clinical activity was observed at the MTR; 2 of the 4 patients with esophageal carcinomas achieved a complete response, and there were partial responses and disease stabilization in other tumor types. Although the pazopanib dose in the MTR was lower than the currently approved dose of 800 mg once daily in renal cell carcinoma, the median pazopanib concentration achieved was 16 µg/mL, which is within the therapeutic concentration range (15–17.4 µg/mL; refs. 9, 23).

In this trial, there was a high incidence of myelosuppression that is likely a consequence of drug–drug interactions, resulting in increased exposure to the chemotherapy components of this regimen. Coadministration of pazopanib 200 mg (n = 14) and 400 mg (n = 8) once daily with paclitaxel 175 mg/m² and carboplatin every 21 days decreased paclitaxel clearance by 30% and 17%, respectively, and increased paclitaxel C\text{max} by approximately 40%. Mean paclitaxel clearance decreased by 14% and mean paclitaxel C\text{max} increased by 36% after administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m² in a weekly regimen (18). These results indicate that maximal inhibition of paclitaxel clearance is achieved at pazopanib doses at or below 200 mg. It is known that paclitaxel is a substrate of CYP3A4 and CYP2C8 and that pazopanib is a weak inhibitor of these cytochrome enzymes, which is likely the basis for the altered pharmacokinetics of paclitaxel when given with pazopanib. In contrast to the primarily metabolic elimination of paclitaxel, carboplatin is primarily excreted through the kidneys, and inhibition of cytochrome enzymes was not expected to alter the pharmacokinetics of carboplatin. However, coadministration of pazopanib resulted in an increase in carboplatin AUC(0–23) and C\text{max} relative to administration of carboplatin and paclitaxel without pazopanib. Although the mechanism of this apparent interaction remains unknown, this is similar to what has been observed with coadministration of other small-molecule VEGFR tyrosine kinase inhibitors such as BIBF 1120 (24) and AZD2171 (25), namely, an increase in carboplatin AUC. Interestingly, no change in the pharmacokinetics of carboplatin was observed when paclitaxel and carboplatin were administered in the presence of sorafenib dosed intermittently (26). A study with a more dense blood sampling scheme is required to characterize the pharmacokinetics of carboplatin to determine more accurately the extent of a pharmacokinetic drug–drug interaction between pazopanib and carboplatin or other platinum-containing regimens. Administering paclitaxel and carboplatin at lower doses than in this study may be an alternative, because in combination with pazopanib the increases in paclitaxel and carboplatin AUC and C\text{max} would still provide adequate therapeutic exposure.

In conclusion, pharmacokinetic analysis revealed that exposures to paclitaxel and carboplatin were higher during concurrent treatment with pazopanib relative to treatment without pazopanib. This 3-drug combination has shown clinical activity at the MTR of paclitaxel 175 mg/m² and carboplatin AUC5 every 21 days with pazopanib 200 mg daily, and alternative strategies of administration, such as lower doses of chemotherapy or intermittent dosing of pazopanib, are being explored to see whether a more tolerable side effect profile can be achieved.

Disclosure of Potential Conflicts of Interest

M.M. Dar has held the post of Medical Director in GlaxoSmithKline and also has ownership interest (including patents) in GlaxoSmithKline stock. H.A. Ball has ownership interest (including patents) in GlaxoSmithKline stock.
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References


Molecular Cancer Therapeutics

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