Tirapazamine Plus Carboplatin and Paclitaxel in Advanced Malignant Solid Tumors: A California Cancer Consortium Phase I and Molecular Correlative Study

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ABSTRACT

Purpose: Tumor hypoxia confers chemotherapy resistance. Tirapazamine is a cytotoxin that selectively targets hypoxic cells and has supra-additive toxicity with platinum and taxanes in preclinical studies. We conducted a Phase I study of tirapazamine, carboplatin, and paclitaxel and assessed potential plasma markers of hypoxia as surrogates for response.

Experimental Design: Forty-two patients with advanced solid tumors were treated at four dose levels; parallel dose escalations were carried out in chemotherapy-naïve and previously treated subjects. Pre and post-therapy plasma levels of the hypoxia-induced proteins plasminogen activator inhibitor-1 and vascular endothelial growth factor were measured.

Results: Three of four chemotherapy-naïve patients developed dose-limiting toxicities at dose level 4 (grade 3 stomatitis/infection, grade 3 emesis, and grade 4 febrile neutropenia). Four of seven previously treated patients developed dose-limiting toxicities at dose level 3, including one death [grade 3 myalgia, grade 3 infection/grade 4 neutropenia, grade 3 infection/grade 4 neutropenia, and grade 5 infection (death)/grade 4 neutropenia]. Of 38 patients assessable for response, 3 had a complete response, 1 a partial response, 1 an unconfirmed partial response, and 23 had stable disease in at least one evaluation; 10 quickly progressed. One complete responder had normalization of vascular endothelial growth factor and plasminogen activator inhibitor-1 levels.

Conclusion: Dose levels 3 (carboplatin AUC of 6, 225 mg/m² paclitaxel, and 330 mg/m² tirapazamine) and 2 (carboplatin AUC 6, 225 mg/m² paclitaxel, and 260 mg/m² tirapazamine) are the maximum tolerated doses for chemotherapy naive and patients treated previously, respectively. Dose level 3 is the experimental arm of a Phase III Southwest Oncology Group trial (S0003) in advanced non-small cell lung cancer. Potential markers of tumor hypoxia may be useful correlates in studies of hypoxic cytotoxins and are being prospectively investigated in S0003.

INTRODUCTION

Hypoxia affects ≤50% of human tumor cells and negatively influences the response to both radiation and standard chemotherapeutic agents (1–6). For example, cisplatin had little or no cytotoxic activity against hypoxic tumor cells in a preclinical model despite killing a large proportion of nonhypoxic cells (7). Therefore, therapies that potentiate cytotoxicity against hypoxic cancer cells should theoretically increase the efficacy of platinum-based chemotherapy (8, 9).

Hypoxic conditions alter cellular homeostasis, e.g., malignant cells subjected to hypoxia are induced to transcribe a discrete set of genes (10), including the genes coding for PAI-1 and VEGF2 (11). Hypoxia may then exert selection pressure on tumor populations by promoting angiogenesis, p53 mutations, and resistance to apoptosis (12). Furthermore, tumor hypoxia has been shown to increase the metastatic potential of cancer cells, leading to the conclusion that hypoxia influences tumor phenotype as well as clinical outcome (13). This notion is supported by the observation that tumor hypoxia (as measured by Eppendorf oxygen electrodes) is correlated with an increased incidence of distant metastases and treatment failure in a variety of tumors, including soft tissue sarcomas, cervical cancer, and head and neck carcinomas (14–16).

Tirapazamine, the prototype for a novel class of anticancer compounds called “hypoxic cytotoxins,” is a benzotriazine compound that exhibits substantial differential toxicity for hypoxic cells. At equivalent tirapazamine concentrations, hypoxic murine and/or human tumor cells were found to be ≤200 times more sensitive than nonhypoxic cells (7).

Received 3/4/03; revised 6/3/03; accepted 6/9/03.

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This work was supported in part by CA62505, CA63265, Bristol Myers Squibb (P. N. L.), the Hope Foundation (P. N. L.), and the American Cancer Society CRTG 0019701CCE (P. N. L.).

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2 The abbreviations used are: VEGF, vascular endothelial growth factor; AUC, area under the curve; NCI, National Cancer Institute; DLT, dose-limiting toxicity; NSCLC, non-small cell lung cancer; IGFBP, insulin-like growth factor-binding protein-3; MTD, maximum tolerated dose.

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Table 1  Dose escalation scheme

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Tirapazamine (mg/m²)</th>
<th>Carboplatin (AUC)</th>
<th>Paclitaxel (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>260</td>
<td>6</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>260</td>
<td>6</td>
<td>225</td>
</tr>
<tr>
<td>3</td>
<td>330</td>
<td>6</td>
<td>225</td>
</tr>
<tr>
<td>4</td>
<td>390</td>
<td>6</td>
<td>225</td>
</tr>
</tbody>
</table>

more sensitive than aerobic cells to killing by tirapazamine (17). Preclinical studies have also tested the combination of tirapazamine with platinum-containing compounds in hypoxic tumor models. Combinations of tirapazamine with either cisplatin or carboplatin show enhanced antitumor activity in a number of in vivo and in vitro models. In some models, the cytotoxicity of tirapazamine plus a platinum or a taxane is substantially greater than the additive effects of both drugs. Studies in mice have demonstrated enhanced antitumor activity for the three-drug regimen of tirapazamine, carboplatin, and paclitaxel versus carboplatin/paclitaxel in the MV-522 human lung carcinoma xenograft model, forming the basis for this clinical study (18).

The combination of carboplatin-paclitaxel has shown encouraging activity in a number of different tumor types, including NSCLC, and its toxicity profile has been well characterized. A recent Phase III trial (S9509) showed that paclitaxel-carboplatin has increased tolerability compared with vinorelbine-cisplatin, prospectively defined as the ability to complete therapy and the percentage of patients taken off study attributable to toxicity (19). Furthermore, a recent Phase III trial in NSCLC of cisplatin with or without tirapazamine demonstrated improved response and survival in patients treated with the combination (20). Finally, a recently concluded Phase I trial demonstrated the feasibility of delivering a 3-h infusion of paclitaxel at 225 mg/m² with tirapazamine (390 mg/m²) and cisplatin (75 mg/m²) every 3 weeks (21). In view of these preclinical and clinical observations, we conducted a Phase I trial of tirapazamine plus paclitaxel and carboplatin, administered on a single day, in patients with advanced solid tumors, using therapeutic doses of paclitaxel and carboplatin and escalating doses of tirapazamine over four dose levels (Table 1; Ref. 22).

MATERIALS AND METHODS

Patient Selection. Patients with histologically or cytologically confirmed cancer not curable by standard means who had a life expectancy of >12 weeks and an adequate Zubrod performance status (0, 1, or 2) were eligible. Patients were stratified according to whether they had received previous chemotherapy. Previous chemotherapy and/or radiotherapy must have been completed ≥4 weeks before study entry, and all treatment-related toxicities had to be completely resolved. Adequate hematological (WBC ≥ 3,000/µl, absolute neutrophil count ≥ 1,000/µl, and platelet count ≥ 100,000/µl), renal (creatinine within institutional limits of normal and calculated creatinine clearance ≥ 60 ml/min), and hepatic (serum bilirubin ≤ 1.5 mg/dl and aspartate aminotransferase within twice the institutional upper limit of normal) function were required. Because of possible tirapazamine-related ototoxicity, patients with clinically severe hearing loss were not eligible to participate. Patients who had previously received carboplatin and paclitaxel concurrently were excluded. Patients who were pregnant or who had unstable medical conditions (such as uncontrolled congestive heart failure) or other uncontrolled intercurrent illnesses precluding investigational therapy were also excluded. Patients were required to use a medically acceptable contraceptive throughout the treatment period and for 3 months after cessation of treatment with tirapazamine. This study was approved by the NCI-Cancer Therapy Evaluation Program and the institutional review boards of each California Cancer Consortium site. All patients gave written informed consent to participate.

Baseline Evaluation. Before study entry, all patients underwent a complete history and physical examination. Baseline imaging studies of all known sites of disease were obtained within 4 weeks of initial therapy. An audiometric evaluation was required for all patients because of potential ototoxic effects of tirapazamine. Laboratory studies included a complete blood count with differential and platelet count, comprehensive metabolic panel (which includes electrolytes, serum creatinine, total bilirubin, and aspartate aminotransferase). Patient plasma was collected before cycles 1 and 2 for molecular correlative studies (see below).

DLT. DLT was defined as any Grade 3 or 4 nonhematological toxicity (including nausea/vomiting with maximal antiemetic prophylaxis), Grade 3/4 thrombocytopenia, and Grade 4 neutropenia with fever (defined as a temperature of 38.3°C or 101°F) or a documented infection, occurring during the first course of treatment. Toxicity was graded according to the NCI common toxicity criteria version 2.0.

MTD. The MTD was defined as the highest dose level at which not >1 patient experienced a DLT, when ≥6 patients were treated at that dose and were evaluable for toxicity. The MTD was one dose level below the DLT level. Separate MTDs were determined for each stratified group (i.e., treated previously and untreated previously).

Study Design and Treatment Plan. The dose escalation schedule is summarized in Table 1. Study drugs were administered once during each 3-week treatment cycle to each stratified group according to the schedule outlined in Table 1. Each cycle of treatment consisted of dosing on day 1 with follow-up through day 21. Tirapazamine was given i.v. before paclitaxel (as a 3-h infusion), which was followed by carboplatin. A maximum of eight cycles was planned. Appropriate premedications were administered to prevent emesis, diarrhea, and hypersensitivity reactions. Treatment was continued in the absence of disease progression, provided that patients were clinically benefiting and tolerating the treatment.

Parallel dose escalations (three per cohort) were carried out in previously untreated patients and previously treated patients, but the dose level for the previously treated stratum was not allowed to exceed that of the previously untreated stratum. Both strata were allowed to accrue to the same dose level simultaneously. All patients treated at a particular dose level were observed for a minimum of 21 days after the start of the first course (i.e., the length of the treatment cycle) before accrual to the next dose level was allowed.

Patients received a minimum of one treatment cycle. Treatment continued in individual patients at the same dose level if
Table 2  Patient characteristics

<table>
<thead>
<tr>
<th>Patients enrolled (number)</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated previously</td>
<td>26</td>
</tr>
<tr>
<td>Treated previously</td>
<td>16</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>61 (41–80)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>20 (48%)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>PS 0</td>
<td>17</td>
</tr>
<tr>
<td>PS 1</td>
<td>14</td>
</tr>
<tr>
<td>PS 2</td>
<td>11</td>
</tr>
<tr>
<td>Tumor types</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>22</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
</tr>
<tr>
<td>Bladder cancer (urothelial)</td>
<td>3</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>2</td>
</tr>
<tr>
<td>Esophageal, gastric, parotid, uterine, colon, and thyroid cancers</td>
<td>1 each</td>
</tr>
<tr>
<td>No. previous chemo regimens(a)</td>
<td>2</td>
</tr>
</tbody>
</table>

\(a\) For patients in the previously treated stratum only.

Table 3  Most common hematologic and nonhematologic toxicities (Grade 3 or 4): Cycle 1

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils/granulocytes</td>
<td>12</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Total WBC</td>
<td>17</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Anemia requiring transfusions</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

RESULTS

Patient Demographics. Forty-two eligible patients with a median age of 61 years (range 41–80) were accrued between March 2000 and June 2002. Patient characteristics are summarized in Table 2. Twenty-six patients were chemotherapy naive, whereas 16 patients had been treated with at least one previous chemotherapy regimen. Patients treated previously had received a median of two previous regimens before protocol therapy. There were 20 males and 22 females. Most patients had a good performance status, with the majority having PS 0/1 (74%).

Dose Escalation and Toxicities. At dose level 4 of the previously untreated stratum, 3 of 4 simultaneously enrolled patients developed DLTs: grade 3 emesis, grade 3 infection, and febrile neutropenia with grade 3 infection. One patient in dose level 4 also developed complete hearing loss, which resolved within 4 days. Subsequently, dose level 3 was identified as the MTD for previously untreated patients, and by protocol design, no further accruals were allowed beyond dose level 3 for either patient stratum. A total of 16 previously untreated patients were treated at this expanded MTD level. Attributable grade 3 or 4 hematological and nonhematological toxicities were as follows: (a) grade 3 or 4 neutropenia (without infection) in 4 patients (25%); (b) grade 3 nausea/emesis in 2 patients (12%); (c) grade 3 dehydration in 2 patients (12%); and (d) one patient each developed grade 3 thrombocytopenia, grade 3 infection, grade 3 hypotension, grade 3 rash, and grade 3 myalgia. In the previously treated stratum, 3 of 6 evaluable patients had DLTs at dose level 3, grade 3 fatigue in the first patient, grade 3 myalgia with grade 4 infection in the second, and grade 3 infection in the third. Dose level 2 was identified as the MTD level for this stratum where none of the six patients enrolled had a treatment-related DLT (please refer to Tables 3 and 4 for toxicity summaries). The median number of cycles was 3 for both the
previously treated (range 1–6) and previously untreated cohorts (range 1–8).

**Efficacy.** Evaluation of response rate was not a principal objective of this study, but objective responses were observed. Of the 38 patients assessable for response, complete responses were seen in 3 patients (one previously treated NSCLC patient and two chemotherapy-naïve patients with an unknown primary cancer), and a partial response was observed in another patient with carcinoma of unknown primary, for an overall response rate of 10%. One other patient had an unconfirmed partial response. Twenty-three patients exhibited stable disease (including patients clinically stable after one radiographic disease assessment).

**Molecular Correlates.** The goal of these correlative studies was to assess the feasibility of measuring changes in hypoxia-induced gene products. Levels of PAI-1 and VEGF were measured by ELISA in pretreatment plasma specimens from 34 and 36 patients, respectively (Fig. 1). PAI-1 levels ranged from 8.3 to 455 ng/ml with a mean value of 112 ng/ml and a median value of 83.35 ng/ml (normal value: ≤43 ng/ml). VEGF levels ranged from undetectable to 291 pg/ml, with a mean value of 39.6 pg/ml and a median value of 17.35 pg/ml (normal value: ≤120 pg/ml). In this limited and heterogeneous sample set, no statistically significant correlations could be demonstrated between PAI-1 or VEGF plasma levels and clinical outcome or status of previous therapy. A positive correlation between PAI-1 and VEGF plasma levels was observed ($P < 0.0001$, Pearson $r = 0.5514$), indicating that, in an individual patient, if one marker was elevated, the other marker tended to be elevated as well.

Plasma was also obtained after one cycle of therapy for measurement of levels of PAI-1 (in 14 patients) and VEGF (in 15 patients). Post-treatment changes in PAI-1 and VEGF levels were assessed and compared with clinical responses. Comparisons of plasma PAI-1 and VEGF levels in 13 individual patients before and after one cycle of therapy are shown in Fig. 2, A and B, respectively. In this sample set, one patient had progressive disease while on therapy, one patient had a partial response, and 2 patients had a complete response. All others had stable disease during therapy. For both PAI-1 and VEGF, the patient with progressive disease showed a sharp increase in plasma concentrations after one cycle of therapy. One patient with a complete response had a decrease in both PAI-1 and VEGF levels, whereas the other patient with a complete response had a decrease in PAI-1 but an increase in VEGF. The patient with a partial response showed a decrease in PAI-1 with a minimal increase in VEGF.

**DISCUSSION**

Hypoxic tumor cells have been shown to be resistant to radiotherapy and are variably resistant to conventional chemotherapeutic agents (23). The difference in radiation sensitivity between aerobic and hypoxic conditions, referred to as the oxygen enhancement ratio, is typically in the range of 2.5 to 3 in human tumors. In the absence of oxygen, radiation-induced radicals which can cause DNA damage, may be reversed by donation of hydrogen from nonprotein sulfhydryls, providing a mechanism for hypoxia-induced radioresistance (23). Although
Phase I Trial of Tirapazamine + Carbo/Taxol

![Change in PAI-1 Protein Plasma Levels in Individual Patients](image1)

![Change in VEGF Protein Plasma Levels in Individual Patients](image2)

Fig. 2 PAI-1 and VEGF plasma levels in matched pre and post-treatment samples. PAI-1 and VEGF levels before and after one cycle of therapy were charted in individual patients to determine whether changes in plasma levels were predictive for clinical response. Bold dotted lines, the patient with progressive disease; bold solid lines, the patients with objective clinical responses. All other patients had stable disease during treatment. A, PAI-1 levels; B, VEGF levels.

these observations provided the basis for early studies attempting to improve radioresponsiveness by the use of hyperbaric oxygen or radiosensitizing agents, such as misonidazole, neither approach has achieved general clinical application. In contrast, clinical studies with the novel hypoxic cytotoxin tirapazamine have yielded promising results (18).

Koong et al. (20) studied the interaction between tirapazamine and paclitaxel-carboplatin using the MV-522 human lung carcinoma xenograft model in nude mice. As a single agent, tirapazamine did not yield any substantial anti-tumor activity in this human lung tumor model. However, a substantial increase in tumor growth inhibition was seen in animals treated with the tirapazamine-paclitaxel-carboplatin triplet as compared with animals treated with paclitaxel-carboplatin alone. Specifically, the triplet yielded a 50% complete tumor response rate, whereas no complete responses were observed with the non-tirapazamine-containing doublet. Interestingly, tirapazamine did not appear to increase the toxicity of the paclitaxel-carboplatin doublet in the animals, based on the minimal impact on body weight and the absence of any toxic deaths in the mice treated with tirapazamine-containing regimens. These encouraging preclinical data led to the development of the current study.

This Phase I trial demonstrated the feasibility and tolerability of the combination of carboplatin and paclitaxel, both given at full cytotoxic doses, in combination with tirapazamine. The toxicities observed were those that would be expected with the individual agents, including stomatitis, esophagitis, neutropenia and infection, myalgia, and transient hearing loss. No unexpected toxicities occurred, and some objective responses were seen. The tirapazamine dose and toxicities observed in this study at the MTD level achieved compares favorably to those seen in other trials combining tirapazamine with chemotherapy and/or radiation, e.g., the MTD of tirapazamine in combination with cyclophosphamide or with cisplatin was 260 mg/m² (24, 25). Subsequently, several Phase II and III studies have used the combination of tirapazamine with cisplatin (75 mg/m² every 3 weeks) at doses of 260–390 mg/m² with good tolerance (26–29). When used as a single agent in combination with radiation, tirapazamine has been well tolerated at doses of ≤260 mg/m² thrice weekly (30). Tirapazamine has also been administered in combination with cisplatin and radiation at doses of ≤290 mg/m² during the weeks when cisplatin was given and 160 mg/m² three times weekly during non-cisplatin weeks (31).

This study also examined the role of measurement of potential plasma markers of tumor hypoxia as surrogates for response. Preclinical microarray studies in a head and neck cancer cell line have demonstrated that a group of four genes with secreted products exhibited increased expression under hypoxic conditions: (a) VEGF; (b) IGFBP-3; (c) endothelin-2; and (d) PAI-1 (11). Interestingly, PAI-1 exhibited the greatest level of induction in response to hypoxia. PAI-1 is a critical component of the normal hemostatic system and has already been associated with tumor invasion and metastasis (32). Furthermore, elevated PAI-1 levels have been correlated with an inferior outcome in a variety of solid tumors, including NSCLC. IGFBP-3 is a pro-apoptotic gene that is transcriptionally up-regulated in response to hypoxia. However, studies by Koong et al. (11) have failed to demonstrate evidence of apoptosis despite induction of IGFBP-3, suggesting alternate mechanisms of growth regulation in response to hypoxia. VEGF is a well-characterized hypoxia-inducible angiogenic cytokine that plays a central role in tumor-related angiogenesis, a critical process in tumor growth, invasion, and metastases (33). VEGF is abnormally overexpressed in a variety of tumor types, detectable in patient serum or plasma, and correlates with worse prognosis (34–36). Recently, it has also been demonstrated that osteopontin, an acidic glycoprotein important in bone formation, was induced 10-fold in the serum of patients with pancreatic cancer, a highly hypoxic tumor.³ Osteopontin induces endothelial cell migration and also up-regulates the endothelial cell migration induced by VEGF (37). In one study, patients with stage I

³ A. Koong, personal communication.
adenocarcinoma of the lung whose tumors expressed osteopon-
tin and VEGF were found to have a significantly worse prog-
nosis compared with those whose tumors did not express these
markers (37). Unfortunately, changes in the plasma levels of
these secreted proteins after cytotoxic chemotherapy have not
yet been fully investigated.

In this trial, we measured plasma levels of two important
markers of tumor hypoxia, VEGF and PAI-1, before and after
treatment. Meaningful statistical correlations between the levels
of these markers and tumor response could not be obtained from
this limited data set. However, it was intriguing to note that all
3 of the patients who had a measurable response to therapy had
a decrease in the level of PAI-1, whereas the one patient with
progressive disease for whom the levels of these markers are
available had a marked increase in both PAI-1 and VEGF after
one cycle of treatment. The possibility that changes in levels of
VEGF and PAI-1 after only one cycle of treatment may corre-
late with eventual clinical response is a hypothesis that deserves
exploration in future studies.

This Phase I trial formed the basis for SWOG 0003, a
recently completed Phase III trial randomizing patients with
metastatic NSCLC to carboplatin (AUC 6) and paclitaxel (225
mg/m²) with or without tirapazamine (330 mg/m²). This trial
will determine, in a cooperative group setting, whether the addition of tirapazamine to standard palliative chemotherapy in
advanced NSCLC will improve the dismal median survival (~8
months) associated with this disease. In addition, serial plasma
specimens will be obtained from patients accrued to this study to
determine circulating osteopontin, PAI-1, and VEGF levels and
to correlate changes in these levels with tumor response. This
study should help clarify the role of determining plasma levels of
tumor hypoxia markers in predicting response to therapy.

ACKNOWLEDGMENTS

We thank Tracey Baratta (City of Hope) for data management
support and Christopher Ruel for statistical assistance. We also thank
Dr. Percy Ivey of the Cancer Therapy Evaluation Program of the NCI
for her support.

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