Phase I Study of Tirapazamine Plus Cisplatin/Etoposide and Concurrent Thoracic Radiotherapy in Limited-Stage Small Cell Lung Cancer (S0004): A Southwest Oncology Group Study

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ABSTRACT

Purpose: To determine the feasibility and a recommended phase II dose of tirapazamine when combined with chemoradiotherapy in limited-stage small cell lung cancer (LSCLC).

Experimental Design: Concurrent chemoradiotherapy consisted of two cycles of cisplatin, etoposide, and once-daily radiation to 61 Gy. Tirapazamine (260 mg/m²) was given 1 h before cisplatin with planned dose escalation to 330 mg/m² in the absence of dose-limiting toxicity, defined as ≥33% esophagitis (grade 3 or above). Consolidation therapy consisted of two cycles of tirapazamine (330 mg/m²), cisplatin, and etoposide. Complete responders received prophylactic cranial irradiation.

Results: Thirty patients were enrolled at the 260 mg/m² tirapazamine dose. All had performance status of 0–1. By comparison with S9713, a predecessor Southwest Oncology Group study in LSCLC that used the same concurrent chemoradiotherapy without tirapazamine, the present trial showed a higher rate of grade 3–4 esophagitis (34% versus 22%), vomiting (34% versus 23%), and febrile neutropenia (7% versus 2%). The consolidation phase was relatively well tolerated, with grade 4 neutropenia in 44% and febrile neutropenia in 5% of patients. There were two treatment-related deaths: one from neutropenic fever and one from respiratory infection. The overall response rate was 80%, and the median survival was 22 months.

Conclusions: Protocol-defined dose-limiting toxicity was observed at the initial tirapazamine dose, precluding dose escalation. Compared with S9713, the addition of tirapazamine increased the incidence of vomiting, neutropenia, and febrile neutropenia, although the overall toxicity profile remained acceptable. In view of the observed favorable survival, further study of tirapazamine in LSCLC is warranted.

INTRODUCTION

Small cell lung cancer accounts for 20% of all lung cancers, and one third of the patients have limited-stage tumor (LSCLC) at presentation (1). The treatment for LSCLC has evolved over time. Two meta-analyses have concluded that thoracic irradiation adds to the efficacy of chemotherapy in this setting (2, 3). Randomized phase III trials have shown that early administration of thoracic irradiation is superior to delayed administration (4, 5). During the 1980s, cisplatin and etoposide became the chemotherapy regimen of choice for use during concurrent therapy in LSCLC because of less toxicity than observed with other regimens (6). Indeed, cisplatin/etoposide is unique in its ability to be administered in full dose during thoracic irradiation. An important study by the Southwest Oncology Group (SWOG), SWOG-8269, which used concurrent early once-daily thoracic irradiation with etoposide and vincristine, showed a median survival of 18 months and a 2-year survival of 40% (7). Subsequent SWOG trials have maintained the “core” regimen of concurrent cisplatin/etoposide and thoracic irradiation while investigating different investigational approaches to consolidation therapy. None of these therapeutic strategies have improved survival over that observed with the initial SWOG-8269 regimen (8). Although intergroup trial 0096 (INT 0096) reported improved efficacy with etoposide and a twice-daily hyperfractionated radiation schedule (45 Gy) compared with a once-daily standard fractionation radiation (45 Gy; Ref. 9), this approach has not been adopted by many practitioners (10). Clearly, new strategies designed to increase the anti-tumor activity of concurrent thoracic irradiation are needed.

Tumor hypoxia has been shown to affect the malignant...
progression of transformed cells and their response to therapy (11). Clinical studies have demonstrated a strong correlation between pretreatment tumor pO2 and tumor radiosensitivity, distant metastasis, and survival in patients with solid cancers (12–14). Studies using computed tomography (SPECT) and iodine-123-radiolabeled iodoazomycin arabinoside as radiotracer suggested that hypoxia exists in patients with SCLC (15, 16). In addition, the use of a hypoxic cell radiosensitizer has been noted to enhance radiation efficacy in human xenografts (17).

Tirapazamine (Tirazone) is a benzotriazine di-N-oxide with selective cytotoxicity for hypoxic tumor cells (18). In a hypoxic environment, the drug is reduced to form cytotoxic free radicals, causing chromosomal aberrations and resulting in cell death. In the presence of oxygen, free radicals are oxidized back to inert parent compounds that are rapidly cleared.

In vitro studies show that tirapazamine is 40–300-fold more toxic to hypoxic cells than to oxygenated cells. In vivo, tirapazamine increases the antitumor effect of fractionated radiotherapy when given concurrently (18). Tirapazamine has also been shown to enhance the effect of platinum-based chemotherapy (19, 20). In MV52 human lung cancer xenografts, the addition of tirapazamine to paraplatin and paclitaxel resulted in a 50% complete response rate compared with 0% for chemotherapy alone (20). Clinically, the combination of tirapazamine, radiation therapy, and cisplatin chemotherapy has been shown to be promising in phase II trials for several solid tumors (21, 22).

The maximum tolerated dose of tirapazamine as a single agent or in combination with chemotherapies is 390 mg/m2; however, this dose may not be required for maximum efficacy. Tirapazamine at a dose of 260 mg/m2 in combination with cisplatin has been reported to have antitumor activity equivalent to 390 mg/m2 in advanced non-small cell lung cancer (NSCLC; Ref. 23). When given concurrently with radiotherapy, toxicities were acceptable up to doses of 260 mg/m2, administered 3 times a week for 12 doses (24). When given concurrently with cisplatin and fractionated radiotherapy for cervical cancers, the maximum tolerated doses for tirapazamine were 290 mg/m2 given on the same day as cisplatin every 3 week during radiation and 220 mg/m2/dose for six additional doses during weeks 2 and 4 of radiation (22). There is a known steep dose–response relationship for tirapazamine-related toxicities, which are uncommon at doses ≤260 mg/m2 (25). On the basis of these data, the SWOG lung committee conducted a phase I study of cisplatin/etoposide/tirapazamine in combination with once-daily thoracic irradiation (61 Gy) followed by consolidation with two cycles of cisplatin/etoposide/tirapazamine in patients with LSCLC, with the starting tirapazamine dose of 260 mg/m2/dose for four doses delivered on the same day as cisplatin during radiotherapy and 330 mg/m2/dose for two doses during the adjuvant phase. The primary objective was to determine tolerability and a recommended dose for subsequent study in a phase II setting. Secondary objectives were to determine estimates of therapeutic efficacy, defined by response rates, progression-free survival, and overall survival.

Because tirapazamine has not previously been delivered concurrently with large-field thoracic irradiation, we used nonhematologic toxicity, specifically the incidence of grade 3 or higher radiation-related esophagitis and pneumonitis, as the toxicity criteria for dose escalation. The overall rate of these two toxicity parameters in INT 0096 was 37% for the hyperfractionated arm and was considered to be tolerable (9). In contrast, the combined rate of 54% in SWOG-9229, which tested the role of prolonged oral etoposide exposure during radiotherapy, was considered too high (26). We therefore consider that it is safe to dose escalate if ≤30% of patients experienced grade 3 or higher esophagitis plus pneumonitis and unsafe if ≥55% of the patients experienced such toxicity.

PATIENTS AND METHODS

Patients. The study was approved by the Clinical Trial Evaluation Program of the National Cancer Institute, the SWOG Clinical Trial Review Committee, and the local Institutional Review Boards of all participating institutions. Limited stage was defined as tumor confined to one hemithorax, hilar, mediastinal, or supraclavicular area, which could be encompassed within a single radiation portal. Patients with malignant pleural and pericardial effusion were excluded. Eligibility criteria included the following: histologic or cytologic confirmation of SCLC at diagnosis; age ≥18 years; Zubrod performance status of 0–1; adequate hematologic (absolute neutrophil count >1500/μl and platelet count >100,000/μl), hepatic (total bilirubin ≤1.5 times the normal limit, aspartate aminotransferase, alanineaminotransferase, and alkaline phosphatase ≤2 times the normal limit), and renal function (normal serum creatinine or an estimated creatinine clearance >60 ml/min); no previous chemotherapy or thoracic radiotherapy; grade 1 or lower sensory neuropathy symptoms based on the National Cancer Institute common toxicity criteria (version 2.0); no concomitant malignancies; and no ongoing pregnancy. All patients gave informed consent. Before enrollment, each patient underwent a complete history and physical examination, laboratory tests, chest X-ray, computed tomography of the chest and abdomen, either computed tomography or magnetic resonant imaging of the brain, and bone scan if indicated. Positron emission tomography scans were not required for staging, restaging, or radiation treatment planning. Patients were required to reregister for consolidation chemotherapy. Adequate hematologic function and lack of progression documented on chest imaging studies (either chest X-ray or computed tomography scans) were required before proceeding with consolidation chemotherapy. Criteria for removal from the protocol treatment included disease progression while on study, unacceptable toxicity, chemotherapy or radiation treatment delay >3 weeks, and voluntary withdrawal by the patients for any reason.

Concurrent Chemoradiotherapy. Treatment commenced within 1 week of enrollment. The treatment scheme is shown in Fig. 1. On the basis of the core cisplatin/etoposide/radiation therapy regimen used in previous SWOG studies, initial chemotherapy consisted of 50 mg/m2/day cisplatin administered i.v. on day 1, 8, 29, and 36 and 50 mg/m2/day etoposide i.v. on days 1–5 and 29–33, administered concurrently with thoracic irradiation. Tirapazamine was infused i.v. 1–2 h before each cisplatin infusion and 1–3 h before thoracic irradiation. Premedication with dexamethasone and a 5-hydroxytryptamine agonist were recommended to minimize the emetogenic effect of tirapazamine before each infusion. A total of four tirapazamine
doses were given during the concurrent phase. The starting tirapazamine dose with concurrent chemoradiotherapy was 260 mg/m², with the plan to escalate to 330 mg/m² if it was found to be well tolerated, using the rate of grade 3 or higher esophagitis and pneumonitis as dose-limiting toxicity (see statistical section below).

Chemotherapy was held for 1 week if the absolute neutrophil count was <1,000/µl or the platelet count was <100,000/µl. If the blood counts did not return to acceptable levels after 1 week, the doses of cisplatin, VP-16, and tirapazamine were reduced by 12–50% as specified in the protocol. The cisplatin dose was decreased by 50% for any grade 2 neurotoxicity, and both cisplatin and tirapazamine were held for any grade 3 or higher neurotoxicity or ototoxicity until resolution of symptoms. The cisplatin dose was reduced by 50% in patients with serum creatinine of 1.5–2 mg/dl and creatinine clearance <50 ml/min.

Thoracic radiotherapy was begun on day 1 of the first cycle of chemotherapy and administered once daily for 6.5 weeks. The clinical target volume, defined as primary tumor with 1.5 cm margins, ipsilateral hilum, and adjacent mediastinum, received 45 Gy at 1.8 Gy/fraction/day. The planning target volume was not used. Supraclavicular lymph nodes were treated only if they were directly involved with tumor. A 16-Gy boost was delivered through reduced off-spinal cord fields in eight fractions of 2 Gy daily to the gross target volume defined as the primary tumor and clinically involved lymph nodes (node >1 cm on the short axis on imaging studies or biopsy-proven positive) plus a 1.5-cm margin. Target doses were prescribed to the isocenter, and the doses within the target volumes were kept within 10% of the prescribed doses. Homogeneity correction was not used. Three-dimensional treatment planning was highly encouraged but not mandatory, and use of lung window was recommended for delineating the primary tumor. Rapid radiation quality review was instituted to ensure study compliance. Three-dimensional treatment planning was used in 24 of the patients for the entire course and in 26 of 29 patients who received the boost dose. Tumor motion was evaluated by observing patient respiratory motion on fluoroscopy and ensuring that the tumor coverage was adequate. Radiation interruption or delays were strongly discouraged and were allowed only for febrile neutropenia, any grade 4 hematologic toxicity or grade 3 or higher esophagitis or pneumonitis. The maximum spinal cord dose was limited to 50 Gy.

**Consolidation Chemotherapy.** Patients were required to reregister for consolidation chemotherapy. Only patients with stable or responsive disease and with adequate hematologic function (absolute neutrophil count >1,500/µl and platelets >100,000/µl) proceeded to consolidation chemotherapy. Consolidation consisted of 60 mg/m² cisplatin on day 1, 120 mg/m² etoposide on days 1–3, and 330 mg/m² tirapazamine on day 1 of weeks 11 and 14. Similar treatment delay or dose modification criteria as in concurrent chemotherapy were applied to consolidation treatment. The use of hematopoietic growth factors was left to the discretion of the treating physicians, based on current treatment guidelines.

**Prophylactic Cranial Irradiation.** Patients with a complete response after consolidation chemotherapy were recommended to receive prophylactic cranial irradiation to a total dose of 30 Gy in 15 fractions over 3 weeks. Prophylactic cranial irradiation was administered within 6 weeks of hematologic recovery from the last cycle of chemotherapy. Repeat brain imaging before prophylactic cranial irradiation was recommended but not required.

**Response and Toxicity Criteria.** Treatment-related toxicities were classified according to the National Cancer Institute common toxicity criteria, version 2.0. Radiation-related esophagitis was graded as follows: grade 1, mild dysphagia, unable to eat regular diet; grade 2, dysphagia requiring predominantly puree, soft, or liquid diet; grade 3, dysphagia requiring i.v. fluid hydration; grade 4, complete obstruction, inability to swallow saliva, requiring enteral or parenteral nutritional support or perforation. Tumor response was scored according to the RECIST criteria (27).

**Study Design and Statistical Analysis.** This study was designed to assess the feasibility and toxicity of limited dose escalation (two dose levels) of tirapazamine during concurrent etoposide and thoracic irradiation, followed by etoposide and a fixed dose of tirapazamine. The incidence of grade 3 or higher radiation-related esophagitis and pneumonitis were used as dose-limiting toxicities. The tirapazamine dose was to be considered unsafe if ≥55% of patients experienced grade 3 or higher esophagitis plus pneumonitis and safe if ≤30% of pa-
patients experienced grade 3 or higher esophagitis plus pneumonitis. Twenty-five patients at each tirapazamine dose level would provide an 81% power to distinguish between the null hypothesis that the dose was unsafe versus the alternative of a safe dose, using a one-sided test based on the binomial distributions with a significance level of 4%. This translated to the followings: if 9 or fewer patients developed grade 3 or greater esophagitis plus pneumonitis, the dose would be escalated to the next level, whereas if 10 or more patients experienced these toxicity, the trial would be terminated and the maximum tolerated dose would have been reached.

RESULTS

Patient Characteristics. Between December 2000 and September 2001, 30 patients with LSCLC from 18 institutions were enrolled at the initial tirapazamine dose of 260 mg/m². The characteristics of these patients are shown in Table 1. Twenty-nine patients (97%) were eligible for response evaluation. The median follow-up for all patients was 18 months (range, 1–31 months).

Dose Escalation and Toxicity. The study was designed to test two dose levels of tirapazamine administered concurrently with etoposide and thoracic irradiation. If the first dose, 260 mg/m², was well tolerated, the plan was to escalate to the second dose. However, based on prospectively defined dose-limiting toxicities and observed toxicities as described below, the maximum tolerated dose for tirapazamine delivered with concurrent etoposide and thoracic irradiation was 260 mg/m². Therefore, tirapazamine dose escalation was not pursued.

Toxicity was scored separately for the concurrent and the consolidation portions of the treatment protocol. Twenty-nine patients were eligible for toxicity assessment in the concurrent phase. One other patient received a tirapazamine dose of 330 mg/m²/day during the concurrent phase, which was significantly higher than specified in the protocol because of administrative errors, and were therefore deemed ineligible for toxicity evaluation. The principal toxicities during the concurrent phase are summarized in Table 2. Twenty-five (86%) patients experienced grade 3 or greater toxicity. Predominant hematologic toxicity was grade 3–4 neutropenia, which was observed in 16 patients, and febrile neutropenia in 4 patients. Predominant nonhematologic toxicities were radiation-related esophagitis, nausea/vomiting, and dehydration. Ten patients experienced grade 3 or greater esophagitis, defined as a dose-limiting toxicity precluding dose escalation of tirapazamine. One patient died from febrile neutropenia.

We evaluated several clinical parameters to identify potential predictors for failure to complete all treatment during the concurrent phase in these patients, using either Fisher’s exact test or logistic regression method. These included the use of three-dimensional treatment planning, the maximum radiation field length, age, pretreatment performance status, and pretreatment weight loss. Only pretreatment performance status reached statistical significance (P = 0.045), whereas pretreatment weight loss was of borderline significance (P = 0.06). None of the other three factors was a predictor of whether the patients finished this part of the study.

Twenty eligible patients proceeded with consolidation chemotherapy, of whom 18 were evaluable for toxicity. Two other patients never started consolidation treatment and were therefore not evaluable. The toxicities reported for the consolidation chemotherapy are shown in Table 3. The predominant toxicities were hematologic, with eight patients experiencing grade 4 neutropenia. All but one recovered with granulocyte colony-stimulating factor support. One patient was hospitalized with grade 4 neutropenia and thrombocytopenia after the first cycle of consolidation chemotherapy. During the hospitalization, the patient developed sudden respiratory distress, which progressed to rapid cardiopulmonary arrest. Autopsy revealed residual necrotic cancer with necrotizing bronchopneumonia and pulmonary edema.

Table 1  Patient characteristics (N = 30)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
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<tr>
<td>Median (range) age (yrs)</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Female</td>
<td>13</td>
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<tr>
<td>Weight loss</td>
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<td>≥5%</td>
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<tr>
<td>Performance status</td>
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<tr>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
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Table 2  Principal toxicities during the concomitant phase

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>9  9  0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7  9  0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3  2  0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4  1  0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2  2  0</td>
</tr>
<tr>
<td>Infection</td>
<td>5  0  1</td>
</tr>
<tr>
<td>Radiation therapy-related esophagitis</td>
<td>7  3  0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 0 0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>6  1  0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0  0  0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1  0  0</td>
</tr>
<tr>
<td>Total</td>
<td>12 12 1</td>
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</table>

Table 3  Principal toxicities during the consolidation phase

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade (N = 18)</th>
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</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>4  7  0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2  8  0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2  1  0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1  0  0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2  1  0</td>
</tr>
<tr>
<td>Infection</td>
<td>3  0  1</td>
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<tr>
<td>Dysphasia</td>
<td>1  0  0</td>
</tr>
<tr>
<td>Total</td>
<td>3 10 1</td>
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</table>
were treatment-related toxicity in six, personal reasons in one, tumor progression in one, and treatment-related death in one. Of the 21 patients who completed treatment, 1 was ineligible for consolidation because of failure to have restaging studies performed in a timely fashion. Therefore, 20 eligible patients proceeded with consolidation chemotherapy, of whom 2 never started treatment. Of the remaining 18 patients, 15 completed treatment as planned, 2 terminated early because of side effects, and 1 died during treatment.

For the concurrent phase, the achievable mean dose intensities were 92% for cisplatin (range, 50–104%), 94% for tirapazamine (range, 15–127%), and 98% for etoposide (range, 20–105%). The achievable mean dose intensities for the consolidation phase were 100% (range, 66–200%) for cisplatin, 100% (87–114%) for tirapazamine, and 94% (33–104%) for etoposide.

Radiation was completed as planned for 24 patients. In five patients, radiation therapy was terminated before the 61 Gy dose because of esophagitis in four and personal reasons in one. Prolonged radiation interruption, defined as interruption longer than 2 weeks, occurred in four patients because of radiation-related esophagitis in three and unknown cause in one.

**Response.** Twenty-nine patients were assessable for response. Complete response was noted in 6 patients (20%), partial response in 18 (60%), stable disease in 3 (10%), and progressive disease in 1 (3%). In two patients, the response was not assessable because of early death in 1 and inadequate data in the other. The overall response rate was therefore 80%. Although this study was not designed with a primary end point of efficacy, the median survival was 22 months (Fig. 2).

**DISCUSSION**

The introduction of new agents into the treatment of LSCLC presents a challenge because of the potential curability of these patients. Nevertheless, the standard of care in the United States, cisplatin/etoposide and concurrent thoracic irradiation, has changed very little over the last 15 years (28). The findings of INT 0096 demonstrating improved efficacy with twice-daily thoracic irradiation (9) have not been widely adopted (10), most likely because of the inconvenience and increased toxicities associated with this regimen. Most recent clinical research studies have attempted to increase treatment efficacy in LSCLC by introducing new agents into concurrent chemoradiotherapy regimens using once-daily radiotherapy schedules. Several new agents have been investigated, including paclitaxel, irinotecan, and topotecan, but to date, none have proven of sufficient benefit to justify inclusion during routine clinical practice (29).

Tirapazamine is a novel agent of considerable interest for inclusion with chemoradiotherapy because of its selective cytotoxicity to hypoxic cells that are resistant to standard fractionated radiotherapy. In addition, tirapazamine demonstrated time-dependent synergism with cisplatin-based chemotherapy in preclinical models (30). On the basis of these data, it has been combined with cisplatin and radiotherapy in the management of locally advanced head and neck and cervical cancers, with promising results in phase I and II trials (21, 22). Whether tirapazamine functions equally well as a chemotherapy potentiator in patients with metastatic cancer is less clear. Results of phase III randomized trials of tirapazamine in NSCLC have been mixed. An initial phase III randomized study (CATAPULT 1) comparing cisplatin alone versus cisplatin and tirapazamine in stage IV NSCLC showed a survival advantage for the tirapazamine arm (31). A subsequent study (CATAPULT 2) comparing etoposide with cisplatin and tirapazamine with cisplatin in a similar patient population favored the etoposide combination, suggesting that tirapazamine, by itself, cannot replace an active chemotherapy (32). Twice as many patients on the tirapazamine arm of CATAPULT 2 went off study early because of toxicity. Both of these studies used tirapazamine at a dose of 390 mg/m². Recently, we completed a randomized trial of paclitaxel and carboplatin with or without tirapazamine in patients with advanced-stage NSCLC (S0003). Unfortunately, preliminary results of this study show that tirapazamine increased toxicity without improving response rates or overall survival (33). Despite lower tirapazamine doses of 260–330 mg/m², more patients on the tirapazamine arm of S0003 went off study because of toxicity. Of interest, analysis of potential plasma markers of tumor hypoxia (plasminogen activator inhibitor-1, vascular endothelial growth factor, and osteopontin) suggested that their predictive values for survival were confined to the tirapazamine arm alone (34).

The study reported here, conducted simultaneously with S0003, was designed to evaluate the feasibility of integrating tirapazamine into chemoradiotherapy in LSCLC. The overall objective was to enhance the efficacy of chemoradiation while maintaining an acceptable toxicity profile. The SWOG lung committee has previously conducted a phase II study, S9713, which used the same concurrent regimen with cisplatin/etoposide and once-daily high-dose thoracic irradiation without tirapazamine in patients with LSCLC, followed by carboplatinum and paclitaxel consolidation (35). The toxicities during the concurrent phase for S0004 and S9713 are compared in Table 4. Compared with S9713, there was more esophagitis, vomiting, and febrile neutropenia with the addition of tirapazamine. Although the overall nonhematologic toxicity rate was higher with S0004 than in S9713, it is similar to that observed with twice-daily radiotherapy in the INT 0096 study (9).

Although the oxygen tension of normal esophageal epithelium is not directly known, immunohistochemical studies have demonstrated heavy binding of the hypoxia marker misonidazole to esophageal epithelium (36, 37). These data suggest that esophageal epithelium may have lower oxygen tensions than
other normal structures and thus may be more susceptible to tirapazamine toxicity. In addition, increased retching from nausea and vomiting, a tirapazamine-related toxicity, may also contribute to symptomatic esophagitis. The addition of amifostine, which has been shown to decrease esophagitis and pneumonitis in NSCLC patients treated with concurrent thoracic irradiation and chemotherapy (38), may help to ameliorate many of the side effects noted in this study.

Two treatment-related deaths were observed in our study, one from febrile neutropenia and the other from obstructive pneumonia not associated with neutropenia. This rate is consistent with reports from the literature of a 2–6% mortality risk for patients with LSCLC treated with chemoradiotherapy (9, 39).

Patients with LSCLC are at risk of both local and distant failures. Local failures after 45 Gy of once-daily thoracic irradiation are 35–75% (9, 40). Twice-daily radiotherapy as used in INT 0096 improved both local control and survival compared with once-daily radiation (9). However, the two radiation regimens tested in INT 0096 are not felt to be biologically equivalent. A dose-escalation study has suggested that 70 Gy at 1.8 Gy once daily may be more equivalent to 45 Gy at 1.5 Gy twice daily based on normal tissue toxicity (41). Long-term follow-up has shown similar or higher 5-year survival rates in patients treated with high-dose once-daily thoracic irradiation compared with 45 Gy twice daily (42, 43). A large phase III randomized study comparing high-dose once-daily thoracic irradiation with 45 Gy twice daily would be necessary to address the issue of radiation dose and fractionation in LSCLC. A trial of this design has been proposed by the US Lung Intergroup. Pending the results of such a trial, SWOG has chosen to use a dose of 61 Gy given once daily in 1.8- to 2.0-Gy fractions, a dose for which there are published data regarding toxicity when used with concurrent cisplatin/etoposide in NSCLC (44, 45).

The overall response rate and the median survival in this study were 80% and 22 months, respectively. These results compare favorably with those reported in the literature for LSCLC. Moreover, emerging data suggest that tirapazamine may be most efficacious when combined with radiation and chemotherapy rather than with chemotherapy alone. In an interim analysis of a phase II randomized study, the combination of tirapazamine, cisplatin, and radiotherapy yielded superior results than the combination of cisplatin, 5-fluorouracil, and radiotherapy in patients with locally advanced head and neck cancer (46). In this regimen, tirapazamine was given at 290 mg/m² before cisplatin in weeks 1, 4, 7 and then alone at 160 mg/m² three times a week in weeks 2 and 3 of radiotherapy. At present, a multi-institutional phase III study is under way to determine the efficacy of this regimen in head and neck cancers.9 Furthering interest in tirapazamine are preliminary data suggesting that either hypoxia imaging with ¹⁸F-fluoride-misonidazole positron emission tomography scans or measurements of surrogate plasma markers for tumor hypoxia may be used to identify patients most likely to benefit from this hypoxic cytotoxin (21, 34, 47).

In light of the promising median survival observed in S0004, further study of tirapazamine combined with chemoradiation in LSCLC is warranted. A recently activated phase II trial (S0222) is designed to optimize tirapazamine dose and schedule to enhance the efficacy of chemoradiation. In this study, tirapazamine is administered at 260 mg/m² as a single dose during weeks 1 and 4 before cisplatin and at 160 mg/m² three times a week during weeks 2 and 6 during thoracic irradiation only. This study incorporates a correlative scientific objective by exploring the role of potential plasma markers of tumor hypoxia to determine their predictive power for efficacy of tirapazamine (48, 49).

### REFERENCES


Table 4 Comparison of selective grade 3–4 toxicities during concurrent chemoradiotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Study</th>
<th>S0004 (N = 29)</th>
<th>S9713 (N = 86)</th>
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<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
<td>Grade 3 (%)</td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Vomiting</td>
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<td>22</td>
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NOTE. Values are the percentages of patients affected.

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