ORIGINAL ARTICLE

Gemcitabine and Irinotecan for Patients with Untreated Extensive Stage Small Cell Lung Cancer: SWOG 0119

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Introduction: To evaluate the activity of a nonplatinum-, nonetoposide-containing regimen for patients with extensive stage small cell lung cancer.

Methods: Patients with untreated extensive stage small cell lung cancer were treated with gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 on days 1 and 8 of a 21-day cycle for a maximum of six cycles. Patients with brain metastases were eligible if asymptomatic or controlled after radiation.

Results: Eighty-four eligible patients with untreated extensive stage small cell lung cancer with adequate organ function and a performance status of 0–2 were accrued. The median age was 64 years (range, 42–85) and 45 (54%) were women. Six cycles were completed by 28 (33%) patients. Some degree of diarrhea occurred in 57% (grade 3/4, 18%). Other grade 3/4 toxicities were neutropenia (26%), anemia (10%), thrombocytopenia (8%), febrile neutropenia (5%), fatigue (11%), nausea (10%), and vomiting (8%). The response rate was 32% (95% confidence interval: 22%–43%) among the 81 patients with measurable disease. The median survival was 8.5 months (95% confidence interval: 7.0–9.8) with 1- and 2-year survival rates of 26% and 7%, respectively. Salvage therapy data were captured by prospective collection, and only 50% of patients were treated secondarily.

Conclusion: The overall response rate with the combination of gemcitabine and irinotecan was disappointing, and the median survival rate was lower than expected. Further development of this combination in small cell lung cancer is not recommended.

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Lung cancer is the leading cause of cancer mortality in the United States with an estimated 174,470 deaths in 2006.[1] Approximately 15% of these deaths will be caused by small cell lung cancer, an initially chemotherapy-sensitive but aggressive cancer.[2] Cisplatin and etoposide constitute the current systemic standard of care for small cell lung cancer in the United States.[3] With concurrent chemoradiotherapy, 15% to 20% of the 30% of patients who present with limited stage small cell lung cancer may be cured.[4] Despite initial response rates approaching 90%, relapsing patients and those with extensive stage small cell lung cancer invariably become refractory to therapy and, ultimately, die of the disease.[5] One strategy to suppress or prevent the emergence of a resistant clone is to use multiple, non–cross-resistant agents, applied concurrently or sequentially.[6,7] Therapy with concurrent agents is constrained by overlapping toxicities, and sequential treatment is limited by inadequate non–cross-resistance.[3,8–10] Further progress will require the development and integration of new agents with nonoverlapping toxicity or improved cytotoxicity.

Gemcitabine and irinotecan appear to fit this profile in several respects. Each is independently active in small cell lung cancer, and the combination can be administered without reduction in dose intensity. As single-agent therapies, gemcitabine or irinotecan has response rates of 27% to 50%[11,12] and 14% to 47%[13–15] for chemotherapy-naive patients and those previously treated with chemotherapy, respectively. The activity of irinotecan in extensive stage small cell lung cancer is further highlighted by findings from JCOG 9511, a phase III study, that showed irinotecan plus cisplatin to yield superior survival rates compared with etoposide plus cisplatin.[16]

As combination therapy, gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 administered on days 1 and 8 of a 21-day schedule are well tolerated,[17,18] and the combination demonstrates synergy in vitro over a wide range of doses in breast and small cell lung cancer cell lines.[19] For these reasons, we chose to evaluate gemcitabine and irinotecan in a phase II trial to determine the activity and tolerance of this noncisplatin-, nonetoposide-based combination for patients with untreated extensive stage small cell lung cancer.

PATIENTS AND METHODS

All patients were required to have (1) histologically documented small cell lung cancer; (2) extensive stage disease defined as tumor extending beyond one hemithorax,

mediastinal, hilar, or supraclavicular area and that could not be encompassed within a single radiation port (malignant pleural effusion constituted extensive stage disease); (3) measurable or nonmeasurable disease; (4) no previous chemotherapy for this cancer; (5) Zubrod performance score of 0–2; (6) granulocyte count greater than $1500/\mu l$; (7) platelet count greater than $100,000/\mu l$; (8) aspartate aminotransferase and alanine aminotransferase less than 2.5 times institutional normal value; and (9) total bilirubin less than 1.25 times institutional normal value. Required radiographic evaluation before study participation included computed tomography of the chest and abdomen and computed tomography/magnetic resonance imaging of the brain. Brain metastases were allowed if asymptomatic or previously treated with radiation and no longer associated with symptoms and not requiring steroid therapy. Ineligibility criteria included pregnancy or nursing, other active malignancy, or less than a 2-week duration since surgery. The study was reviewed and approved by the institutional review board at each participating institution. Each patient gave informed consent.

Treatment Plan

Gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 were administered intravenously on days 1 and 8 of a 21-day cycle for a maximum of six cycles. A 5-HT3 receptor antagonist was recommended before therapy. Response evaluation was performed every two cycles, and therapy was discontinued for disease progression. After completion of protocol treatment, follow-up data were requested every 3 months for subsequent chemotherapy and survival.

Dose Modification

Dose modifications were based on toxicity assessed on the day of treatment. Day 1 therapy was given at full dose if granulocytes were more than $1500/\mu l$ and platelets were more than $100,000/\mu l$. Doses were administered at 75% of planned if granulocytes were less than $1,500/\mu l$ or platelets were less than $100,000/\mu l$ and were delayed 1 week for repeat evaluation if granulocytes were less than $1,000/\mu l$ or platelets were less than $75,000/\mu l$. If more than a 1-week delay was required or an episode of febrile neutropenia developed in the patients during the previous cycle, then all future doses were given at 75% of the original doses. If hematologic recovery had not occurred within 3 weeks from the planned start date of the cycle, then the patient was removed from study. For day 8 therapy, both drugs were omitted if granulocytes were less than $1500/\mu l$ or platelets were less than $100,000/\mu l$.

Dose modifications for nonhematologic toxicity included for grade 2/3 diarrhea uncontrolled by loperamide, withholding irinotecan until the patient improved to grade 1 and then treatment restarted at 75% of dose permanently. For grade 4 diarrhea uncontrolled by loperamide, irinotecan was held until toxicity resolved to grade 1 or lower and further doses were limited to 50% as a permanent dose reduction. For grade 2 mucositis or higher, both agents were held until resolution, and permanent dose reductions were implemented if mucositis reached grade 3/4. If grade 3/4 edema occurred, the dose of gemcitabine was permanently reduced. For other nonhematologic drug-related toxicity, excluding nausea, vomit-ing, fatigue, fever without grade 4 neutropenia, or alopecia, permanent dose reductions were instituted if grade 2 or higher.

Statistical Planning, Outcome Definitions, and Analysis Methods

The primary endpoint of the study was overall survival. A meta-analysis of studies focused on extensive stage small cell lung cancer using etoposide and cisplatin showed a median survival of 9.5 months.[3] Thus, the results of this trial would be considered promising if the true median survival from registration were 13.5 months or longer and would be considered of no further interest if the true median survival were 9 months or shorter. The planned accrual of 75 patients allowed for a one-sided 0.05 level test to rule in favor of accepting either the null median survival of 9 months or the alternative of 13.5 months with 89% power. This assumed 12-month accrual period was followed by 12 months of additional survival follow-up.

It was assumed that 80% of enrolled patients would have measurable disease. Therefore, response would be assessed in approximately 60 patients, which would be sufficient to estimate the response rate (confirmed plus unconfirmed, complete and partial) to within ±13% (95% confidence interval [CI]). Rates of specific toxicities could be estimated to within, at worst, ±12% (95% CI). Any toxicity occurring with at least 5% probability was likely to be seen at least once (97.9% chance).

Overall survival (OS) was calculated as the time from registration to SWOG 0119 to death from any cause or last contact. Progression-free survival (PFS) was calculated as the time from registration to SWOG 0119 to either progression of disease or death from any cause or last contact. Response was defined using RECIST (Response Evaluation Criteria in Solid Tumors).[20] Survival curves were estimated by the product-limit method[21] and compared using the log-rank test.[22]

RESULTS

Eighty-five patients were accrued to SWOG 0119 between January 2002 and February 2003. One patient was ineligible and was not included for analysis in this data set. The remaining 84 patients form the basis of this report. The analyses reported reflect the available data through July 23, 2005.

The characteristics of the eligible patients are summarized in Table 1. The median age was 64 years (range, 42–85). There were 39 males and 45 females. The performance status was 0–1 in 84% and 2 in 16%.

Twenty-eight patients (33%) received all six planned cycles of chemotherapy. The major reason for not completing therapy was progression of cancer (37 patients, 44%). Other reasons included death (six patients, 7.0%), which included three who were adverse events (9, 11%), refusal (1, 1%), and development of lymphoma (1, 1%). One patient discontinued for unknown reasons, and another was removed from protocol treatment after it was discovered that presumed metastatic lesions were benign and the patient had been incorrectly staged at baseline. The median number of cycles received was four. Grouped by performance status of 0, 1, or 2, the

TABLE 1. Patient Characteristics

No. (%) of eligible patients	84 (100)
Gender	
Male	39 (54)
Female	45 (46)
Age, yr, median (range)	64 (42–85)
<60, no. (%)	31 (37)
60–69, no. (%)	28 (33)
70+, no. (%)	25 (30)
Race	
White	73 (87)
Nonwhite	11 (13)
Performance status, no. (%)	
0/1	68 (84)
2	13 (16)
Weight loss	
<5%	46 (57)
5%–10%	24 (30)
>10%	11 (13)

TABLE 2. Maximum Toxicity: Hematologic and Selected Nonhematologic (*n* = 84)

	Grade					
	0	1	2	3	4	5
Anemia	25	38	13	7	1	0
Granulocytopenia	41	3	18	17	5	0
Leukopenia	37	18	19	6	4	0
Thrombocytopenia	56	16	5	7	0	0
Abdominal pain/cramps	64	12	4	4	0	0
Anorexia	46	19	12	7	0	0
Diarrhea	36	23	10	14	1	0
Dyspnea	52	0	20	10	1	0
Fatigue	16	33	26	7	2	0
Febrile neutropenia	80	0	0	3	1	0
Hyponatremia	64	13	0	4	3	0

median number of cycles received was six, three, three, and the percentages of patients receiving more than two cycles were 95%, 74%, and 54%, respectively.

The hematologic and selected common toxicities that occurred during chemotherapy are listed in Table 2. There were six deaths potentially related to treatment: aneurysm (one), myocardial infarction (one), thrombosis (one), arrhythmia (one), hypotension (one), and a death within 30 days of treatment for which treatment could not be ruled out as a cause. Grade 3/4 hematologic toxicities were neutropenia (26%), leukopenia (12%), anemia (10%), and thrombocytopenia (8%). Febrile neutropenia occurred in 5%. Diarrhea occurred in 57% (grade 1 [27%], grade 2 [12%], grade 3 [17%]), grade 4 [1%]). The only other grade 3/4 toxicity occurring in more than 10% of patients was dyspnea (13%), which likely was related to malignancy or comorbid disease.

Response was evaluated 6 weeks (two cycles) after the start of treatment, but was adequately assessed in only 70

TABLE 3. Response Evaluation in Patients with Measurable Disease

	Gemcitabine/CPT-11, No. (%)
Complete response	0 (0)
Partial response	14 (17)
Unconfirmed partial response	12 (15)
Stable/no response	15 (19)
Increasing disease	22 (27)
Early death	2 (2)
Symptomatic deterioration	3 (4)
Assessment inadequate	13 (16)
Total	81 (100)

(83%) patients. Measurable disease was not a requirement for study entry. Partial responses, confirmed and unconfirmed, were seen in 26 of 81 patients with measurable disease (32%; 95% CI: 22%–43%) (Table 3). There were no complete responses. Stable disease was seen in 15 (19%) and progression in 27 (32%). The median number of cycles delivered for those achieving a response, stable disease, or progression was 6, 5, and 2, respectively.

Univariate analyses were performed for overall and progression-free survival for prognostic factors including albumin, lactate dehydrogenase, pleural effusion, single versus multiple lesions, weight loss, and performance status. Only elevated lactate dehydrogenase above institutional upper limit of normal (7 versus 13 months, $p = 0.002$) and multiple versus single metastatic lesions (8 versus 11 months, $p = 0.004$) were found to be prognostic for overall survival. Patients with a performance status of 0 or 1 versus 2 survived a median of 9 versus 4 months, but the difference was not significant. Only multiple versus single metastatic lesions were prognostic for progression-free survival (3 versus 5 months, $p = 0.03$).

Second-line chemotherapy administered after completion of the trial was recorded in posttreatment follow-up forms and indicated that only 50% received further treatment. Seventy-five percent of patients surviving long enough to complete all protocol therapy (six 21-day cycles or a minimum of 126 days) did go on to receive further treatment. In all cases, etoposide and either cisplatinum or carboplatin were delivered as the salvage treatment. Of the patients with progression, stable disease, or response, 85%, 75%, and 64% received further treatment, respectively.

Survival and progression-free survival are shown in Figures 1 and 2. The median progression-free survival was 3.4 months (95% CI: 2.4–3.9). The median survival was 8.5 months (95% CI: 7.0–9.8) with 1- and 2-year overall survival rates of 26% and 7%, respectively.

DISCUSSION

This large phase II study of gemcitabine and irinotecan for extensive stage small cell lung cancer was designed to evaluate a nonplatinum-, nonetoposide-containing regimen for overall survival. The regimen would be considered promising if the true median survival were more than 13.5 months
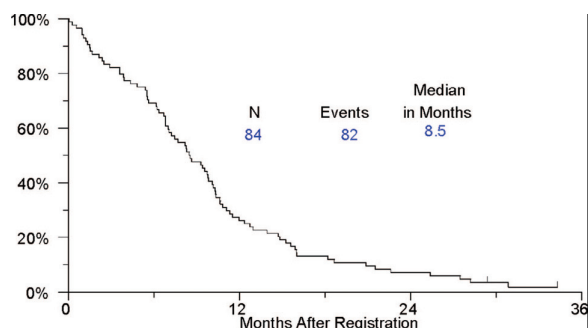
FIGURE 1. Overall survival. Median survival, 8.5 months (95% confidence interval [CI]: 7.0– 9.8); 1-year survival rate, 26% (95% CI: 17%–35%).
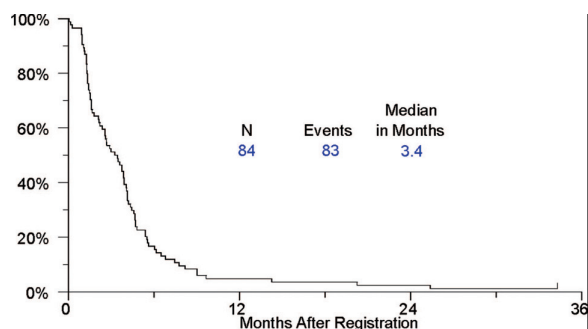

FIGURE 2. Progression-free survival. Median progression-free survival, 3.4 months (95% confidence interval: 2.4–3.9).

and would be considered of no further interest if the median survival were less than 9 months. With a median survival of 8.5 months, we do not recommend further development of this regimen as first-line therapy for extensive stage small cell lung cancer.

There was a discrepancy between response rate and the median survival for this nonplatinum-, nonetoposide-based regimen. Although both were low, the overall survival approached that achieved in meta-analyses of extensive stage small cell.[20] Conversely, the response rate of 32%, the stable disease rate of 19%, and the progression-free survival of only 3.4 months were particularly low and suggest that only the minority of patients benefited from this therapy. Accordingly, the univariate analysis for response was not correlated with survival. The cause of this discordance is not clear, but one possible explanation is much of the therapeutic benefit may have derived from cross-over or second-line treatment. Arguing against this hypothesis is the relatively low percentage (50%) of patients who were estimated to have received alternate treatment.

A window of opportunity trial, like this one, has as its main advantage the prospect of evaluating the activity of agents in a chemotherapy-naive state. Its disadvantage is that an ineffective investigational therapy may delay initiation of known effective treatment or worse, prevent altogether the use of any second-line treatment if the performance status of the patients declines sufficiently during investigational therapy. Although overall survival was within acceptable bound-

aries in this trial, it is worrisome that only an estimated 50% of patients received second-line platinum/etoposide-based treatment, suggesting that rapid progression and decline of performance status precluded treatment. For patients who lived longer than 126 days, the fraction of patients receiving second-line treatment was greater, ranging from 65% to 85% depending on response status. This less-than-complete cross-over should serve as a warning when designing window-of-opportunity trials with new agents in the setting of tumors with rapid growth, if conventional treatment has substantial activity. Prospective, planned capture of second-line treatment is particularly important for this trial design. A two-stage design with early stopping rules is also warranted.

In summary, we believe that efforts should continue to develop a treatment that does not share resistance with platinum or etoposide. Such a regimen, however, must have substantial activity if it is to be tested as an initial treatment in extensive stage small cell lung cancer. Otherwise, patients may be denied the opportunity to receive standard treatment because of rapid disease progression or deteriorating clinical status. Gemcitabine and irinotecan are not sufficiently active to justify further development of this regimen as first-line therapy for extensive stage small cell lung cancer.

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