Phase II Study of Gemcitabine and Cisplatin in Patients with Previously Untreated Extensive Stage Small Cell Lung Cancer: Southwest Oncology Group Study 9718

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Background: This phase II study (S9718) evaluated the antineoplastic activity and tolerability of the combination of gemcitabine and cisplatin in previously untreated patients with extensive stage small cell lung cancer (ES-SCLC).

Methods: Chemonaive patients with ES-SCLC, received gemcitabine 1250 mg/m^2 intravenously (IV) over 30 minutes on days 1 and 8 and cisplatin 75 mg/m^2 IV over 30 to 60 minutes on day 1. Treatments were repeated every 21 days for a maximum of six cycles.

Results: A total of 88 patients were enrolled in the study; seven patients were not eligible and one did not receive treatment; 80 patients were fully assessable for survival, response, and toxicity. Objective response was observed in 42 patients (53%; 95% confidence interval [CI]: 41%–64%) with two patients (3%; 95% CI: 0%–8%) achieving a complete response. Median PFS was 5 months (CI, 4.2-5.9 months), and median overall survival was 8.8 months (95% CI: 7.8–9.5 months). The 1- and 2-year survival rates were 27.5% (95% CI: 17.7%–37.3%) and 4% (95% CI: 0%–8%), respectively. The most common toxicity was neutropenia. Grade 3 and 4 neutropenia was noted in 17 (21%) and 17 (21%) patients, respectively. Two patients developed febrile neutropenia, with subsequent full recovery. Twenty-one patients (23%) developed grade 3 thrombocytopenia. Grade 4 thrombocytopenia was seen in only one patient. The most common nonhematologic toxicities included grade 3 and 4 vomiting in 12 (21%) patients and fatigue in nine (10%) patients. Two patients (3%) died of respiratory infections while on treatment.

Conclusion: The combination of gemcitabine and cisplatin is an active and reasonably well tolerated regimen for the treatment of ES-SCLC. It does not appear to offer any compelling advantages over other commonly used two drug regimens in this disease.

Key Words: Cisplatin, Gemcitabine, Small cell lung cancer, Lung cancer, Small cell, Chemotherapy.

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Of the estimated 213,000 new cases of lung cancer that will be diagnosed in the United States in 2007, approximately 15% to 20% will have a small cell subtype.[1,2] For the two thirds of patients presenting with extensive stage small cell lung cancer (ES-SCLC), effective short-term palliation can be achieved with chemotherapy, but cure is rare. The current standard of care for patients with ES-SCLC and a good performance status is four to six cycles of cisplatin or carboplatin combined with etoposide or irinotecan.[3–6] New treatment approaches incorporating other chemotherapy agents with activity in SCLC are warranted.

Gemcitabine is an antimetabolite analogue of the nucleoside deoxycytidine with two fluorine atoms incorporated into the sugar ring.[7–9] It is metabolized intracellularly to the active 5′-di- and 5′-triphosphates, which inhibit DNA polymerization. Gemcitabine has demonstrated antineoplastic activity against a broad spectrum of solid tumors and is currently approved for use in pancreatic, breast, ovarian and non-small cell lung cancers (NSCLC).

Initial interest in gemcitabine in SCLC was stimulated by its in vitro antitumor activity in two SCLC cell lines, 54A and 54B.[10] This led the National Cancer Institute of Canada (NCI-C) Clinical Trials Group to conduct a phase II trial of gemcitabine in previously untreated patients with SCLC.[11] Twenty-nine patients with ES-SCLC extensive stage disease were enrolled in the study. Patients were treated on a weekly schedule for three consecutive weeks, with treatment cycles repeated every 28 days. The first 17 patients received gem-

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citabine at a dose of 1000 mg/m^2 and the last 12 patients received a dose of 1250 mg/m^2. The overall response rate in the 26 assessable patients was 27%. The median duration of response was 12.5 weeks and median survival was 12 months. The regimen was well tolerated with modest hematologic toxicity.

The most active current standard chemotherapy regimen in SCLC is a combination of cisplatin with etoposide (PE). Gemcitabine and cisplatin is an attractive doublet because of their different mechanisms of action and nonoverlapping toxicities. Furthermore, this two-drug combination has demonstrated significant antineoplastic activity with reasonable toxicity in a number of solid tumors such as transitional cell carcinoma of the urothelium and NSCLC.[12,13] The current trial was undertaken by the Southwest Oncology Group (SWOG) to evaluate the efficacy of gemcitabine plus cisplatin in chemotherapy-naive patients with ES-SCLC. The schedule and chemotherapy doses employed in this trial were derived from a phase III study conducted in NSCLC.[14]

PATIENTS AND METHODS

Eligibility

Patients were required to have histologically or cytologically confirmed ES-SCLC. Patients were considered to have extensive disease if their tumor extended beyond one hemithorax, mediastinal, hilar, or supraclavicular area that could not be encompassed within a single radiation port. All patients were required to have measurable or assessable disease documented by computed tomography, magnetic resonance imaging, radiography, physical or nuclear examination; be 18 years of age or older; have a performance status of 0–2; and have acceptable hepatic, cardiac, hematologic, and renal function as documented by a serum creatinine less than or equal to the institutional upper limit of normal and calculated creatinine clearance of 50 ml/min or more. Previous radiation therapy and previous surgery for SCLC were allowed, but previous chemotherapy was not. At least 2 weeks must have elapsed since surgery or completion of radiotherapy, and patients must have recovered from all associated toxicities. Patients with brain metastases were eligible if the brain metastases were treated and/or asymptomatic. No previous malignancies were allowed other than adequately treated nonmelanoma skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which the patient was in complete remission, or any other cancer from which the patient had been disease free for at least 5 years. All patients were informed of the investigational nature of this study and signed a written informed consent in accordance with local institutional review board and federal guidelines.

Treatment Plan

Patients received gemcitabine 1250 mg/m^2 intravenously (IV) over 30 minutes on days 1 and 8 and cisplatin 75 mg/m^2 IV over 30 to 60 minutes on day 1 of each cycle. Treatments were repeated every 21 days for a maximum of six cycles. Patients continued on treatment until disease progression or completion of six cycles, whichever occurred first. Appropriate antiemetic regimens containing a 5-hydroxytryptamine antagonist were recommended for all patients. Recommendations for pretreatment hydration before cisplatin included 1 to 2 liters of 5% dextrose in normal saline or normal saline over 10 to 24 hours if given as an inpatient or 1 liter over a minimum of 4 hours as an outpatient. Prophylactic use of granulocyte colony–stimulating factor was not permitted. Granulocyte colony–stimulating factor could be used for the treatment of prolonged neutropenia or for febrile neutropenia. Treatment at the time of disease recurrence or progression after six cycles was at the discretion of the individual investigator.

Dose Modifications

Patients experiencing a nadir granulocyte count of less than 500/μl or a nadir platelet count of less than 10,000/μl or requiring the use of granulocyte colony–stimulating factor were required to undergo a permanent 25% dose reduction of gemcitabine. If the neutrophil count was less than 1500/μl and/or the platelet count was less than 100,000/μl on day 1 of any cycle, chemotherapy was held until recovery. Day 8 gemcitabine was omitted if the absolute neutrophil count was less than 1000/μl and/or the platelet count was less than 75,000/μl. If the absolute neutrophil count was between 1000 and 1499/μl or the platelet count was between 75,000 and 99,000/μl, on day 8, gemcitabine dose was reduced to 750 mg/m^2. All gemcitabine dose reductions were permanent. Dose modifications for other grade 3 and 4 toxicities were specified in the protocol. Patients who required longer than a 2-week delay in treatment were removed from the study.

Response and Toxicity Criteria

Standard SWOG criteria were used for response determination.[15] Progression-free survival (PFS) was calculated from the date of entry into the study to the date of documentation of progression or death (in the absence of progression). Survival was calculated from the date of entry into the study until the date of death. Both intervals were determined using the Kaplan-Meier method. Toxicity grading was done according to the Common Toxicity Criteria, version 2.0.[16] Complete blood counts were obtained before each treatment administration and serum chemistries obtained at the beginning of each 21-day cycle. Disease was reassessed at 9 weeks, 18 weeks, and at least every 6 months after treatment was completed.

Statistical Considerations

The main objective of S9718 was to test whether the combination of gemcitabine and cisplatin has promise in terms of increasing survival and response rates in patients with ES-SCLC. The regimen would be considered promising if the true median survival from registration was 13.5 months or longer and would be considered of no further interest if the true median survival was 9 months or shorter. With a planned 75 patients accrued over 18 months, an additional 1 year of follow-up and assuming exponential survival, the power of a one-sided 0.05 level test of 9- versus 13.5-month survival would be 0.80. Response rates (confirmed plus unconfirmed, complete, and partial) and rates of specific toxicities could be estimated to within at worst $\pm$11% (95% confidence interval

[CI]) with 75 patients. Any toxicity occurring with at least 5% probability was likely to be seen with 75 patients at least once (97.9% chance).

Overall survival and PFS were determined based on the method of Kaplan and Meier.[17] CIs for the median overall and PFS were calculated according to the method of Brookmeyer and Crowley.[18]

RESULTS

Patient Characteristics

Between July of 1998 and June of 1999, 88 patients were enrolled in the study. Seven patients were ineligible: two did not have extensive stage disease, one had a histology other than small cell, and four had inadequate documentation of eligibility requirements. Another patient refused to receive any protocol treatment and was not included in this analysis. The remaining 80 patients were eligible and assessable for survival, response, and toxicity. Their characteristics are displayed in Table 1. The median age was 61 (range, 38–78) and a slight majority of patients (52%) were male. Most patients had a performance status of 0-1, but 14 patients (17%) had a performance status of 2.

Response and Survival

Response to treatment is displayed in Table 2. Objective response was observed in 42 patients (53%; 95% CI: 41%–64%) with two patients (3%; 95% CI: 0%–8.7%) achieving a complete response. Progressive disease or early death occurred in 15 (19%) patients. Four (5%) patients had stable disease. Inadequate assessments precluded response determination in 19 patients. Median PFS was 5 months (95% CI: 4.2–5.9 months), and median overall survival was 8.8 months (95% CI: 7.8–9.5 months) (Figure 1). The 1- and 2-year survival rates were 27.5% (95% CI: 17.7%–37.3%) and 4% (95% CI: 0–8%), respectively.

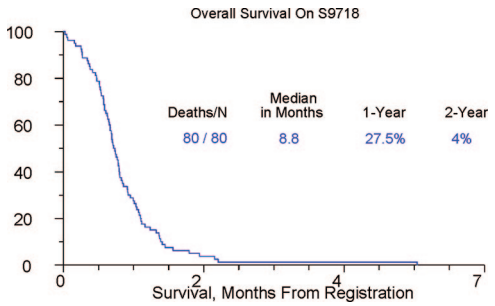

FIGURE 1. Overall survival from time of trial registration for the 80 eligible patients.

Toxicity

All 80 eligible patients are assessable for toxicity. The most frequent grade 3 and 4 toxicities are listed in Table 3. The most common toxicity was neutropenia. Grade 3 and 4 neutropenia was noted in 17 (21%) and 17 (21%) patients, respectively. Twenty-six percent (21 patients) developed grade 3 thrombocytopenia, but grade 4 thrombocytopenia was seen in only one patient. Three (4%) patients received platelet transfusions, and seven (9%) patients received packed red blood cell transfusions. Two patients developed febrile neutropenia with full recovery. The most significant nonhematologic toxicities included grade 3 nausea in 18 patients (23%), grades 3 and 4 vomiting in 12 patients (15%), fatigue in nine patients (11%), constipation/bowel obstruction

TABLE 1. Patient Characteristics (n = 80)

Variable	No. of Patients	%
Median age, yr (range)	61.0 (38–78)	
Male:female	42:38	52:48
Performance status, 0–1:2	66:14	83:17
Previous radiation therapy		
Yes	2	3
No	78	97
Previous surgery		
Yes	2	3
No	78	97

TABLE 2. Treatment Outcome (n = 80)

Response	No. of Patients	%
Overall	42	53 (41–64)[a]
Complete	2	3
Partial	40	50
Stable	4	5
Progressing disease	13	16
Early death	2	3
Assessment inadequate	19	24

[a] 95% confidence interval.

TABLE 3. Toxicity (Grade 3 or Higher) (n = 0)

Adverse Effect	Grade 3 No. (%) of Pts	Grade 4 No. (%) of Pts	Grade 5 No. (%) of Pts
Hematologic/infections			
Neutropenia	17 (21)	17 (21)	0 (0)
Leukopenia	13 (16)	5 (1)	0 (0)
Thrombocytopenia	21 (26)	1 (1)	0 (0)
Anemia	9 (11)	1 (1)	0 (0)
Respiratory infection	1 (1)	0 (0)	2 (3)
Gastrointestinal			
Nausea	18 (23)	0 (0)	0 (0)
Vomiting	11 (14)	1 (1)	0 (0)
Constipation/bowel obstruction	7 (9)	0 (0)	0 (0)
Constitutional			
Fatigue/malaise/lethargy	9 (11)	0 (0)	0 (0)
Metabolic			
Hyponatremia	3 (4)	3 (4)	0 (0)
Maximum grade any toxicity	37 (46)	23 (29)	2 (3)

pts, patients.

in seven patients (9%), and hyponatremia in six patients (8%). No patient developed grade 3 or higher renal insufficiency, ototoxicity, or peripheral neuropathy. Two patients (3%) died of treatment-related causes (respiratory infections).

Only 32 patients (40%) completed all six cycles of treatment. Twenty-patients (25%) discontinued treatment due to toxicity, and 19 patients (24%) discontinued chemotherapy due to disease progression. The remaining nine patients stopped therapy for the following reasons: no response (two patients), development of symptoms in previously detected brain metastases (one patient), death due to respiratory infection (one patient), refusal unrelated to adverse events (one patient), declining performance status (one patient), nontreatment-related severe syncopal episodes (one patient), incorrect assessment of disease progression (one patient), and detection of superior vena cava syndrome that required radiotherapy (one patient).

DISCUSSION

Since the establishment of PE as the standard of care for treatment of ES-SCLC in the early 1980s, many attempts have been made to further improve therapeutic outcome in this disease. These efforts have included substituting another agent for etoposide, replacing cisplatin with carboplatin, using nonplatinum doublets or platinum-based triplets, and using alternating or sequential regimens or high-dose chemotherapy with hematopoietic stem cell support.[19] To date, none of these approaches have been better than PE.

The current study was developed by the SWOG after the demonstration by the NCI-C in 1994 of the promising activity and favorable toxicity profile of single-agent gemcitabine in previously untreated patients with ES-SCLC.[11] Evaluating its use in combination with cisplatin appeared to be a logical next step given the nonoverlapping toxicities and different mechanisms of action of these two agents and the promising activity of this combination in a number of other solid tumors including NSCLC. S9718 represents the first and only study evaluating the combination of gemcitabine and cisplatin as initial systemic therapy in patients with ES-SCLC. We have demonstrated that this regimen is active and has a relatively favorable toxicity profile. The median survival of 8.8 months is comparable with the outcome with many previous phase II studies in ES-SCLC but does not suggest any substantial advantage for this regimen over the standard PE.

The activity of gemcitabine in ES-SCLC has been further validated in trials evaluating its use as second-line treatment and in combination with carboplatin. The Eastern Cooperative Oncology Group performed a phase II trial of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle in 46 patients with SCLC who had experienced treatment failure with one previous chemotherapy regimen.[20] An objective response was noted in 11.9% of patients with an overall median survival of 7.1 months. A subsequent phase II trial evaluated the combination of carboplatin (area under the curve of 5) on day 1 and gemcitabine 1100 mg/m^2 on days 1 and 8 of a 21-day cycle in 69 patients with ES-SCLC.[21] Overall response rate was 43%, and median survival was 9.2 months.

Efforts have been made to build on the single-agent activity of gemcitabine by incorporating it into triplet regimens. As has been the case with other such efforts with triplet regimens, no compelling evidence of improved antineoplastic efficacy was noted, although toxicity was increased with the three-drug combination.[22] In a randomized phase II study, the combination of cisplatin, etoposide, and gemcitabine was compared with cisplatin plus gemcitabine in 140 patients with ES-SCLC or poor-prognosis limited-stage SCLC.[23] Similar response rates (63% versus 57%), time to disease progression (6 months versus 7 months), and median survival (9.5 months versus 10 months) were noted in the cisplatin, etoposide, and gemcitabine and cisplatin plus gemcitabine arms, respectively. The PEG regimen was associated with more severe hematologic toxicity.

Recently, SWOG reported the preliminary results of a phase II trial evaluating the incorporation of gemcitabine into a nonplatinum doublet in ES-SCLC.[24] Eighty-four previously untreated patients received a combination of gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 on days 1 and 8 of a 21-day cycle. Response rate was a disappointing 32%, and median survival was 9 months.

In conclusion, this multicenter phase II trial has demonstrated that the combination of gemcitabine and cisplatin is an active and reasonably well tolerated regimen for the treatment of ES-SCLC. However, it clearly does not offer any compelling advantages compared with other commonly used two-drug regimens in this disease and will not be further pursued by SWOG. Ultimately, further progress may await better insights into the molecular biology of SCLC. Approaches using molecularly targeted agents have been associated with a modest degree of success in non-NSCLC. Incorporation of mechanism-based biologic agents into the treatment of SCLC is awaited with interest.

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