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Original Article

SINGLE AGENT GEMCITABINE IN REFRACTORY OR RELAPSED SMALL-CELL LUNG CANCER. PHASE II STUDY

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ABSTRACT

Purpose: Gemcitabine has shown a broad range of activity in solid tumors, including previously untreated small-cell lung cancer (SCLC). The objective of this phase II trial was to investigate the activity of gemcitabine in patients with relapsed SCLC.

Patients and Methods: SCLC patients with measurable disease who had experienced treatment failure with one prior chemotherapy regimen were considered eligible. Patients were required to have performance status of 0 to 2 and adequate organ function. Treatment consisted of gemcitabine 1,000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. Patients were stratified according to their previous response to first-line chemotherapy (primary refractory v primary sensitive disease).

Results: Twenty eight patients were enrolled onto this study (12 refractory and 16 sensitive patients). Twenty eight were assessable for response, survival and toxicity. Median patient age was 60 years, and median ECOG performance status was 1. Principal grade 3/4 hematologic toxicities included neutropenia (28.6%) and thrombocytopenia (25%). The main grade 3/4 non-hematologic toxicities were pulmonary (7.1%) and neurologic toxicity (14.3%). Objective responses occurred in 14.3% of patients overall, including one patient with refractory SCLC (8.3%) and three patients with sensitive SCLC (18.8%). Median survival for the overall group was 7.1 months. Survival was not significantly different for patients with refractory versus sensitive disease.

Conclusion: Gemcitabine has modest activity in previously treated SCLC patients. The favorable toxicity profile warrants further investigation, either in combination chemotherapy regimens or with targeted biologic compounds

Key Words: Lung cancer, small cell lung cancer, chemotherapy, gemcitabine

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INTRODUCTION

Small-cell Lung Cancer (SCLC) accounts for approximately 20% of the 170,000 new lung cancer cases diagnosed each year in the United States[1]. Despite high response rates to first-line chemotherapy, most patients will ultimately experience relapse and die from systemic metastasis. Median survival for patients with extensive-stage SCLC is generally less than 10 months.[2]

Standard options for first-line care have usually included cisplatin or carboplatin with etoposide or an anthracycline regimen such as cyclophosphamide, doxorubicin, and vincristine (CAV)[3]. Response rates to these regimens are greater than 50%, and some have reported rates as high as 80%, with no advantage for alternating regimens[4] or dose-intense therapy.[5]

No standard chemotherapy regimen has emerged for patients with SCLC who experience relapse after initial chemotherapy. Activity of chemotherapy drugs in this second-line setting has been inferior to treatment for primary disease. Standard options for relapsed SCLC include the CAV regimen after failure of a first-line platinum regimen or, more recently, single-agent topotecan[6]. Topotecan showed an objective response rate of 39% in 48 previously untreated SCLC patients in an Eastern Cooperative Oncology Group (ECOG) phase II trial[7]. Overall median survival was 10 months in this trial, with a 39% 1-year survival rate. Neutropenia was the most frequent toxicity observed. A subsequent trial treated SCLC patients with topotecan after an initial cisplatin-etoposide regimen failed[8]. Eleven percent of patients achieved a partial response. Median survival in this pretreated population was 4.6 months. Another phase II trial of topotecan in 101 previously treated SCLC patients exhibited an overall response rate of 38% (including six complete responses), with a median survival time of 5.4 months.[6]

A randomized study of CAV versus topotecan in patients with sensitive but relapsed SCLC showed equivalent response rate and survival for the single-agent topotecan, with superior quality-of-life scores and symptom control for patients treated with topotecan.[9] Nonetheless, response rates were modest for both arms at 24% and 18% for topotecan and CAV, respectively. Median survival was less than 6 months in each arm of

this trial. New options are clearly required for patients with relapsed SCLC.

Primary refractory patients, whose tumors progress through initial chemotherapy or who experience relapse less than 90 days from the end of chemotherapy, have an especially poor prognosis[10]. A phase II trial of oral etoposide included patients with sensitive and primary refractory disease[11]. The response rate was 13% (one of eight patients) in patients with primary refractory disease compared with 64% (nine of 14 patients) for patients with primary sensitive disease. Other trials have supported this major difference in response rate to subsequent chemotherapy on the basis of sensitivity to first-line treatment.[12]

Other new chemotherapy agents have shown activity in previously untreated SCLC, including paclitaxel, docetaxel, irinotecan, vinorelbine, and gemcitabine, and therefore are worthy of further investigation in the relapsed SCLC setting[13]. Gemcitabine has shown a broad spectrum of antitumor activity in a variety of solid tumors[14]. Gemcitabine is metabolized intracellularly to its active metabolite gemcitabine diphosphate, which inhibits DNA polymerization. This antimetabolite has been approved for treatment of non–small-cell lung cancer in combination with cisplatin on the basis of a randomized trial demonstrating improved response rate and survival compared with single-agent cisplatin alone[15]. SCLC cell lines were shown to be sensitive to gemcitabine in in vitro studies[16]. In previously untreated SCLC patients, gemcitabine showed a response rate of 27% in 26 assessable patients[17]. Toxicity in this trial was moderate, with neutropenia seen in 18% of cycles and thrombocytopenia seen in less than 2% of cycles. Another trial from the Southwest Oncology Group showed that the combination of gemcitabine and cisplatin produced an overall response rate of 56% in patients with extensive SCLC[18]. Gemcitabine in combination with carboplatin has also been shown to provide equivalent activity to a standard combination of cisplatin and etoposide. A randomized trial found a response rate of 61% and 62%, respectively, for the two regimens, with no significant difference in median survival at 9.0 and 8.5 months.[19]

On the basis of the activity of gemcitabine as a single agent in untreated SCLC and the need for new and better-tolerated therapies for relapsed SCLC in patients who experience treatment failure with first-line regimens, the primary objective of this study was to evaluate the objective response rate of gemcitabine in SCLC patients for whom one prior chemotherapy regimen had failed. Secondary objectives were to evaluate the duration of remission and survival in patients with previously treated SCLC who received gemcitabine as second-line therapy; to evaluate the toxicities of gemcitabine as second-line therapy; and to determine whether response, remission duration, or survival differences exist between patients with primary refractory SCLC and those with primary sensitive but relapsed SCLC treated with gemcitabine.

PATIENTS AND METHODS

Primary refractory disease was defined as relapse during first-line chemotherapy or less than 90 days after completing initial chemotherapy, and sensitive disease was defined as relapse 90 days after completion of first-line chemotherapy. The study was done at El Salam Oncology Centre Ministry of Health

Eligible patients had:

- Pathologically proven SCLC.
- Patients with either limited- or extensive-stage disease were allowed.
- Disease progression after initial chemotherapy was required. This was defined as either a lack of response to first-line chemotherapy, progression after partial response, or relapse after an initial complete response to first-line chemotherapy. Initial chemotherapy could include a single agent, combination regimen, or an alternating drug regimen (eg, CAV alternating with platinum and etoposide).
- Patients were required to have at least one site of bidimensionally measurable disease.
- Patients were required to have recovered completely from prior therapy, with no ongoing toxicity greater than grade 1.
- No prior gemcitabine chemotherapy was allowed.
- Prior radiotherapy was permitted, but measurable disease outside the radiation field or clearly progressive disease within the radiation port was required.
- Patients were required to have an ECOG performance status of 0 to 2.
- Adequate laboratory values including renal function, hepatic function, and bone marrow reserve were required.

Protocol design:

The administration schedule of chemotherapy included gemcitabine given at an initial dose of 1,000 mg/m² intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Cycles were repeated in patients with acceptable toxicity and no evidence of disease progression. Patients who had less than grade 2 toxicity on the first cycle of therapy received an escalated dose of gemcitabine at 1,250 mg/m² on subsequent cycles.

Response Evaluation:

All patients had their disease re-evaluated after the first two cycles of chemotherapy and every two subsequent cycles. Standard response criteria were required, and a 4-week re-evaluation was required to confirm all patients with a partial or complete response, during which time no evidence of progression could have occurred, to qualify patients as having a true response.

A two-stage statistical design was used to permit early termination if preliminary results indicated minimal efficacy. A target response rate of 20% was deemed sufficient to warrant further study, whereas a response rate 5% was insufficient for further investigation. This trial design therefore called for 10 assessable patients to be entered onto the first stage of the trial. If one or more responses were observed among these initial patients, an additional[20] assessable patients would be entered. If five or more responses were observed among 35 assessable patients, the treatment would be considered worthy of further consideration. If fewer than four responses were observed, gemcitabine would not be considered for further testing. Therefore, with 18 assessable patients, this trial design allowed a 46% probability of stopping early with a true objective response rate of 5%, and an 84% probability of declaring the drug promising with a true objective response rate of 20%. The accuracy of estimating objective response rate provided a maximum 95% confidence interval (CI) width of 34.6%. Survival curves were estimated by the method of Kaplan and Meier.[20]

RESULTS

This study included a total of 28 patients from December 5, 2003, through April 8, 2005 (Stage 1), and from June 1, 2004, through September 4, 2006 (Stage 2). They were assessable for response and survival. In this cohort, there were 17 male and 11 female patients (Table 1). The majority of patients had received no prior surgical treatment, and 57% of patients were treated with prior radiation. All 28 patients had received one prior chemotherapy regimen, including a single agent (7%), one combination regimen (86%), or an alternating regimen (7%) of single agents or combination drugs. Seventy-one percent of patients in this study were reported to have achieved either a partial response (39.3%) or a complete response (32.1%) to first-line chemotherapy. Patients had a good performance status, with 79% of patients having performance status of 0 or 1, and 78.6% of patients had less than 5% weight loss in the previous 6 months. The median age was 60 years (range, 41 to 83 years).

Table 1: Characteristics of refractory and relapsed patients.

	Refractory		Relapsed		Total	
Characteristic	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**
Sex						
Male	8	66.7	9	56.3	17	60.7
Female	4	33.3	7	43.7	11	39.3
Race						
White	11		15	93.8	26	92.9
Black	1		1	6.2	2	7.1
Previous surgery for lung cancer						
None	20	83.3	13	81.3	23	82.1
Diagnostic only	2	16.7	2	12.5	4	14.3
Both diagnostic and therapeutic	0	0.0	1	6.2	1	3.6
Previous radiotherapy for lung cancer						
No	5	41.7	7	43.7	12	42.9
Yes	7	58.3	6	56.3	16	57.1
Previous chemotherapy						
Yes, single	1	8.3	1	6.2	2	7.1
Yes, combinations	10	83.3	14	87.6	24	85.7
Yes, both single and combination	1	8.3	1	6.2	2	7.1
Best response to most recent regimen of chemotherapy						
Complete response	2	16.7	7	43.8	9	32.1
Partial response	3	25	8	66.7	11	39.3
No change	3	25	1	6.2	4	14.3
Progression	4	33.3	0	0.0	4	14.3
Performance status at start of treatment						
0	3	25	3	18.7	6	21.4
1	8	66.7	8	50	16	57.1
2	1	3.8	6	37.5	7	25
Weight loss in previous 6 months						
None	8	66.7	9	56.2	17	60.7
< 5% of body weight	2	16.7	3	18.8	5	17.9
5% to 10% of body weight	1	8.3	2	12.5	3	10.7
> 10% of body weight	1	8.3	2	12.5	3	10.7
Age at registration (years)						
< 50	1	8.3	1	6.2	2	7.1
50 and < 60	5	41.7	7	43.8	12	42.9
60 and < 70	3	25	5	31.2	8	28.6
70	3	25	3	18.8	6	21.4
Median		59.6		60.1		60.1
Mean		60.0		61.0		60.6
Range	45.6 to 76.0		41.3 to 83.0		41.3 to 83.0	

Response to therapy is shown in table (2) according to whether the patient had primary refractory disease or primary sensitive cancer that subsequently relapsed. No patient achieved a complete response. The partial response rate among refractory patients was 8.3%. Among patients with relapsed sensitive disease, the partial response rate was 18.8%, leading to an overall response rate of 14.3% (two-stage 90% CI, 4.9% to 23.7%). Among those patients responding to therapy, there were two male and two female patients. Two of the four patients had achieved a complete response to first-line chemotherapy, one patient had stable disease after first-line chemotherapy, and one patient had primary refractory disease, progressing through initial chemotherapy. Duration of remissions to gemcitabine (defined as time from onset of response until the patient was last known to be in remission) lasted 1.8 to 4.1 months.

Table 2: Response data.

	Refractory		Relapsed		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Complete response	1	0.0	0	0.0	0	0.0
Partial response	1	8.3	3	18.8	4	14.3
Stable disease	1	8.3	0	0.0	1	3.6
Progressive disease	10	83.4	12	75.0	22	78.6
Not assessable	0	0.0	1	6.2	1	3.6

Not assessable: Withdrew after one cycle and died without follow-up measurements; withdrew during cycle 1 and did not have follow-up measurements.

Toxicity:

Toxicities are listed in table (3). The primary toxicities were hematologic among the 28 patients assessed for toxicity. Grade 3/4 leucopenia occurred in five patients (17.9%), grade 3/4 neutropenia occurred in 8 patients (28.6%), and grade 3/4 thrombocytopenia occurred in 7 patients (25%). Other grade 3 and 4 toxicities included anemia, pulmonary toxicity, neuromotor toxicity, bleeding, nausea, vomiting, liver function abnormality, anorexia, cardiac, skin, edema, fatigue, dehydration, dysuria, and metabolic abnormalities. There were no toxic deaths reported in this trial. Sixteen (57%) of 28 patients had at least one gemcitabine dose held, and 8 (28.6%) had at least one dose reduced; nearly all of these were for neutropenia or thrombocytopenia and occurred on day 15 of the cycle.

Analysis of toxicity data showed that in 46.4% of patients, the worst toxicity experienced was grade 3, and in 21.4% of patients, the worst toxicity was grade 4. Therefore, the overall rate of grade 3 or greater worst degree of toxicity was 64.3% (90% CI, 52.5% to 77.7%). The only grade 4 toxicities were leucopenia (3.6%), neutropenia (7.1%), thrombocytopenia (7%), anemia (3.6%), and liver toxicity (2.3%).

Table 3: Toxicity Data

	Grade* (N = 28)		
	1,2	3	4
Leukopenia	12	4	1
Granulocytopenia	10	6	2
Thrombocytopenia	14	5	2
Anemia	18	1	1
Hemorrhage	4	2	—
Fever (no infection)	11	—	—
Nausea	8	1	—
Vomiting	6	—	—
Pulmonary	6	2	—
Cardiac	1	—	—
Hypertension	1	—	—
Hypotension	1	—	—
Skin	2	1	—
Alopecia	4	—	—
Neurosensory	2	—	—
Neuromotor	5	4	—
Metabolic	3	1	—
Anorexia	8	1	—
Edema	3	1	—
Myalgia	2	—	—
Fatigue	8	—	—
Hyponatremia	1	—	—
Dehydration	1	—	—
Dysuria	—	1	—
Worst degree	10	13	5

*1, mild; 2, moderate; 3, severe; 4, life threatening.

Although four patients were reported to have grade 3 neuromotor toxicity, three of the four patients actually experienced lethargy and fatigue with diffuse weakness rather than a true neurologic event. One patient did develop grade 3 weakness associated with numbness in the feet, which was not further evaluated. A drug-related toxicity cannot be excluded in this patient.

Grade 3 pulmonary toxicity was reported in two patients characterized by a worsening cough in one patient and shortness of breath in another patient. One patient had a history of congestive heart failure and developed cough and edema on day 15 of chemotherapy. A chest x-ray indicated heart failure, but medication toxicity could not be excluded. Another patient developed shortness of breath 1 to 2 hours after the first gemcitabine dose. This patient continued to receive therapy and experienced gradual improvement while receiving corticosteroid therapy.

Survival:

Overall survival of patients treated in this study is shown in figure (1). The median overall survival time

was 7.1 months for the 28 assessable patients. Figure (2) shows overall survival plotted according to the Kaplan-Meier curve for the 12 patients with refractory disease and 16 patients who had experienced relapse. Median survival time for the patients with refractory disease was 6.9 months, compared with 7.3 months for patients who had experienced relapse and had primary sensitive disease. These survival times were not statistically different (P >0.05).

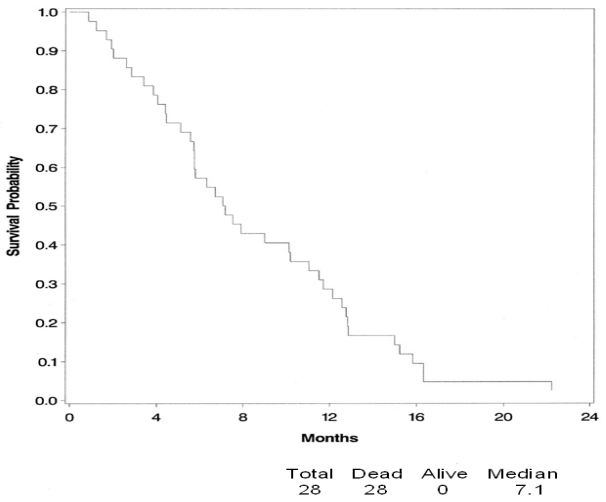

Fig. 1: Overall survival.

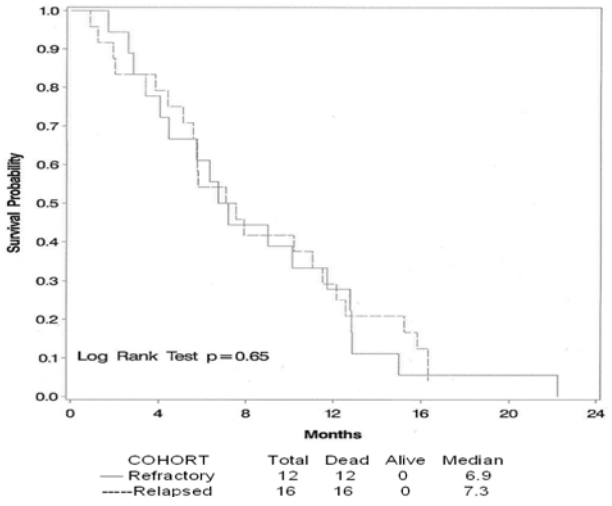

Fig. 2: Overall survival for patients with refractory disease and those who experienced relapse separately.

DISCUSSION

The current study demonstrated that gemcitabine is a well-tolerated treatment regimen causing few grade 4 toxicities in SCLC patients who have received prior first-line therapy. This study shows an overall response rate of 14.3% (two-stage 90% CI, 4.9% to 23.7%), and an overall median survival time of 7.1 months.

The response rate and survival observed in this study was in keeping with prior studies in which second-line chemotherapy was used for SCLC[10]. Among the available options for relapsed SCLC, single-agent topotecan and the three-drug combination of CAV have become the most commonly used therapies[21]. Other single agents have shown activity; however, it remains to be determined which of the current options provides the optimal outcome for these patients. Another study of gemcitabine in patients with refractory SCLC found a similar response rate of 13%, with a 17-week median survival time[22] although 76% of patients had received more than two prior chemotherapy regimens. Future studies will also need to focus on quality-of-life end points in this poor-prognosis group. Investigation of new agents for this difficult disease, including new biologically targeted therapies, may provide more effective control of the tumor with diminished toxicity.

The response rate observed was numerically superior in the patients with relapsed sensitive disease compared with patients with primary refractory disease at 18.8% versus 8.3%, respectively. These differences were not significantly different on the basis of Fisher's exact test (P = .37). Perhaps a larger population would have shown that response rate is significantly inferior in patients with refractory disease. Survival was not significantly different in patients with primary refractory versus sensitive but relapsed SCLC. It is likely that the failure to detect survival differences between patients with primary refractory and sensitive but relapsed SCLC was due to the small sample size in this particular trial.

Given the good toxicity profile of this agent in this study, it is reasonable to conclude that this agent may now be considered to be one option for second-line chemotherapy in extensive SCLC patients.

CONCLUSION

Gemcitabine is a modestly active agent in patients who have received prior chemotherapy for SCLC. Given the statistical design of this study, the four observed partial responses provide an argument that gemcitabine is worthy of further consideration in this patient population. Additional investigation will clarify the role for this agent, either alone or in combination or in conjunction with new targeted therapies. A continued focus on early detection through better screening methods, chemoprevention of lung cancer, and primary prevention through smoking cessation programs remain paramount in the reduction of mortality from SCLC and other tobacco-related malignancies. It is through the cooperative group mechanism that many of these interventions will be best evaluated.

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