

Pemetrexed in Second Line and beyond Small Cell Lung Cancer

A Hoosier Oncology Group Phase II Study

Shadia Jalal, MD,* Rafat Ansari, MD,† Ramaswamy Govindan, MD,‡ Sumeet Bhatia, MD,§ Daniel Bruetman, MD,|| William Fisher, MD,¶ Gregory Masters, MD,# Angela White, MBA,** Daniel Stover, MT (ASCP),** Menggang Yu, PhD,†† and Nasser Hanna, MD*

Introduction: Small cell lung cancer (SCLC) is initially a chemotherapy-sensitive disease. Nevertheless, drug-resistance results in disease recurrence in most patients. Many drugs, including antime-tabolites, are active, but only minimal progress has been made in improving survival times for those with advanced disease. Based on the need to discover better systemic therapies, we conducted a phase II study of pemetrexed in patients with relapsed SCLC.

Patients and Methods: Eligible patients had SCLC or poorly differentiated neuroendocrine cancers of the lung, Eastern Cooperative Oncology Group performance status of 0 to 2, and had received less than or equal to two prior chemotherapy regimens (additional targeted agents were allowed). Both chemotherapy-sensitive (relapse ≥ 90 days from completion of first line therapy) and chemotherapy-resistant (progressive disease during or within 90 days from completion of first line treatment) patients were eligible and analyzed separately. Pemetrexed was administered at 500 mg/m² intravenously every 21 days for up to six cycles. All patients received folic acid, vitamin B12, and steroid prophylaxis. The primary objective of the trial was to estimate the clinical benefit rate (complete plus partial response plus stable disease) in each group.

Results: From January 2005 to September 2005, 20 patients were enrolled in the chemotherapy-sensitive arm and 23 patients in the chemotherapy-resistant arm. The majority of patients were men, the median age of the two groups were 62.5 and 65, respectively; 75%

had a performance status of 0 or 1, and more than 50% had received more than one prior regimen. Grade 3/4 toxicities were as expected for pemetrexed. Progressive disease was the best response in 16 patients (80%) in the chemo-sensitive group and 19 patients (83%) in the chemo-refractory group. One patient had a partial response and three had stable disease in each group.

Conclusion: Pemetrexed has minimal single agent activity in re-lapsed SCLC.

Key Words: Small cell lung cancer, Pemetrexed.

(*J Thorac Oncol.* 2009;4: 93–96)

Small cell lung cancer (SCLC) accounts for approximately 13 to 15% of lung cancers.¹ The majority of patients present with extensive stage (ES) with evidence of wide spread metastases. Despite an initial response to chemotherapy, patients with SCLC inevitably relapse and progress resulting in death in nearly all patients. Over the past decade, only minimal improvements have been made in the treatment of ES SCLC.² Many agents tested over the last three decades have demonstrated some activity, but only topotecan is approved by the U.S. Food and Drug Administration to treat SCLC in the second-line setting. Unfortunately, therapy with topotecan results in a median survival time of only 6 months, and most patients do not respond even for short periods of time.³ More effective therapies are desperately needed.

Some antifolates have demonstrated activity against SCLC. For example, treatment with methotrexate resulted in responses in 25 to 30% of patients in one study and was frequently integrated into multidrug regimens against SCLC.⁴ In contrast, 5-fluorouracil had no activity against SCLC in two studies.^{5,6}

Pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN) is a multitargeted antifolate agent, the primary mechanism of which is inhibition of thymidylate synthase.⁷ Pemetrexed also inhibits other folate-dependent enzymes involved in purine synthesis, including dihydrofolate reductase and glycinamide ribonucleotide formyl transferase and is U.S. Food and Drug Administration approved to treat patients with advanced non-SCLC and mesothelioma. An in vitro growth inhibition study by Chan et al.⁸ showed pemetrexed

*Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, Indianapolis; †Northern Indiana Cancer Research Consortium, South Bend, Indianapolis; ‡Washington University Medical Center, Siteman Cancer Center, St. Louis, Missouri; §Community Regional Cancer Center, Indianapolis, Indianapolis; ||Center for Cancer Care at Goshen Health System, Goshen, Indianapolis; ¶Medical Consultants, P.C. c/o Ball Memorial Hospital Cancer Center, Muncie, Indianapolis; #Christiana Care Health Services, Inc., Newark, Delaware; **Hoosier Oncology Group, Indianapolis, Indianapolis; and ††Division of Biostatistics, Indiana University School of Medicine, Indianapolis, Indianapolis.

Disclosure: Ramaswamy Govindan has received honoraria from Eli Lilly, Genentech, Astra Zeneca and research funding from Eli Lilly, Genentech, Merck. Nasser Hanna is a consultant in Eli Lilly and has received honoraria and research support from Eli Lilly.

Address for correspondence: Shadia Jalal, MD, 535 Barnhill Drive, Indianapolis, IN 46202. E-mail: sjalal@iupui.edu

Copyright © 2008 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/09/0401-0093

delayed growth of SCLC cell lines. A randomized phase II trial by Socinski et al.⁹ evaluating cisplatin/pemetrexed or carboplatin/pemetrexed combinations in patients with ES SCLC suggested these were active combinations; however, the single agent activity of pemetrexed had not been defined. We, therefore, conducted a study of single agent pemetrexed in patients with relapsed SCLC to characterize its activity.

PATIENTS AND METHODS

Patient Selection/Eligibility

Eligible patients had histologic or cytologic proof of small cell cancers of any site or poorly differentiated neuroendocrine cancers of the lung. All patients had measurable disease per the Response Evaluation Criteria in Solid Tumors criteria and had adequate bone marrow function as defined by absolute neutrophil count more than or equal to $1500/\text{mm}^3$, platelet count more than or equal to $100,000/\text{mm}^3$ and hemoglobin more than or equal to 8 g/dL, renal function (creatinine clearance ≥ 45 mL/min), and liver function (bilirubin $\leq 1.0 \times$ upper limit of normal and aspartate aminotransferase $\leq 2.5 \times$ upper limit of normal). Patients had an Eastern Cooperative Oncology Group performance status of 0 to 2 and must have received treatment with at least one but not more than two prior chemotherapy regimens (including one regimen containing a platinum agent). Patients who received radiation must have completed their radiation at least 14 days before being registered for the protocol.

Exclusion criteria included symptomatic central nervous system metastasis, uncontrolled pleural effusions, pregnancy or lactation, inability or unwillingness to interrupt aspirin or other nonsteroidal anti-inflammatory agents, unwillingness to take folic acid or vitamin B12 supplementation, or medical problems of significant severity (e.g., unstable respiratory or cardiac disease). Patients previously treated with pemetrexed were not eligible. The study was conducted by the Hoosier Oncology Group, a community-based cooperative group. The protocol was approved through institutional ethics review boards, and all patients provided written informed consent before treatment.

Pretreatment studies included history and physical examination, complete blood count with differential, blood chemistries, and a computed tomography scan of chest or chest radiograph. On study evaluations (every 21 days) included a limited history and physical examination, complete blood count and blood chemistries, performance status evaluation, and toxicity rating. Disease assessment by chest radiograph or computed tomography scan was performed before each cycle of therapy to ensure patients with other treatment options were not rapidly progressing.

Treatment Schedule

All patients received pemetrexed $500 \text{ mg}/\text{m}^2$ intravenously over approximately 10 minutes. Pemetrexed was repeated every 3 weeks for up to six cycles or until patients had either progressive disease or intolerable side effects. Patients received folic acid (350–1000 μg oral daily) approximately 1 week before the first dose of pemetrexed and continued that daily during treatment. Vitamin B₁₂ was also given (1000 μg

intramuscular injection) beginning 1 week before the first dose of pemetrexed and was repeated every 9 weeks during treatment. Dexamethasone (4 mg oral twice daily) was given for 3 days every cycle beginning the day before pemetrexed.

Dose Modifications

Dose adjustments at the beginning of a subsequent cycle were based on neutrophil and platelet nadir values from the preceding cycle of therapy. An absolute neutrophil count more than or equal to $1.5 \times 10^9/\text{L}$ and platelet count more than or equal to $100 \times 10^9/\text{L}$ were required before the start of a new cycle. If a patient developed neutropenic fever, or thrombocytopenia with platelet count less than $50,000/\text{m}^3$ with any bleeding, treatment was resumed at 75% of previous dose of pemetrexed. A 50% dose reduction was advised for grade 3–4 mucositis. Treatment was resumed at 75% of the previous dose for other grade 3–4 nonhematologic toxicities (with the exception of alopecia, nausea, vomiting, or grade 3 transaminase elevations).

Statistical Considerations

The trial used a two-stage design and evaluated chemotherapy-sensitive and chemotherapy-resistant patients separately. For chemotherapy-sensitive patients (those who relapsed ≥ 90 days from completion of first line therapy), a total of 18 patients were to be accrued to the first stage. If more than or equal to eight patients exhibit disease control (complete response (CR), partial response (PR), stable disease (SD)), the study was to be continued to the second stage and an additional 28 patients were enrolled. If more than or equal to 23 patients of the 46 total patients on this arm have nonprogressive disease, the regimen was to be considered worthy of further study in this population. For chemotherapy-resistant patients (those who relapsed within 90 days from completion of first line therapy), a total of 21 patients were to be accrued to the first stage. Further recruitment was to continue to the second stage if more than or equal to three patients had a response, whereby 29 additional patients were then to be enrolled. If more than or equal to eight patients of 50 had disease control, the regimen was to be considered worthy of further study. The sample size was calculated using a one-sided alpha of 10% and a power of 90%. All toxicities were graded according to the Common Terminology Criteria for Adverse Events Version 3.0.

Study Endpoints

All endpoints were collected and analyzed for the two patient populations (chemo-sensitive and chemo-resistant) separately. The primary objective of the study was to estimate the clinical benefit rate (CR, PR, SD) of pemetrexed in the two patient populations. The secondary objectives were to determine the toxicity, time to disease progression, and to estimate overall survival.

Response was assessed using the Response Evaluation Criteria in Solid Tumors criteria. Time to disease progression was defined as time from start of treatment until the criteria for disease progression was met. Overall survival was defined as the number of days from the day of first treatment to death or the last date of patient contact (whichever is earlier).

RESULTS

Patient Characteristics

From January 2005 to September 2005, 20 chemo-sensitive patients and 23 chemo-resistant patients were accrued to the study from 14 sites within the Hoosier Oncology Group. Two patients had extrapulmonary small cell carcinoma, with the remaining 41 patients having SCLC. Patient characteristics are displayed in Table 1. Criteria to proceed to stage II was not met for either arm. The median number of cycles of pemetrexed was 2 (range, 1–6). No dose delays or modifications were required.

Toxicity

Grade 3/4 toxicities are summarized in Table 2. Grade 3/4 hematologic toxicities were minimal, and grade 3/4 non-hematologic toxicities were consistent with previous data for single agent pemetrexed.

Response and Survival

Progressive disease as the best response was noted in 16 patients in the chemo-sensitive group (80%) and 19 patients (83%) in the chemo-refractory group. In the chemo-sensitive group, one patient (5%) achieved a partial response and three patients (15%) achieved stable disease. In the chemo-resistant group, one patient (4%) had a partial response and three patients (13%) had stable disease. At the time of final analysis (March, 2008), 17% of patients on the trial were alive (two in each group). Median time to disease progression in the chemo-sensitive and chemo-resistant arms

TABLE 2. Key Grade 3/4 Toxicities

Toxicity	Chemo-sensitive		Chemo-resistant	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Neutropenia	1 (5%)	1 (5%)	1 (4.3%)	2 (8.7%)
Thrombocytopenia	0	1 (5%)	2 (8.7%)	2 (8.7%)
Anemia	2 (10%)	0	2 (8.7%)	0
Febrile neutropenia	2 (10%)	0	0	0
Fatigue	4 (20%)	0	5 (21.7%)	0
Hyperbilirubinemia	0	1 (5%)	2 (8.7%)	0
AST elevation	2 (10%)	0	0	0
Nausea	0	0	1 (4.3%)	0
Constipation	0	0	0	1 (4.3%)
Diarrhea	1 (5%)	0	0	1 (4.3%)
Mucositis	0	0	1 (4.3%)	0
Rash	1 (5%)	0	0	0
Infection	1 (5%)	0	1 (4.3%)	0

AST, aspartate aminotransferase.

was 1.28 months (95% confidence interval [CI]: 0.69–1.54) and 1.22 months (95% CI: 1.12–1.31), respectively, and median survival time was 4.4 months (95% CI: 2.7–10.3) and 2.7 months (95% CI: 1.8–7.7), respectively.

DISCUSSION

Our study evaluated single agent pemetrexed in relapsed SCLC and did not meet the predetermined criteria for increasing the sample size to 96 patients. Response rates were disappointing and the majority of patients had early progressive disease. Single agent pemetrexed has minimal activity in patients with previously treated SCLC, including those with previously chemotherapy-sensitive disease.

Other investigators have reported their experience with pemetrexed in patients with previously treated SCLC. Gronberg et al.¹⁰ treated patients with pemetrexed at 900 mg/m² and also reported minimal activity in both chemotherapy-sensitive and chemotherapy-resistant patients (12% stable disease and 84% progressive disease in sensitive arm, 11% partial response and 89% progressive disease in resistant arm). Raju et al.¹¹ enrolled 121 patients (56 chemotherapy-sensitive and 65 chemotherapy-resistant) with relapsed SCLC who had received only one prior chemotherapy regimen. Patients were treated with pemetrexed at doses ranging from 500 to 900 mg/m². Preliminary results indicated a disappointing clinical benefit rate (CR, PR, SD) of 20% in the chemotherapy-sensitive arm and 21.7% in the chemo-refractory arm. There were no responses with 500 mg/m² and only one partial response was seen with 900 mg/m².

In addition, a phase III trial comparing platinum with etoposide versus pemetrexed was closed early when an initial analysis reported that the pemetrexed arm was unable to meet the predefined end point of noninferiority. Interim results of this study (known as GALES) were presented at the 2008 meeting of the American Society of Clinical Oncology. In this study, chemo-naïve patients with ED SCLC were randomized to either the combination of pemetrexed (500 mg/m²

TABLE 1. Baseline Characteristics

Characteristics	No. of Patients (%)	
	Chemo-sensitive (n = 20)	Chemo-resistant (n = 23)
Age (yrs)		
Median	62.5	65
Range	44–78	41–78
Sex		
Male	12 (60%)	17 (74%)
Female	8 (40%)	6 (26%)
ECOG PS		
0	7 (35%)	7 (30%)
1	8 (40%)	10 (44%)
2	5 (25%)	6 (26%)
Prior treatments		
One chemotherapy	6 (30%)	9 (39%)
Two chemotherapy	10 (50%)	3 (13%)
>2 (3rd line targeted therapy)	4 (20%)	11 (48%)
Smoking history		
Current	7 (35%)	11 (48%)
Former	12 (60%)	12 (52%)
Never	1 (5%)	0
Median time since prior regimen (range)	149 d (28–515)	59 d (21–405)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

intravenously day 1) and carboplatin (area under the curve 5 intravenously day 1) or etoposide (100 mg/m² days 1, 2, 3) and carboplatin (area under the curve 5 intravenously day 1). The interim analysis included 364 patients on the pemetrexed arm and 369 on the etoposide arm. Progression free survival was noted to be inferior for patients on the pemetrexed arm compared with those on standard therapy (3.68 versus 5.32 months with hazard ratio = 1.79). Overall response rates were also inferior for the pemetrexed arm (24.9% versus 40.5% with *p* value <0.001).¹²

Nearly all chemotherapy agents active against non-SCLC are also active in SCLC. Pemetrexed seems to be an exception to this observation. Recent evidence suggests that tumors associated with a high expression of thymidylate synthase may be resistant to the effects of pemetrexed.¹³ It seems that squamous cell lung cancers (with high levels of thymidylate synthase activity), for example, are resistant to pemetrexed, whereas nonsquamous lung cancers are more sensitive.^{14,15} Ceppi et al. have recently reported that thymidylate synthase expression in SCLC is high.¹⁶ This may explain why pemetrexed has minimal activity against SCLC.

There have been few advances in the systemic treatment of SCLC over the last 25 years. This is due, in part, to the lack of a comprehensive understanding of key signaling pathways in SCLC. There is clearly a chemotherapy-sensitive population of cells, which can be effectively treated with many chemotherapeutics; however, there is a chemotherapy-resistant clone, which resists most treatment and ultimately results in the patient's death. This level of complexity of SCLC is underscored by data published by Davies et al.,¹⁷ who evaluated somatic mutations of the protein kinase gene family in 26 primary lung neoplasms (seven adenocarcinomas, seven squamous cell carcinomas, six large cell carcinomas and six carcinoids) and seven lung cancer cell lines (which included one neuroendocrine cancer). They reported 148 somatic mutations in 141 genes (higher incidence than observed in other cancers). Most of the mutations were thought to be passenger ones that are not believed to play a significant role in the cancer phenotype. Nevertheless, more than 40 nonsynonymous substitutions were detected, which might possibly be implicated in oncogenesis (driver mutations). Some heterogeneity was noted in the mutational spectrum among the different lung cancer cells screened in that study as well. For example, the largest number of somatic mutations was noted in NCI-H1770 cell line, which was derived from a lung neuroendocrine tumor.

As illustrated by our study and those involving many other therapies (chemotherapy and targeted agents), the continued exploration of empiric therapies is unlikely to result in major advances for patients suffering from SCLC, and a better understanding of the biology of the disease is greatly needed.

ACKNOWLEDGMENTS

Eli Lilly funded the study.

REFERENCES

- Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small cell lung cancer in the United States over the past three decades: analysis of surveillance, epidemiologic and end results database. *J Clin Oncol* 2006;24:4539–4544.
- Chute J, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999;17:1794–1801.
- O'Brien M, Ciuleanu T, Tsekov H, et al. Survival benefit of oral topotecan plus supportive care versus supportive care alone in relapsed, resistant SCLC. *Lung Cancer* 2005;49(suppl 2):S54.
- Morrison VA, Luikart SD. Chemotherapy of lung cancer. In MC Perry, ed. *The Chemotherapy Source Book*. Baltimore, MD: Williams and Wilkins, 1992. Pp. 932–947.
- Stewart DJ, Dahrouge S, Soltys KM, Evans WK. A phase II study of 5-fluorouracil plus high-dose folinic acid in the treatment of recurrent small cell lung cancer. *Am J Clin Oncol* 1995;18:130–132.
- Havsteen H, Sörensen S, Rorth M, Dombernowsky P, Hansen HH. 5-Fluorouracil in the treatment of small cell anaplastic carcinoma of the lung: a phase II trial. *Cancer Treat Rep* 1981;65:123–125.
- Adjei AA. Pemetrexed (Alimta): a novel multitargeted antifolate agent. *Exp Rev Anticancer Ther* 2003;3:145–156.
- Chan DC, Chen VJ, Zhang Z, et al. Studies of pemetrexed and gemcitabine, alone and in combinations, in human lung cancer models. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings; Vol 24, No. 18S (June 20 suppl), 2006:17114.
- Socinski MA, Weissman W, Hart LL, et al. Randomized phase II trial of pemetrexed combined with either cisplatin or carboplatin in untreated extensive-stage small-cell lung cancer. *J Clin Oncol* 2006;24:4840–4847.
- Grønberg BH, Bremnes RM, Aasebø U, et al. A prospective phase II study: high-dose pemetrexed as second-line chemotherapy in small-cell lung cancer. *Lung Cancer*. 2008; doi:10.1016/j.lungcan.2008.04.003.
- Raju RN, Neubauer MA, Smith DA, et al. Pemetrexed (P) in relapsed small cell lung cancer (SCLC): preliminary results of a phase II trial. *J Clin Oncol*, 2007 ASCO Annual Meeting Proceedings; Vol 25, No. 18S (June 20 suppl), 2007:7716.
- Socinski MA, Smit EF, Lorigan P, et al. Phase III study of pemetrexed plus carboplatin (PC) versus etoposide plus carboplatin (EC) in chemonaïve patients (pts) with extensive-stage disease small cell lung cancer (ED-SCLC): interim results. 2008 ASCO Meeting.
- Eismann U, Oberschmidt O, Ehnert M, et al. Thymidylate synthase gene expression in solid tumors predicts for response to pemetrexed in vitro. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings; Vol 24, No. 18S (June 20 suppl), 2006:13058.
- Scagliotti G, Park K, Patil S, et al. Favorable benefit to risk profile for pemetrexed plus cisplatin versus gemcitabine plus cisplatin in a large phase III study of first-line therapy in advanced non-small cell lung cancer. *Eur J Cancer* 2007;(suppl 5):363.
- Peterson P, Park K, Fossella F, et al. Is pemetrexed more effective in patients with non-squamous histology? A retrospective analysis of a phase III trial of pemetrexed versus docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). *Eur J Cancer* 2007;(suppl 5):363–364.
- Ceppi P, Volante M, Ferrero A, et al. Thymidylate synthase expression in gastroenteropancreatic and pulmonary neuroendocrine tumors. *Clin Cancer Res* 2008;14:1059–1064.
- Davies H, Hunter C, Smith R, et al. Somatic mutations of the protein kinase gene family in human lung cancer. *Cancer Res* 2005;65:7591–7595.