Phase 1/2 Dose Escalating Study of Twice-Monthly Pemetrexed and Gemcitabine in Patients with Advanced Cancer and Non-small Cell Lung Cancer

Arkadiusz Z. Dudek, MD, PhD, Timothy Larson, MD,† Michael J. McCleod, DO,‡ Daniel J. Schneider, MD,§ Jonathan E. Dowell, MD,‖ Tarit K. Banerjee, MD, FACP,¶ Kishan J. Pandya, MD,# Jane L. Bromund, MSN, RN,** Ruqin Chen, MS,** Matthew J. Monberg, MS,** and Coleman K. Obasaju, MD***

Introduction: Pemetrexed is synergistic with gemcitabine in preclinical models of non-small cell lung cancer (NSCLC). The optimal dose and utility of gemcitabine and pemetrexed was evaluated in a dose-escalating study.

Methods: The phase 1 study included patients with advanced tumors, whereas the phase 2 study included patients with locally advanced or metastatic NSCLC. Gemcitabine was infused over 30 minutes, followed by pemetrexed administered over 10 minutes on day 1 of a 14-day cycle. Treatment continued for 12 cycles or until disease progression. All patients received folic acid, Vitamin B_{12}, and steroid prophylaxis.

Results: Maximum tolerated dose was gemcitabine 1500 mg/m^2, followed by pemetrexed 500 mg/m^2. Fifty-three patients (29 male, 24 female) were enrolled in the phase 2 study. Response rate was 20.8% (95% CI: 0.108–0.341), and the clinical benefit rate (CR + PR + SD) was 64.2%. Median time to disease progression was 4.6 months (95% CI: 2.79–6.18), median survival was 10.1 month (95% CI: 5.95–14.09, censorship = 20.75%), and 1-year survival was 41.0%. Common grade 3 or 4 adverse events (% of patients) were neutropenia (28.3%), fatigue (22.6%), and febrile neutropenia (9.4%).

Conclusions: Twice-monthly gemcitabine and pemetrexed was well tolerated, with overall survival and clinical benefit indicating disease activity in NSCLC patients.

*University of Minnesota Comprehensive Cancer Center, Minneapolis, Minnesota; †Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota; ‡Florida Cancer Specialists, Fort Myers, Florida; §Minnesota CGOP, Minneapolis, Minnesota; ‖Dallas VA Medical Center, Dallas, Texas; ¶Marshfield Clinic Research Foundation, Wisconsin; #University of Rochester, Rochester, New York; **Eli Lilly and Company, Indianapolis, Indiana.

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Address for correspondence: Arkadiusz Z. Dudek, MD, PhD, University of Minnesota, MMC 480, 420 Delaware St SE, Minneapolis, MN 55455. E-mail: dudek002@umn.edu

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Up to 48% of patients with non-small cell lung cancer (NSCLC) are diagnosed with locally advanced stage III or metastatic stage IV disease, making them ineligible for curative surgery and likely to have a poor prognosis.[1,2] Platinum-based doublets are associated with substantial hematologic toxicity, nephrotoxicity, nausea, and vomiting, despite providing a survival benefit compared with single-agent platinum or nonplatinum agents.[3] Furthermore, no survival differences have been observed between any of the different platinum-based doublets[4,5] or between platinum and nonplatinum doublets.[6,7]

Preclinical studies evaluating pemetrexed and gemcitabine have reported synergy of the combination in non-small cell lung carcinoma xenografts,[8,9] as well as other tumor types.[8,9] Pemetrexed has shown comparable efficacy to docetaxel with reduced toxicity as a single agent for the second-line treatment of locally advanced or metastatic NSCLC.[10] Supplementation with Vitamin B_{12} and folic acid has been shown to reduce the toxicity of pemetrexed.[11] Gemcitabine has demonstrated independent antitumor activity in locally advanced or metastatic NSCLC.[12,13] Initial phase 2 studies in NSCLC combining these two agents have employed a 90-minute delay between administration.[14,15] A pharmacokinetic study,[16] however, and subsequent phase 2 studies of the combination[17,18] have indicated that this delay in administration may be unnecessary. Most clinical studies employing pemetrexed and gemcitabine in stage IIIB-IV NSCLC have used a 21-day schedule.[14,15,17,18] By comparison, dosing once every 2 weeks theoretically offers the potential of increased dose intensity and added patient convenience. The potential benefit of this regimen is supported by the findings of a phase 2 study of docetaxel and gemcitabine, in which a twice-monthly regimen resulted in a response rate of 55.7%.[19]

The current nonrandomized dose-escalating phase 1 and 2 study was designed to determine the optimal dose of

twice-monthly gemcitabine followed by pemetrexed, as well as evaluate the efficacy and safety of this regimen when administered without a 90-minute delay. A phase 1 addendum was also conducted to evaluate the reverse sequence of biweekly pemetrexed 500 mg/m^2, followed by gemcitabine 1500 mg/m^2.

METHODS

Patients were enrolled in three types of research protocols (phase 1, phase 2, and phase 1 addendum) from seven institutions in the United States between April 2003 and September 2005. Protocols were approved by each institution's committee on human experimentation. The trial has been registered with a public database (www.clinicaltrials-.gov).

Patient Selection

Phase 1 and Phase 1 Addendum

Phase 1 protocols were open to patients with solid-tumor cancer that was not curable by standard treatments. Eligible patients were at least 18-year-old and had an Eastern Cooperative Oncology Group performance status of 0 or 1, a life expectancy ≥12 weeks, and adequate organ function and bone marrow reserve (defined as absolute neutrophil count $\geq 2.0 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; hemoglobin ≥9 g/dl; bilirubin ≤1.5 times institutional upper limit of normal [ULN]; alkaline phosphatase, aspartate transaminase, and alanine transaminase ≤3 times institutional ULN; and calculated creatinine clearance ≥45 ml/min using the Cockroft and Gault formula).[20] Patients were eligible if they had received only one prior chemotherapy treatment or. prior radiation therapy to <25% of the bone marrow if completed ≥2 weeks before enrollment.

Phase 2

The phase 2 protocol used the same eligibility criteria as above, with the exception of the following additional restrictions. Eligible patients had histologically or cytologically confirmed locally advanced or metastatic NSCLC (stage IIIb with pleural effusion or stage IV), measurable by RECIST criteria[21] and not surgically resectable. Prior radiation therapy to <25% of the bone marrow was allowed if completed ≥4 weeks before enrollment (whole pelvis irradiation was not allowed). Patients who had received prior chemotherapy, immunotherapy, or biologic therapy for NSCLC were excluded.

Drug Schedule

Drug products were supplied by Eli Lilly and Company (Indianapolis, IN). Phase 1 and 2 treatment protocols consisted of gemcitabine administered over 30 minutes, followed immediately by pemetrexed delivered over 10 minutes on day 1 of a 14-day cycle. The drug sequence for the phase 1 addendum protocol was reversed, with pemetrexed given initially followed immediately by gemcitabine. All treatment protocols were continued for 12 cycles or until progressive disease.

Dose-Escalation Scheme

The initial dose was gemcitabine 1250 mg/m^2 followed by pemetrexed 500 mg/m^2. Three patients entered the initial dose level. Doses were incremented until the maximum tolerated dose (MTD) was reached. MTD was defined as the dose causing more than one third of patients to have a dose-limiting toxicity (DLT) following the first treatment cycle. Toxicities were graded using the Common Toxicity Criteria [CTC Version 2.0].[22]

Statistical Considerations (Phase 2 Only)

This open-label, phase 2 trial was conducted in two stages.[23] Up to 48 qualified patients were enrolled with the possibility of stopping the study early for either lack of efficacy or unacceptable toxicity. During the first stage, 18 qualified patients were enrolled. If greater than three patients responded, accrual continued until a minimum of 48 patients were included. If responses are seen in 12 or fewer patients, this regimen will be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise. The probability of stopping early after stage one was ≥48.0% if the true response rate was ≤15% (H_0), and ≤2.4% if the true response rate was ≥35% (H_a). The overall probabilities of type I and type II errors were 0.021 and 0.105, respectively.

The primary objective was the demonstration of an improvement in response rates. The study was also designed to evaluate time to disease progression (TTP), overall survival, and toxicity in this population. The Kaplan-Meier method was used to estimate TTP and overall survival.[24]

RESULTS

Phase 1

A total of 40 patients were enrolled into the phase 1 portion of the study. Primary tumor types included lung (37.5%), mesothelioma (12.5%), head and neck (10%), pancreas (10.0%), and esophagus cancers (7.5%). The median age was 57.5 years, and 62.5% were male. The MTD was determined to be gemcitabine 1500 mg/m^2, followed by pemetrexed 500 mg/m^2. DLTs at this level were grade 3 diarrhea, hypotension, and atrial fibrillation. An unconfirmed CR or PR was observed in five patients at the MTD. DLTs and unconfirmed responses for all dose levels are summarized in Table 1.

Phase 2

Patient Characteristics

A total of 53 patients enrolled in the phase 2 portion of the study. Baseline patient characteristics are summarized in Table 2. Median age was 64.0 years, 81.1% has stage IV disease, and 60.4% had an Eastern Cooperative Oncology Group performance status of 1. For all treated patients, the median number of cycles administered was 5.0. Patient drug exposure is summarized in Table 3. Twenty-three (43.4%) patients had one or more dose adjustments, with 14 (26.4%) patients requiring dose reduction, 5 (9.4%) of whom required two or more reductions. Dose delays occurred in 15 (28.3%) patients and were most commonly due to a grade 3 or 4

TABLE 1. Phase 1 Results

Dose Level	G	P	*N*	Cycle 1 DLTs	Types of DLTs[ab]	Responses
1	1250	500	3	1	Grade 4 neutropenia	1
2	1500	500	9	2	Grade 3 diarrhea; grade 3 hypotension, grade 3 atrial fibrillation	5
3	1750	500	10	2	Grade 3 shortness of breath; grade 3 anxiety, grade 3 insomnia	2
4	2000	500	6	4	Grade 3 fatigue, grade 4 thrombocytopenia; grade 3 maculopapular rash; grade 4 hepatitis acute, grade 4 respiratory failure, grade 4 atrial fibrillation, grade 4 renal insufficiency, grade 4 hypotension, grade 4 depressed level of consciousness; grade 3 anemia, grade 3 lower abdominal pain, grade 3 necrotic renal mass	0
5	1500	600	6	4	Grade 4 pulmonary embolism, grade 3 hypoxia; grade 3 shortness of breath, grade 3 diarrhea, grade 3 febrile neutropenia (2); grade 4 weakness of limbs, grade 3 dehydration; grade 3 abdominal pain, grade 4 small bowel obstruction, grade 4 constipation, grade 3 pancreatitis, grade 3 lipase increased, grade 3 hemoglobin (anemia)	1

DLT, dose limiting toxicity; G, gemcitabine; *N*, number of patients assigned to each dose level; P, pemetrexed.
[a] Individual patients may have experienced more than one type of DLT within a dose level. Individual patients are separated in this column by a semicolon.
[b] DLT was defined as grade 4 neutropenia lasting >5 d, grade 4 febrile neutropenia, grade 4 thrombocytopenia, or grade ≥3 nonhematologic toxicity (excluding alopecia, nausea, or vomiting, and transaminase elevations).

TABLE 2. Baseline Characteristics: Phase 2 Study Only

Variable	*N* = 53
Age	
Median, yr (range)	64.4 (35–80)
>65 yr	29 (54.7%)
Gender	
Male	29 (54.7%)
Female	24 (45.3%)
ECOG performance status	
0	20 (37.7%)
1	32 (60.4%)
Not available	1 (1.9%)
Pathologic diagnosis	
Histopathologic	35 (66.0%)
Cytologic	18 (34.0%)
Stage of disease	
Stage IIIB	10 (18.9%)
Stage IV	43 (81.1%)
Prior radiation therapy	
None	41 (77.4%)
1	9 (17.0%)
2	2 (3.8%)
3+	1 (1.9%)
Prior surgical procedures	
None	32 (60.4%)
1	17 (32.1%)
2	3 (5.7%)
3+	1 (1.9%)

ECOG, Eastern Cooperative Oncology Group; *N*, number of patients within phase 2 intent-to-treat population.

TABLE 3. Summary of Dose Administration for the Phase 2 Study

Dosing Variable	*N* = 53
No. cycles	
Sum (range)	309 (1–12)
Mean	5.8
Median	5.0
No. patients with dose adjustments	23 (43.4%)
No. with delays	15 (28.3%)
No. with omissions	1 (1.9%)
No. with reductions	14 (26.4%)
No. patients with	
1 dose reduction	9 (64.3%)
2 dose reductions	5 (35.7%)
3 dose reductions	0
No. dose reductions	
Sum	19 (6.1%)
Mean	1.4
Median	1.0
Relative dose intensity for pemetrexed	
Mean	92.0%
Median	98.1%
Range	58.9–107.5%
Relative dose intensity for gemcitabine	
Mean	92.4%
Median	98.1%
Range	66.6–118.2%

adverse event. Median dose intensity (actual dose/planned dose) was 98.1% for both gemcitabine and pemetrexed.

Antitumor Activity

Tumor response rates are shown in Table 4. Confirmed partial responses were recorded in 11 (20.8%) of the 53 of patients in the intent-to-treat population (95% CI: 0.108–0.341). Stable disease was reported for 23 patients (43.4%); PD was reported for 14 patients (26.4%); response was unknown/unavailable for 5 (9.4%) patients. The median duration of response was 10.3 months (95% CI: 3.22–20.04), and the clinical benefit rate (CR + PR + SD) was 64.2%. Sustained duration of response was 63.6% at 6 months and 45.5% at 12 months. Median TTP was 4.6 months (see Figure 1*A*; 95% CI: 2.79–6.18, censorship = 37.7%). Median sur-

TABLE 4. Tumor Response: Phase 2 Study

Response Variable	*N* = 53
Complete response, *n* (%)	0 (0.0%)
95% CI	NE–NE
Partial response, *n* (%)	11 (20.8%)
95% CI	0.108–0.341
Stable disease, *n* (%)	23 (43.4%)
95% CI	0.298–0.577
Progressive disease, *n* (%)	14 (26.4%)
95% CI	0.153–0.403
Unknown/unavailable, *n* (%)	5 (9.4%)
Median duration of response, mo	10.3
95% CI	3.22–20.04
Clinical benefit rate[a], *n* (%)	34 (64.2%)

[a] Clinical benefit was defined as the number of patients with complete response, partial response, or stable disease.

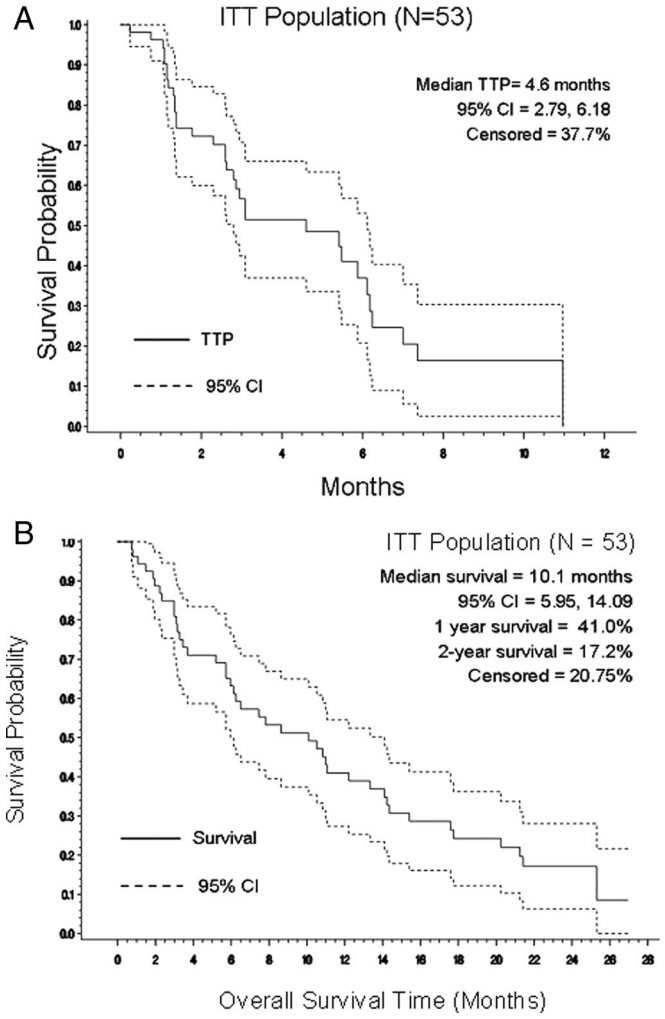

FIGURE 1. *A, B,* Time to disease progression and survival for the phase 2 study. CI, confidence intervals; ITT, intent-to-treat; TTP, time to disease progression.

vival was 10.1 month (95% CI: 5.95–14.09, censorship = 20.8%) with survival rates of 41.0% at 1 year and 17.2% at 2 years.

Drug Safety

Grade 3 or 4 hematologic and nonhematologic toxicities are summarized in Table 5. The most common grade 3 or 4 hematologic events (% of patients) were neutropenia (28.3%), febrile neutropenia (9.4%), and thrombocytopenia (5.7%). The most common grade 3 or 4 nonhematologic events were fatigue (22.6%), cellulitis (7.5%), dehydration (7.5%), and dyspnea (7.5%). Three patients developed serious adverse events related to dizziness. Of these, two discontinued treatment due to severe (grade 3) abnormal coordination and grade 2 vertigo, whereas one developed a balance disorder but completed the study. Overall, 15 (28.3%) patients received one or more blood transfusions. All 15 (28.3%) patients received packed red blood cells; platelets were received by one patient (1.9%).

Phase 1 Addendum

Of 13 patients enrolled in the phase 1 addendum, 8 received the correct drug sequence of pemetrexed and gemcitabine (evaluable patients) and 5 received the incorrect drug sequence of gemcitabine and pemetrexed (nonevaluable patients). Two patients each in the evaluable and nonevaluable groups had unconfirmed PRs. DLTs were observed for 3 of 8 evaluable patients and 1 of 5 nonevaluable patients at a pemetrexed and gemcitabine dose of 500/1500 mg/m^2. Administration of the reverse sequence was discontinued early per the stopping rules when three DLTs were observed.

TABLE 5. Summary of Hematologic and Nonhematologic Toxicities in Phase 2 Study

	Patient-Based (*N* = 53)			Cycle-Based (*N* = 312)
	Grade 3 *N* (% pts)	Grade 4 *N* (% pts)	Grade 3/4 (% pts)	Grade 3/4 *N* (% cycles)
Hematologic				
Neutropenia	7 (13.2)	8 (15.1)	28.3	21 (6.7)
Febrile neutropenia	4 (7.5)	1 (1.9)	9.4	5 (1.6)
Thrombocytopenia	3 (5.7)	0 (0.0)	5.7	3 (1.0)
Anemia	2 (3.8)	0 (0.0)	3.8	3 (1.0)
Nonhematologic				
Fatigue	11 (20.8)	1 (1.9)	22.6	14 (4.5)
Cellulitis	3 (5.7)	1 (1.9)	7.5	5 (1.6)
Dyspnea	3 (5.7)	1 (1.9)	7.5	5 (1.6)
Dehydration	4 (7.5)	0 (0.0)	7.5	4 (1.3)
Alopecia (grade 1 or 2)	3 (5.7)	—	—	4 (1.3)
Diarrhea	3 (5.7)	0 (0.0)	5.7	3 (1.0)
Constipation	2 (3.8)	0 (0.0)	3.8	2 (0.6)
Hyponatremia	2 (3.8)	0 (0.0)	3.8	2 (0.6)
Nausea	2 (3.8)	0 (0.0)	3.8	2 (0.6)
Pneumonia	1 (1.9)	0 (0.0)	1.9	1 (0.3)
Rash	1 (1.9)	0 (0.0)	1.9	1 (0.3)
Vomiting	1 (1.9)	0 (0.0)	1.9	1 (0.3)

CONCLUSIONS

This study has demonstrated the safety of combining gemcitabine and pemetrexed as a first-line treatment for locally advanced or metastatic NSCLC when gemcitabine is administered followed without delay by pemetrexed on day 1 of a 14-day cycle. The phase 1 portion of this study has established the MTD of gemcitabine as 1500 mg/m^2 and pemetrexed as 500 mg/m^2. This MTD level is comparable to the dose used for 21-day cycles, in which gemcitabine was administered at 1250 mg/m^2 on days 1 and 8 and pemetrexed was given at 500 mg/m^2 on either day 1 or 8.[14,15,17,18] In the present study, the MTD dose was well tolerated in the phase 2 study, with neutropenia (28.3%) as the most common toxicity. Furthermore, the dose intensity exceeded previous studies employing 21-day cycles of gemcitabine and pemetrexed in locally advanced or metastatic NSCLC (77.3% for gemcitabine and 87.2% for pemetrexed).[15]

The combination of gemcitabine and pemetrexed is active, with a response rate in our phase 2 study of 20.8% and a median survival of 10.1 month. Two previous studies of 21-day gemcitabine and pemetrexed in first-line NSCLC with a 90-minute delay between treatments were conducted by Monnerat et al. and Ma et al.[14,15] The Monnerat et al. study produced a response rate of 15.5% and a median survival of 10.1 month, but a grade 3 or 4 neutropenia rate of 61.7% and a grade 3 or 4 febrile neutropenia rate of 16.7%. Ma et al. randomized patients to one of three 21-day schedules of gemcitabine and pemetrexed. The preferred schedule in that study was pemetrexed followed by gemcitabine on day 1 and gemcitabine alone on day 8, which resulted in a slightly higher grade 3 or 4 neutropenia rate of 64.4%, a response rate of 31%, and a median survival of 11.4 months. Compared with studies using a 90-minute delay between treatments on a 21-day cycle, the current study seems to offer greater tolerability and convenience with comparable response rates and median survival times.

Two previous trials of 21-day gemcitabine and pemetrexed in first-line NSCLC without a 90-minute delay between treatments were conducted by West et al. (which administered gemcitabine on days 1 and 8 and pemetrexed on day 8)[18] and Treat et al. (which administered gemcitabine on days 1 and 8 and pemetrexed on day 1).[17] In these two trials, the median dose intensities were 82.2% and 76.8% for gemcitabine and 83.2% and 93.9% for pemetrexed. These rates are lower than the 98.1% and 98.1% median dose intensities observed in the present trial. Furthermore, although median survival rates were similar in all three trials (>10 months), grade 3 or 4 neutropenia was lower in the current trial (28.3%) compared with the trials of West et al. (39.6%) and Treat et al. (43.4%).

The clinical benefit of gemcitabine and pemetrexed in first-line NSCLC were evaluated in a meta-analysis of data from four previous phase 2 trials consisting of 220 total patients.[25] This analysis reported a median TTP of 4.17 months (95% CI: 3.29–5.06) and an overall survival of 10.25 months (95% CI: 8.74–11.17), both of which are similar to the median times reported in the present study.

The primary rationale for the use of nonplatinum doublets in NSCLC is the potential reduction of toxicity when compared with the toxicity associated with platinum-based doublets. In a three-arm phase 3 Coalition of National Cancer Cooperative Groups trial, combination gemcitabine and paclitaxel were associated with similar efficacy, but reduced hematologic toxicity, when compared with platinum-based doublets.[7] Nonplatinum doublets may also be an option for patients who may be resistant to platinum therapy as indicated by genotypic expression.[26,27] Pemetrexed and gemcitabine administered as outlined in the present study met the protocol-defined efficacy criteria, has favorable toxicity profile, and should be further evaluated as a feasible alternative to platinum-based doublets.

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