Pemetrexed Combined with Oxaliplatin or Carboplatin as First-Line Treatment in Advanced Non–Small Cell Lung Cancer: A Multicenter, Randomized, Phase II Trial

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ABSTRACT

Purpose: To determine efficacy and toxicity of two pemetrexed-based regimens in chemonaive patients with locally advanced or metastatic non–small cell lung cancer.

Experimental Design: Patients were randomly assigned to receive pemetrexed 500 mg/m² plus oxaliplatin 120 mg/m² (PemOx) or pemetrexed plus carboplatin AUC6 (PemCb). All drugs were given on day 1 of a 21-day cycle for up to six cycles. Folic acid and vitamin B12 were given to all patients to minimize pemetrexed-related toxicities.

Results: Forty-one patients received PemOx and 39 received PemCb. Objective tumor response rates were 26.8% for PemOx patients (95% confidence interval, 14.2–42.9) and 31.6% for PemCb patients (95% confidence interval, 17.5–48.7). Median time to progression was 5.5 and 42.9 months for PemCb patients (95% confidence interval, 14.2–86.0) and 26.8% for PemOx patients (95% confidence interval, 14.2–41.6). Median overall survival times were 10.5 months for both treatment groups (range, <1 to >20 months). The 1-year survival rate was 49.9% for PemOx patients and 43.9% for PemCb patients. Common toxicity criteria grade 3 or 4 hematologic toxicities among PemOx patients were grade 3 or 4 neutropenia (7.3%), grade 3 thrombocytopenia (2.4%), and grade 3 anemia (2.4%). PemCb patients experienced grade 3 or 4 neutropenia (25.6%), grade 3 or 4 thrombocytopenia (17.9%), and grade 3 anemia (7.7%). Grade 3 vomiting occurred in three PemOx patients and grade 3 fatigue occurred in three PemCb patients. One grade 3 neuropsychiatric toxicity occurred in the PemOx group. Three patients (PemOx 1 and PemCb 2) experienced febrile neutropenia.

Conclusions: Efficacy measures for both regimens seem similar to the most effective chemotherapies for advanced non–small cell lung cancer (platinum combinations) with less hematologic and nonhematologic toxicity. Comparing either of these two regimens to platinum-based therapies in a large randomized trial is warranted.

INTRODUCTION

Seventy-five percent of primary lung malignancies are designated as non–small cell lung cancer (NSCLC) and most of these patients have unselectable, locally advanced (stage IIIb) or metastatic (stage IV) disease with 5-year survival rates that range from 3% to 7% (1). Over the last 10 years, a number of large randomized trials have been conducted in patients with NSCLC. These trials compared platinum-based combinations (either cisplatin or carboplatin) that also include a taxane (paclitaxel or docetaxel), a Vinca alkaloid (vinorelbine), or an antimetabolite (gemcitabine; refs. 2–5). Studies indicate that no single regimen was clearly superior with regard to response rates of 17% to 32% and median survival times (MST) of 7 to 10 months. Although a modest survival benefit was established for cisplatin-based chemotherapy (6), in many of these cases, chemotherapy is merely palliative; in addition, cisplatin administration requires hydration therapy and is often associated with substantial side effects including nausea, vomiting, and renal and neurologic toxicities. Active therapies with improved toxicity profiles are clearly needed in this setting.

Pemetrexed (ALIMTA, Eli Lilly and Company, Indianapolis, IN) is a novel antimetabolite that targets multiple enzymes in the folate pathway (7–10). This agent has shown definitive antitumor activity in phase III studies of malignant pleural mesothelioma (11, 12). The high incidence of severe toxicities observed in early phase pemetrexed studies (9) was later linked to elevated serum homocysteine levels (folate and B12 dietary status marker; ref. 13). Thus, all pemetrexed-treated patients now receive folic acid and vitamin B12 supplements and results suggest that this approach significantly improves the safety profile of pemetrexed (14, 15).

Single-agent pemetrexed and pemetrexed-based combinations have shown activity in NSCLC in both first-line and
second-line settings. Four trials, two single-agent trials (16, 17) and two combinations trials of pemetrexed and cisplatin (18, 19), were conducted before the routine use of folic acid and vitamin B12 in previously untreated patients. The single-agent trials showed overall response rates of 16% and 23%, whereas the combination trials yielded overall response rates of 39% and 45%, with respective MSTs of 11 and 9 months. In the second-line setting, a large randomized phase III trial compared pemetrexed with vitamin supplementation to docetaxel (20). Efficacy measures for the two regimens were highly comparable but clinically relevant toxicities favored pemetrexed therapy.

These studies support further evaluation of pemetrexed-based combinations as first-line treatment for locally advanced or metastatic NSCLC. Oxaliplatin, a diamino-cyclohexane platinum, has a different cytotoxicity profile from cisplatin and can be safely given in the outpatient setting without hydration therapy (21 –23). Likewise, carboplatin-based combinations seem to offer similar, or slightly inferior, efficacy but a better nonhematologic toxicity profile when compared with cisplatin-based combinations (2, 24, 25). Phase I studies evaluated pemetrexed plus oxaliplatin in patients with solid tumors (26) and pemetrexed plus carboplatin (27) in patients with malignant pleural mesothelioma. Both regimens were efficacious and well tolerated. In the present trial, we used a randomized phase II design in chemo-naive patients with locally advanced or metastatic NSCLC to simultaneously evaluate the activity of two regimens and minimize inherent patient selection and other sources of bias that can invalidate comparisons between two single-arm trials.

**MATERIALS AND METHODS**

**Patient Selection**

Patients had histologic or cytologic confirmation of locally advanced or metastatic NSCLC (stage IIIB or IV) that was not amenable to curative therapy. Evidence of bidimensionally measurable disease, as determined by computerized tomography, magnetic resonance imaging, X-ray with lesion diameter of ≥0.5 cm, or palpation with both diameters ≥2 cm was also required. Other inclusion criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of ≥18 years, adequate bone marrow reserve (absolute neutrophil count, ≥2.0 × 10^9/L; platelets, ≥100 × 10^9/L; and hemoglobin, ≥9 g/dL), adequate hepatic function (bilirubin, ≤1.5 times the upper limit of normal; alkaline phosphatase and transaminase levels, ≤3.0 times the upper limit of normal or ≤5 for liver involvement; calculated creatinine clearance, ≥45 mL/min), and adequate birth control measures. Radiotherapy was allowed if completed ≥4 weeks before study entry; however, prior systemic chemotherapy, chemotherapy for pleurodesis, immunotherapy, or biological therapy was not allowed. Other exclusion criteria included active infection, pregnancy, other primary malignancy (except in situ carcinoma of the cervix or adequately treated nonmelanomatous carcinoma of the skin or other malignancy treated with no evidence of recurrence within 5 years prior to study entry), documented brain metastases (brain imaging not required in asymptomatic patients), uncontrolled pleural effusions, significant weight loss (≥10% body weight in the preceding 6 weeks), and an inability to interrupt nonsteroidal anti-inflammatory drugs. The latter criteria was precautionary since using nonsteroidal anti-inflammatory drugs with other antifolates (e.g., methotrexate) can result in delayed renal excretion and prolonged drug exposure.

The study protocol was approved by institutional ethic review boards and conducted according to guidelines for good clinical practice and the Helsinki Declaration. All patients provided written informed consent before treatment.

**Study Design**

The primary objective was to estimate the objective response rates for pemetrexed plus oxaliplatin (PemOx) and pemetrexed plus carboplatin (PemCb) in patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC not previously exposed to cytotoxic chemotherapy. A two-stage Simon design (28), based on response rate (z = 0.03, β = 0.16), governed enrollment size for each treatment group. To simultaneously estimate response rate for two regimens and minimize patient selection bias, we randomly assigned patients to PemOx or PemCb. Baseline stratification factors included serum homocysteine, Eastern Cooperative Oncology Group performance status, disease stage, and investigational center. The Poisson and Simon algorithm (29), using a probability factor of 0.75, was applied to balance the treatment arms for these factors. The trial was not powered to make statistical comparisons between arms. Secondary outcomes included time-to-progressive disease (TTP), overall survival time, and quality of life as determined by the lung cancer symptom scale.

**Statistical Considerations**

For analysis purposes, this randomized trial was treated as two simultaneous phase II studies. The exact binomial method was used to determine the 95% confidence intervals (95% CI) for tumor response rate estimates. Time-to-event efficacy variables were estimated using the Kaplan-Meier Method (30), 95% CIs for the medians were calculated as described by Brookmeyer and Crowley (31).

**Treatment Plan**

In the PemOx arm, patients received pemetrexed 500 mg/m^2 (i.v. infusion over 10 minutes) then oxaliplatin 120 mg/m^2 (i.v. infusion over 120 minutes) on day 1 of a 21-day cycle. This dose and schedule were recommended by Misset et al. (26) in their report of a phase I study with this combination. In the PemCb arm, patients received pemetrexed 500 mg/m^2 (i.v. infusion over 10 minutes) then carboplatin target area under the concentration curve (AUC) 6 (i.v. infusion over 30 minutes) on day 1 of a 21-day cycle. Carboplatin dosing was based on the Calvert formula (32) with glomerular filtration rate estimated using calculated creatinine clearance (Modified Cockroft and Gault lean body weight formula; ref. 33). When pemetrexed 500 mg/m^2 and carboplatin AUC5 was evaluated in a phase I study, Hughes et al. (27) used the 51CrEDTA glomerular filtration rate determination. In clinical practice, it is generally accepted that the carboplatin dose of AUC6 obtained from the Calvert formula using glomerular filtration rate estimated with the Modified Cockroft and Gault lean body weight formula is clinically equivalent to carboplatin AUC5 obtained using 51CrEDTA glomerular filtration rate estimation. All patients received up to 6 cycles of therapy. Greater than six cycles were allowed if the
treatment physician and sponsor agreed that additional treatment would be beneficial to the individual patient. Reasons for early discontinuation included disease progression, unacceptable toxicity, or individual patient decision.

All patients were instructed to take oral daily doses of folic acid (350-1,000 μg) beginning 1 to 2 weeks before the first dose of pemetrexed and for 3 weeks after therapy. Injections of vitamin B₁₂ (1,000 μg i.m.) were given 1 to 2 weeks before the first dose of pemetrexed and at 9-week intervals during treatment. Dexamethasone (4 mg, oral, twice daily) was given the day before, the day of, and the day after each dose of pemetrexed therapy to prevent skin rash. The use of prophylactic antiemetic therapy that included a 5-HT₃ antagonist was recommended. Erythropoietin administration was allowed as supportive care. Granulocyte colony stimulating factors were allowed for treatment of serious neutropenic events but supportive treatment was discontinued at least 24 hours before the start of the next therapy cycle.

Drug doses were modified in the event of unacceptable hematologic (absolute neutrophil count of <1.5 × 10⁹/L or platelets <100 × 10⁹/L) or nonhematologic toxicity (common toxicity criteria grade 3 or 4 diarrhea, grade 3 or 4 mucositis, grade ≥2 neuropathy, or other selected toxicities, excluding grade 3 transaminase elevation, nausea, or vomiting). Study therapy was delayed for up to 42 days in patients who developed renal impairment (calculated creatinine clearance, <45 mL/min). Patients requiring >42 days recovery time discontinued study therapy. All patients who required a dose reduction (25% reduction for most designated toxicities and 50% for grade 3 or 4 mucositis) received a reduced dose for the remainder of the study. Patients discontinued treatment if more than two increments of dose reductions were required.

Efficacy and Safety Evaluations

Baseline tumor measurements (using computerized tomography, magnetic resonance imaging, and/or X-ray) were completed no more than 4 weeks before treatment. Within 2 weeks before treatment and throughout the study, patients were evaluated by complete medical and neurologic exams and Eastern Cooperative Oncology Group performance status assessment. Vitamin deficiency markers (homocysteine, cystathionine, methylmalonic acid, and methylcitrate) were determined 1 to 2 weeks before enrollment. All measurable and evaluable lesions were assessed throughout the study using the same techniques that were used at baseline.

Enrolled patients who met all of the following criteria qualified for efficacy analysis: (a) histologic or cytologic confirmation of locally advanced or metastatic NSCLC that was not amenable to curative therapy, (b) presence of bidimensionally measurable disease, (c) no prior or concurrent chemotherapy, and (d) received at least one cycle of study therapy. Tumor assessments were repeated every other cycle throughout the study using the Southwest Oncology Group standard response criteria (34). The now widely used response evaluation criteria in solid tumors method (35) was not widely implemented in clinical investigations at the time of trial initiation. Documented tumor responses required confirmation with a second assessment 3 to 4 weeks (minimum of 21 days) after the first documentation of response.

Overall survival time was defined as the interval between the randomization date and death. Time-to-progressive disease was defined as the interval between the randomization date and the first date of documented disease progression. These time-to-event measures were censored at the date of the last follow-up visit or death (for TTP only).

Quality of life was assessed with the lung cancer symptom scale (36) at baseline and before every cycle. Patients who had a baseline assessment and at least one post-baseline assessment were evaluated for changes in both individual symptom scales (appetite, fatigue, cough, dyspnea, hemoptysis, and pain) and the average symptom burden index (ASBI; the mean of the six lung cancer symptom scales). The SD of baseline ASBIs was calculated. A patient was categorized as having an improved ASBI if the mean of any two consecutive post-baseline ASBIs for that patient was at least 0.5 SD below the patient's baseline ASBI, a worsened ASBI if the mean was at least 0.5 SD above the baseline value, or a stable ASBI if the mean was within 0.5 SD of the baseline value.

Patients who received at least one dose of PemOx or PemCb were evaluated for safety. Body weight and body surface area measurements were evaluated before each cycle. Hematology, blood chemistry, and calculated creatinine clearance were determined within 4 days before study drug administration for each cycle. Toxicity was assessed before each cycle using version 2.0 of the National Cancer Institute common toxicity criteria scale (37). When possible, follow-up safety evaluations were completed ~30 days after the last therapy dose.

RESULTS

Ninety-one patients were entered into the study at 13 investigative sites in Germany, Spain, United Kingdom, Italy, and Portugal between July 2001 and September 2002. Two patients withdrew informed consent and six others failed to meet initial entry criteria. Although 83 patients were randomized to either PemOx (42 patients) or PemCb (41 patients), 3 (PemOx 1 and PemCb 2) were assigned inadvertently because they did not meet eligibility criteria. Eighty patients (PemOx 41, PemCb 39) were treated and Table 1 summarizes the baseline patient characteristics for this group.

Treatment Administration

A total of 382 chemotherapy cycles, 191 per treatment group, were delivered. The median number of cycles delivered was 6 for both PemOx (range, 1-8 cycles) and PemCb (range, 1-7 cycles). Dose reductions occurred in five (2.6%) PemOx cycles and seven (3.7%) PemCb cycles. The majority of PemOx dose reductions (occurring in 3 of 5 cycles) were related to fatigue. In four PemCb cycles, dose reductions were due to thrombocytopenia. There were 15 clinically relevant cycle delays (PemOx, 8; PemCb, 7), but these interruptions were not linked to a single type of toxicity for either treatment group.

Patients treated with PemCb received 93.7% of the intended weekly mean dose of pemetrexed (166.7 mg/m²) and 103.3% of the planned weekly dose of carboplatin (AUC2). The latter elevation was due to errors associated with calculation of AUC or creatinine clearance. Patients treated with PemOx received 95.3% and 100% of the planned weekly mean doses of pemetrexed and oxaliplatin (40 mg/m²), respectively.

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The most common grade 3 or 4 toxicities were hematologic (Table 4). Neutropenia was the most prevalent toxicity, occurring in 7.3% of PemOx patients and 25.6% of PemCb patients. Three patients (PemOx, 2.4%; PemCb, 5.1%) experienced febrile neutropenia. Thrombocytopenia was reported among 2.4% of PemOx patients and 17.9% of PemCb patients. The most common grade 3 or 4 nonhematologic toxicities were vomiting among PemOx patients (7.3%) and fatigue among PemCb patients (7.7%). One patient treated with PemOx experienced a grade 4 infection (without neutropenia). Seventy-three percent of PemOx patients and 15% of PemCb patients experienced some form of neurotoxicity (grade 1 to 3). Severe neurosensory toxicity occurred only in PemOx patients, with one patient experiencing a grade 3 event and seven patients (17.1%) experiencing grade 2 events. One patient experienced acute oxaliplatin-induced dysesthesia (grade 1) 3 hours after receiving the oxaliplatin injection, associated with sweating, shortness of breath, muscle spasm, and facial reddening. Seven patients (PemOx 3 and PemCb 4) died during the treatment phase of the study. One of these deaths (PemOx arm) was possibly related to study drug.

### Quality of Life Analysis

Patient compliance for completion of the lung cancer symptom scale was high for both treatment groups with 96.9% (185 of 191 expected questionnaires) in PemOx and 92.1% (176 of 191 expected questionnaires) in PemCb. Sixty percent of PemOx patients and 59.4% of PemCb patients had either improved or stable ASBI (Table 3). Changes in the ASBI were not conclusive for 12 patients (PemOx 8 and PemCb 4) because these individuals showed inconsistent changes (either in magnitude or direction) in ASBI. Most patients who showed improvement in ASBI also had improvement in two or more symptoms (26 of 28 total patients), with dyspnea and anorexia improving more frequently than other symptoms.

### Toxicity

The majority of common toxicity criteria grade 3 or 4 toxicities were hematologic (Table 4). Neutropenia was the most prevalent toxicity, occurring in 7.3% of PemOx patients and 25.6% of PemCb patients. Three patients (PemOx, 2.4%; PemCb, 5.1%) experienced febrile neutropenia. Thrombocytopenia was reported among 2.4% of PemOx patients and 17.9% of PemCb patients. The most common grade 3 or 4 nonhematologic toxicities were vomiting among PemOx patients (7.3%) and fatigue among PemCb patients (7.7%). One patient treated with PemOx experienced a grade 4 infection (without neutropenia). Seventy-three percent of PemOx patients and 15% of PemCb patients experienced some form of neurotoxicity (grade 1 to 3). Severe neurosensory toxicity occurred only in PemOx patients, with one patient experiencing a grade 3 event and seven patients (17.1%) experiencing grade 2 events. One patient experienced acute oxaliplatin-induced dysesthesia (grade 1) 3 hours after receiving the oxaliplatin injection, associated with sweating, shortness of breath, muscle spasm, and facial reddening. Seven patients (PemOx 3 and PemCb 4) died during the treatment phase of the study. One of these deaths (PemOx arm) was associated with grade 4 febrile neutropenia and was possibly related to study drug.

### Table 2

<table>
<thead>
<tr>
<th>Tumor response</th>
<th>PemOx arm (N = 41), no. patients (%)</th>
<th>PemCb arm (N = 38*), no. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>11 (26.8) (95% CI, 14.2-42.9)</td>
<td>12 (31.6) (95% CI, 17.5-48.7)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (24.4)</td>
<td>12 (31.6)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (48.8)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (17.1)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (7.3)</td>
<td>7 (18.4)</td>
</tr>
</tbody>
</table>

*One patient in the PemCb arm did not have histology performed at baseline and was excluded from efficacy analyses.
DISCUSSION

In advanced or metastatic NSCLC, cytotoxic chemotherapy seems to have reached an efficacy plateau and third-generation platinum-based doublets represent the standard of care with response rates of 17% to 32% and 1-year survival rates of 30% to 45% (2–5). Although platinum-based therapies modestly improve survival and palliate some tumor-related symptoms in patients with locally advanced or metastatic NSCLC, at times the chemotherapy-related toxic side effects outweigh the benefits. Consequently, a practical short-term goal is to identify new regimens that maintain the same level of efficacy as cisplatin-based combinations but offer a better toxicity profile.

This multicenter noncomparative randomized phase II trial showed encouraging results for both pemetrexed-based regimens (pemetrexed 500 mg/m² plus either oxaliplatin 120 mg/m² or carboplatin AUC6). Objective response rates were 26.8% for PemOx patients and 31.6% for PemCb patients. These results are comparable to the preliminary results reported by Zinner et al. (38) who showed an objective response rate of 29% for stage IIIb/IV NSCLC patients receiving pemetrexed and carboplatin. The MST (10.5 months for both arms) and median time to progressive disease reported in this study (5.5 months for PemOx and 5.7 months for PemCb) compare favorably with results of recent phase II trials of new drug combinations (39, 40). Gemcitabine in combination with docetaxel, irinotecan (39), or paclitaxel (40) has produced overall response rates ranging from 12.8% to 33.9% and MSTs ranging from 8 to 12.8 months. Rocha Lima et al. (39) reported median failure-free survival times of 3.5 months for gemcitabine/irinotecan and 4.5 months for gemcitabine/docetaxel. A phase I evaluation of oxaliplatin plus vinorelbine in 28 chemonaive NSCLC patients showed an objective response rate of 35%, a MST of 9.8 months, and median progression-free survival time of 5 months (41).

Although it is difficult to compare efficacy results between phase II and phase III studies, it is notable that the objective response rates, MST, and median TTPs for both PemOx and PemCb were comparable with the values reported in four large, randomized phase III studies evaluating platinum-based doublets (paclitaxel and cisplatin, gemcitabine and cisplatin, docetaxel and cisplatin, paclitaxel and carboplatin; refs. 2–5). In these comprehensive clinical investigations, objective response rates range from 17% to 32%, MSTs ranged from 7.4 to 11.3 months and median TTPs (or median progression-free survival) ranged from 3.1 to 5.5 months.

The incidence of serious hematologic and nonhematologic toxicities reported in the present study was very low compared with other platinum-based combinations (2–5). Grade 3 or 4 neutropenia, the most common toxicity, occurred in only 7.3% of PemOx patients and 25.6% of PemCb patients. In Eastern Cooperative Oncology Group 1594, 63% to 75% of patients treated with a platinum-based regimen experienced grade 3 or 4 neutropenia (2). In studies conducted by the Italian Lung Cancer Project (4) and the TAX 326 study group (5) the incidence of severe neutropenia (grade 3 or 4) ranged from 38% to 79% in patients receiving platinum-based combinations. In the present study, nonhematologic toxicities were generally rare, with the most common events being grade 3 vomiting (7.3% of PemOx patients) and grade 3 fatigue (7.7% of PemCb patients). Neurosensory toxicity was prevalent among PemOx patients but generally mild or moderate (grade ≤2).

In conclusion, combining pemetrexed with either oxaliplatin or carboplatin is safe and effective for the first-line treatment of locally advanced or metastatic NSCLC. Both regimens seem to provide a favorable risk-benefit profile and may represent a promising alternative for treating advanced or metastatic NSCLC. Comparing either of these two regimens, or perhaps pemetrexed plus cisplatin, to standard platinum-based therapies in a large randomized trial, is warranted.

Table 3 Change in average symptom burden index of patient LCSS

<table>
<thead>
<tr>
<th></th>
<th>PemOx arm (N = 35), no. patients (%)</th>
<th>PemCb arm (N = 32), no. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>14 (40.0)</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Worsened</td>
<td>6 (17.1)</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Stable</td>
<td>7 (20.0)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>NC</td>
<td>8 (22.9)</td>
<td>4 (12.5)</td>
</tr>
</tbody>
</table>

Abbreviations: LCSS, lung cancer symptom scale; NC, not conclusive.

*Magnitude of change and/or direction of change was not consistent.

Fig. 1 Kaplan-Meier distribution of overall survival by treatment group.

Fig. 2 Kaplan-Meier distribution of time to progressive disease by treatment group.


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