A randomized phase III trial comparing standard and high-dose pemetrexed as second-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer


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Background: This phase III randomized trial compared pemetrexed 500 mg/m² (P500) with pemetrexed 900 mg/m² (P900) to determine whether higher dosing benefits non-small-cell lung cancer (NSCLC) patients as second-line therapy.

Patients and methods: Patients with locally advanced or metastatic NSCLC, previously treated with platinum-based chemotherapy, were randomly assigned to receive i.v. P500 or P900 every 3 week.

Results: Accrual was terminated with 588/600 patients enrolled because an interim analysis indicated a low probability of improved survival and numerically greater toxicity on the P900 arm. P900 patients were permitted to continue treatment at P500. No statistical difference was observed between the treatment arms (P500 versus P900) for median survival (6.7 versus 6.9 months, hazard ratio [HR] = 1.0132 [95% confidence interval (CI) 0.837–1.226]), progression-free survival (2.6 versus 2.8 months, HR = 0.9681 (95% CI 0.817–1.147)), or best overall tumor response (7.1% versus 4.3% (P = 0.1616)). The incidence of drug-related grade 3/4 toxicity was typically <5% on both treatment arms, but was numerically higher on the P900 arm for most toxicity categories.

Conclusions: P900 did not improve any efficacy measure over P500. P500 i.v. every 3 week remains the standard pemetrexed dose for second-line treatment of platinum-pretreated advanced NSCLC.

Key words: advanced NSCLC, pemetrexed, second-line chemotherapy

Introduction

Thirty to forty percent of patients with advanced non-small-cell lung cancer (NSCLC) receive second-line treatment after standard first-line platinum-based chemotherapy [1]. Optimizing second-line treatment has become a major research focus [2]. Docetaxel (75 mg/m², i.v., on day 1, every 3 week) was the first agent approved for second-line treatment of advanced NSCLC [3, 4]. Subsequently, a randomized phase III trial comparing docetaxel with pemetrexed as second-line therapy for advanced NSCLC demonstrated that pemetrexed 500 mg/m² (P500) (i.v., on day 1, every 3 week) had comparable efficacy to docetaxel, but less toxicity [5].

Because vitamin B12 and folate supplementation have now become standard with pemetrexed therapy [6], enabling the administration of higher doses than the 500 mg/m² used in the registration trial [5], USA Food and Drug Administration suggested that the proposed observational/compassionate use program should compare overall survival (OS) between patients receiving the standard dose and those receiving higher dose therapy. We conducted a phase III randomized trial of P500 versus pemetrexed 900 mg/m² (P900) to determine whether higher dosing benefits NSCLC patients as second-line therapy. The high dose was chosen on the basis of safety and toxicity analyses of phase I studies [7–9].

Patients and methods

Eligibility criteria

Patients ≥18 years with stage III or IV NSCLC, whose disease had progressed following prior platinum-containing chemotherapy, were eligible. Measurable lesions were not required. Other eligibility requirements included an Eastern Cooperative Oncology Group (ECOG)
performance status (PS) of zero to two, adequate bone marrow reserve, creatinine clearance (CrCl) >45 ml/min using the standard Cockcroft and Gault formula [10] and an estimated life expectancy of 28 weeks. Patients could have had up to two prior systemic anticancer therapies, but not more than one for metastatic disease. Prior radiation to <25% of the bone marrow was permitted if completed ≥21 days before the study. Patients with prior brain metastases could be included if treatment was completed and they were asymptomatic.

Written informed consent was obtained from patients before enrollment. The study was approved by each institution’s ethics committee and they were asymptomatic.

study design and treatment plan

This was a phase III, multicenter, open-label, randomized study of P500 arm versus P900 arm. Patients were assigned a treatment arm via a centralized randomization system that used a minimizing algorithm [11] (probability factor 0.75) to balance for ECOG PS (0–1 versus 2), time since last chemotherapy (<3 or ≥3 months), disease stage (III or IV), previous treatment for brain metastases (yes or no), and gender.

P500 or P900 (Alimta®, Eli Lilly and Company, Indianapolis, IN) was given as a 10-min i.v. infusion on day 1 of a 3-week cycle. Treatment continued until progressive disease (PD) or unacceptable toxicity occurred or until investigator or patient decision. Postdiscontinuation assessments continued until death or study closure. Folic acid, vitamin B12, and dexamethasone administration followed that of Hanna et al. [5].

Treatment was delayed for neutrophils <1.5 × 10^9/l or platelets <100 × 10^9/l. Dose modifications were on the basis of nadir counts from the preceding cycle: 25% reduction for neutrophils <0.5 × 10^9/l and platelets ≤25 × 10^9/l; 50% reduction for platelets ≤50 × 10^9/l. Treatment was also delayed for most grade 3/4 non-hematologic toxic effects or calculated CrCl <45 ml/min. When non-hematologic toxic effects resolved, doses resumed at 50% reduction, except grade 3/4 nausea and vomiting, which did not require a dose reduction, and grade 4 transaminase elevation and grade 3/4 diarrhea, which required a 25% reduction. Dose reescalation was not allowed. Treatment was discontinued in any patient requiring a third dose reduction or treatment interruption ≥42 days.

baseline and treatment assessments

Baseline tumor measurements were taken ≤4 weeks before enrollment via computed tomography or magnetic resonance imaging and X-ray. The same baseline tumor assessment method was repeated every 2–3 cycles for both arms. Tumor response was assessed using modified Response Evaluation Criteria in Solid Tumors [12] and confirmed 3–6 weeks after the first evidence. For responders who discontinued the study for a reason other than PD, tumor assessment continued until progression.

The primary efficacy end point was OS, defined as the date of enrollment to the date of death from any cause. Secondary efficacy outcomes were tumor response rate and progression-free survival (PFS), defined as the date of enrollment to the first date of PD or death. Data from all randomly allocated patients [the intent-to-treat (ITT) population] were used for OS and PFS analyses. Patients with measurable disease who had received more than or equal to two doses of pemetrexed were assessed for tumor response. All patients who received at least one dose of pemetrexed were assessable for safety.

Physical examination, body surface area calculations, calculated CrCl [10], and clinical laboratory tests (hematology and blood chemistry) were completed at baseline and before each cycle. Hematology was repeated on days 8 and 15 and blood chemistries on day 8 of each cycle. For both arms, toxic effects (National Cancer Institute–Common Toxicity Criteria, version 2.0) [13] were noted before each cycle.

Due to the origins of this trial as a compassionate use study, data on specific prior chemotherapy regimens, tumor histology, smoking history, and patient ethnicity are unavailable or inconclusive. Likewise, confirmation of tumor response by independent radiology review was not carried out.

statistical considerations

The planned sample size was 600 patients (300/arm), chosen to provide 80% power to detect a statistically significant survival advantage in the P900 arm using an unadjusted Cox model (two-sided significance level 0.05) and assuming a survival hazard ratio (HR) of 0.76 (corresponding to a 6–8 week survival prolongation) and 420 events at the time of analysis.

OS and PFS were analyzed using Cox proportional hazards regression modeling [14] and Kaplan–Meier estimation [15] and compared using the Wilcoxon and log-rank tests. Tumor response rate was calculated as the proportion of qualified patients with a best tumor response of partial response or complete response and compared between the arms using a chi-square test [16].

Two interim safety analyses and an interim test for futility were scheduled to be carried out by an independent Data Safety Monitoring Committee (DMC). The first was data from 148 patients on study for 26 weeks and the second of data from 396 patients, occurred 4 months after the first interim analysis.

results

patient characteristics

From February 2004 to November 2005, 76 institutions worldwide entered 629 patients into this study. Forty-one patients were not randomly allocated to the study because they declined participation, did not meet inclusion criteria, or died. The other 588 patients were randomly assigned to the P500 arm (295 patients) or the P900 arm (293 patients) and comprise the ITT population for the OS and PFS analyses. The two treatment arms were comparable in patient composition, including disease stage, PS, and response to prior chemotherapy (Table 1).

treatment

Of the 588 patients, 290 P500 and 291 P900 patients received treatment and were assessable for safety. After the DMC’s second interim safety analysis and subsequent recommendation, accrual was stopped (at 588 of the planned 600 patients) due to a low likelihood of a survival difference between the arms and numerical increases in some safety parameters on the high-dose arm. The P900 dose was discontinued, and treatment continued for both arms at 500 mg/m², with 51 P900 patients switched to P500. For extent of exposure and safety data (Table 3), these 51 patients are reported separately.

P900 patients had more dose reductions and delays than P500 patients (Table 3); however, the proportion of patients discontinuing due to toxicity/adverse event was similar: P500 7.6% versus P900 8.8%. There was one death from pneumonitis/pulmonary infiltrates, unassociated with neutropenia, considered related to treatment (P900 arm, cycle 2). The percentage of patients who received poststudy chemotherapy (P500: 43.4%; P900: 46.1%) and the types of therapy they received were similar for both arms (data not shown).
The dataset was closed on 31 October 2006, with 85 (29%) and 79 (27%) patients surviving on the P500 and P900 arms. Efficacy analyses showed no statistically significant difference in median OS [P500: 6.7 months; P900: 6.9 months; HR = 1.013 [95% confidence interval (CI) 0.837–1.226]] or PFS [P500: 2.6 months; P900: 2.8 months; HR = 0.968 (95% CI 0.817–1.147)] between the two groups (Figure 1 and Table 2). Multivariate Cox analyses revealed prognostic factors for survival: PS (P < 0.0001; HR = 0.384, PS 2 worse over 0/1), time since last chemotherapy (P < 0.0001; HR = 0.677, <3 months worse than ≥3 months), and gender (P = 0.0005; HR = 1.455, males worse). There were no statistically significant differences in tumor response and stable disease rates between the arms (Table 2).

**safety**

The incidence of drug-related grade 3/4 toxic effects was low (typically <5%) on both arms (Table 3). The P900 arm had a slightly higher frequency of most toxic effects and need for supportive care, transfusions, and hospitalizations than P500; no difference was statistically significant (Table 3). Similarly, P900–P500 patients exhibited either comparable or increased toxicity over P500 patients.

**discussion**

This randomized phase III study examined if a higher pemetrexed dose could achieve greater efficacy than the standard dose in platinum-pretreated patients with advanced NSCLC. The treatment arms were balanced for the four baseline characteristics (gender, stage at diagnosis, PS, and best response to first-line therapy) that were recently shown to impact survival among patients being treated with second-line
Both the 500 and 900 mg/m² doses achieved comparable efficacy as assessed by OS, PFS, and response rate. Given the modest size of this trial, clinically insignificant differences in survival, however, cannot be ruled out as the 95% CI indicates the P900 arm could be up to 17% worse than P500 or up to 23% better. Although the toxic effects that occurred were not unexpected, frequent, or severe, a modest increase in the frequency of some toxic effects in the P900 arm and a greater need for supportive care were observed and study accrual halted. Hence, although vitamin supplementation permitted administration of the 900-mg/m² doses, the higher dose achieved no benefit, and 500 mg/m² remains the appropriate pemetrexed dose for this patient population.

A recent Japanese study comparing 500 and 1000 mg/m² pemetrexed in a similar patient population also found that the higher dose did not yield improved efficacy [18]. As recently reviewed [19], this lack of a dose–response relationship may be explained by a number of factors: (i) the dose–response relationship is flat within the dose range tested; (ii) high-dose chemotherapy is only effective for a subset of cells in a heterogeneous tumor population; (iii) the duration of higher intratumoral levels of drug is too short to result in increased tumor cell kill; and (iv) the limit of bioavailability (transport, etc.) has been reached. Studies in other solid tumors have likewise failed to observe greater efficacy with high-dose chemotherapy [17]. Both the 500 and 900 mg/m² doses achieved comparable efficacy as assessed by OS, PFS, and response rate. Given the modest size of this trial, clinically insignificant differences in survival, however, cannot be ruled out as the 95% CI indicates the P900 arm could be up to 17% worse than P500 or up to 23% better. Although the toxic effects that occurred were not unexpected, frequent, or severe, a modest increase in the frequency of some toxic effects in the P900 arm and a greater need for supportive care were observed and study accrual halted. Hence, although vitamin supplementation permitted administration of the 900-mg/m² doses, the higher dose achieved no benefit, and 500 mg/m² remains the appropriate pemetrexed dose for this patient population.

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### Table 3. Summary of dosage and safety results

<table>
<thead>
<tr>
<th>Dosage</th>
<th>P500 arm, n = 290</th>
<th>P900 arm, n = 240</th>
<th>P900–P500 arm, n = 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of cycles/patient (SD)</td>
<td>4.3 (3.6)</td>
<td>3.5 (2.4)</td>
<td>8.2 (6.2)</td>
</tr>
<tr>
<td>Median total dose/patient (mg/m²)</td>
<td>1503</td>
<td>2687</td>
<td>4200</td>
</tr>
<tr>
<td>Total number of cycles/arm</td>
<td>1256</td>
<td>833</td>
<td>420</td>
</tr>
<tr>
<td>Cycles requiring reduction (% of total)</td>
<td>14 (1.1)</td>
<td>35 (4.2)</td>
<td>—b</td>
</tr>
<tr>
<td>Cycles requiring delay (% of total)</td>
<td>16.4</td>
<td>19.4</td>
<td>18.3</td>
</tr>
<tr>
<td>Maximum CTC grades 3 and 4 non-hematologic toxic effects possibly drug related (% of patients)c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.8</td>
<td>6.7</td>
<td>13.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.4</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.4</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.4</td>
<td>2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.7</td>
<td>0.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>0.3</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Infection without grade 3/4 neutropenia</td>
<td>2.4</td>
<td>2.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2.1</td>
<td>4.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.4</td>
<td>1.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Neutropenia with infection</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.4</td>
<td>1.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.7</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Hospitalizations and supportive care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusions (% patients receiving ≥1)d</td>
<td>21.7</td>
<td>25.4</td>
<td>25.5</td>
</tr>
<tr>
<td>Erythropoietin/G-CSF</td>
<td>10.8</td>
<td>16.3</td>
<td>17.6</td>
</tr>
<tr>
<td>Hospitalization for drug-related adverse events, all grades (%) of patients</td>
<td>10.7</td>
<td>15.8</td>
<td>21.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.4</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>1.7</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.4</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Fever</td>
<td>0.3</td>
<td>2.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.0</td>
<td>2.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

aCounts new dose reductions. Once a dose was reduced, it stayed reduced. 
bInformation not available. Cannot determine which recorded dose reductions are due to toxicity and which are due to Data Safety Monitoring Committee decision to lower dosage for P900 arm patients. 
cToxic effects listed are those with >2% in any group. 
dAbout 95% of the transfusions in all three groups were for red blood cell or whole blood.

P, pemetrexed; SD, standard deviation; CTC, Common Toxicity Criteria; G-CSF, granulocyte colony-stimulating factor.

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**Figure 1.** Kaplan–Meier curve of (A) overall survival and (B) progression-free survival.

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chemotherapy, although some have demonstrated a dose–response relationship when standard doses of chemotherapy are compared with lower doses [19]. Numerically, higher toxicity scores in the P900 arm of this study are compatible with greater drug exposure in normal cells. Detailed pharmacokinetic testing, however, would be required to further address the dose–response relationship in this population.

The median survival for the P500 arm in this study (6.7 months) differs somewhat from that reported in the registration trial (8.3 months) [5]; however, both studies yielded comparable results for 1-year survival, PFS, and response, and similar percentages of patients (~45%) received poststudy chemotherapy. Furthermore, both studies had similar frequencies of grade 3/4 toxic effects. The difference in median survival between these studies is in keeping with the variability observed in median survival results from randomized trials of docetaxel (75 mg/m2, i.v., on day 1, every 3 weeks) for advanced NSCLC. The original studies of Fossella et al. [4] and Shepherd et al. [3] reported 5.7 and 7.5 months, with results from subsequent trials ranging from 5.8 to 9.5 months [5, 20–26].

This study and the Hanna study [5] both identified PS and time since last chemotherapy as prognostic factors for survival. Additional factors were disease stage (in the Hanna study) and gender (in this study). Patient ethnicity might also affect survival results. Recent studies in Japanese patients progressing after prior platinum-based chemotherapy have reported median survivals >1 year following treatment with gefitinib, docetaxel [27], or two doses of pemetrexed [18]. Likewise, a study of 33 Chinese patients reported a median survival of 9.5 months [21]. Information about ethnicity was not collected in our study, but the absence of sites in eastern Asia may have contributed to the lower median survival.

In addition to ethnicity, histological subtype has recently been shown to impact response to pemetrexed in prospective analyses of first-line chemotherapy [28] and retrospective analyses of second-line chemotherapy [29–30], with better efficacy exhibited by patients with nonsquamous tumors. Histology was not collected in this study, but if there were a higher percentage of squamous cell tumors among the study population than observed in comparator studies, this might have contributed to the lower median survival.

Given the similar efficacy between the doses and the slightly higher toxicity on the P900 arm, P500 remains the appropriate pemetrexed second-line dose for patients with advanced NSCLC.

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Authors’ Disclosure of Potential Competing Interests

The following authors have declared the following potential competing interests: owns stock (not including shares held through a public mutual fund): PP, CMV-G, NI, all Eli Lilly. Carried out contract work: JRF, Eli Lilly. Received honorarium: MHC, Eli Lilly, Sanofi Aventis, Roche, and Astra Zeneca; JRF, Eli Lilly. Received grant for partial expenses for conference participation: SS, Pfizer, Roche, Eli Lilly; PZ, Eli Lilly.


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