Efficacy and Safety of Two Doses of Pemetrexed Supplemented with Folic Acid and Vitamin B₁₂ in Previously Treated Patients with Non-Small Cell Lung Cancer

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Abstract

Purpose: The objective of this study was to evaluate the efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B₁₂ in pretreated Japanese patients with advanced non-small cell lung cancer (NSCLC).

Experimental Design: Patients with an Eastern Cooperative Oncology Group performance status 0 to 2, stage III or IV, and who received previously one or two chemotherapy regimens were randomized to receive 500 mg/m² pemetrexed (P500) or 1,000 mg/m² pemetrexed (P1000) on day 1 every 3 weeks. The primary endpoint was response rate.

Results: Of the 216 patients evaluable for efficacy (108 in each arm), response rates were 18.5% (90% confidence interval, 12.6-25.8%) and 14.8% (90% confidence interval, 9.5-21.6%), mediansurvival times were 16.0 and 12.6 months, 1-year survival rates were 59.2% and 53.7%, and median progression-free survival were 3.0 and 2.5 months for the P500 and P1000, respectively. Cox multiple regression analysis indicated that pemetrexed dose was not a significant prognostic factor. Drug-related toxicity was generally tolerable for both doses; however, the safety profile of P500 showed generally milder toxicity. Main adverse drug reactions of severity grade 3 or 4 were neutrophil count decreased (20.2%) and alanine aminotransferase (glutamine pyruvic transaminase) increased (15.8%) in P500 and neutrophil count decreased (24.3%), WBC count decreased (20.7%), and lymphocyte count decreased (18.0%) in P1000. One drug-related death from interstitial lung disease occurred in the P500.

Conclusion: P500 and P1000 are similarly active with promising efficacy and acceptable safety outcomes in pretreated patients with NSCLC. These results support the use of P500 as a second- and third-line treatment of NSCLC.

Pemetrexed (LY231514; Alimta), a multitargeted antifolate, has shown antitumor activity as a single agent or in combination with other anticancer agents (1, 2). Pemetrexed at doses of 500 or 600 mg/m² has been evaluated in various clinical settings in a broad range of tumors including lung (non-small cell and mesothelioma), colorectal, gastric, pancreatic, head and neck, bladder, cervical, and breast cancers (3–13). In a randomized phase III trial that compared 3-week regimens of single-agent 500 mg/m² pemetrexed versus 75 mg/m² docetaxel in pretreated patients with non-small cell lung cancer (NSCLC), respective response rates (9.1% versus 8.8%) and median survival times (MST; 8.3 versus 7.9 months) did not differ between pemetrexed and docetaxel. However, fewer hematologic adverse effects, such as grade 3 or 4 neutropenia, febrile neutropenia, and neutropenic fever, were observed in patients treated with pemetrexed (3).

Myelosuppression is the predominant dose-limiting toxicity of pemetrexed as reported in phase I studies (14–16). A multivariate analysis identified the correlation between poor folate status (as indicated by elevated plasma homocysteine levels) and increased toxicity to pemetrexed, which led to the requirement that patients in all pemetrexed studies receive folic acid and vitamin B₁₂ supplementation (2, 17). This has been shown to decrease toxicity to pemetrexed without compromising efficacy (18). Without supplementation, the maximum tolerated dose of pemetrexed, given every 3 weeks, has been shown to be 600 mg/m² in heavily pretreated patients (14); however, with supplementation, higher pemetrexed doses have been given without limiting side effects. In a Japanese phase I
study of pemetrexed that included folic acid and vitamin B₁₂ supplementation, the maximum tolerated dose of pemetrexed was 1,200 mg/m² and recommended dose was 1,000 mg/m² given every 3 weeks (19). Pemetrexed pharmacokinetics in Japanese patients was not overly different from those observed in Caucasian patients.

In view of these data, we conducted a randomized, phase II study that confirmed the efficacy and safety of a standard dose of pemetrexed (500 mg/m²; P500) with that of a higher dose (1,000 mg/m²; P1000), including folic acid and vitamin B₁₂ supplementation, in previously treated NSCLC patients.

The primary endpoint was evaluation of response rate. Secondary endpoints were assessments of response duration, progression-free survival (PFS), 1-year survival rate, MST, quality of life (QoL), and adverse events.

Materials and Methods

**Patient selection.** Men and women, between 20 and 75 years old, with a life expectancy of at least 12 weeks and histologically and/or cytologically confirmed advanced NSCLC were eligible for the study. In addition, all patients met the following inclusion criteria: stage III or IV disease, at least one target lesion, one or two prior chemotherapeutic regimens, an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate bone marrow function (neutrophils ≥2,000/μm³, platelets ≥100,000/μm³, and hemoglobin ≥9.0 g/dL), hepatic function (total bilirubin within 1.5 times the upper normal limit, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5 times the upper normal limit, and serum albumin ≥2.5 g/dL), renal function (serum creatinine ≤1.2 mg/dL and creatinine clearance ≥45 mL/min), and pulmonary function (functional oxygen saturation ≥92%).

Patients were excluded from the study for radiographic signs of interstitial pneumonitis or pulmonary fibrosis, serious or uncontrolled concomitant systemic disorders, active infections, the need for chronic oxygen therapy, disease stage, gender, time from prior chemotherapy to the first treatment. This was repeated about every 4 weeks after the first examination.

**Study design and sample size.** This open-label multicenter study had a multi-arm design comparing two arms to the standard chemotherapy regimen. The randomization was done by an independent registration center for each arm. The sample size calculation was based on patients who received at least one dose of pemetrexed. Safety analysis was done on all evaluable patients from two combined arms to compare the treatment arms.

**Treatment plan.** Pemetrexed was administered as an i.v., 10-min infusion on day 1 of a 21-day cycle. Patients were instructed to take orally 1 g/d of a multivitamin containing 500 μg folic acid from 1 week before day 1 of course 1 until 22 days after the last administration of pemetrexed. Vitamin B₁₂ (1000 μg) was injected i.m. 1 week before day 1 of course 1 and repeated every 9 weeks until 22 days after the last administration of pemetrexed.

**Randomization.** Patients were balanced with respect to the following factors: age (<65 vs. ≥65 years), gender (male vs. female), performance status (0 vs. 1 vs. 2), Eastern Cooperative Oncology Group (ECOG) PS (0 vs. 1 vs. 2), race (Asian vs. Caucasian), disease (concomitant systemic disorders, active infections, the need for chronic oxygen therapy), disease (stage III vs. IV), and prior chemotherapy (yes vs. no).

Patients who continued to show evidence of toxicity after reducing the pemetrexed dose were discontinued from the study. Administration of pemetrexed was delayed if patients met any of the following criteria: neutrophils <2,000/μm³, hemoglobin <9.0 g/dL, platelets <100,000/μm³, AST/ALT >2.5 times the upper normal limit, total bilirubin >1.5 times the upper normal limit, serum creatinine >1.2 mg/dL, PS 3 or 4, or grade ≥3 nonhematologic toxicity (except for anorexia, nausea, vomiting, and fatigue). The dose of pemetrexed was decreased to 400 mg/m² in the P500 arm and to 800 mg/m² in the P1000 arm, if any of the following events occurred in the previous course: grade 4 leukopenia or neutropenia, grade ≥3 febrile neutropenia, thrombocytopenia, or platelet transfusion, grade ≥3 nonhematologic toxicity (except for grade 3 anorexia, nausea, vomiting, and fatigue), or AST/ALT increased. The pemetrexed dose was similarly reduced if initiation of the next course was postponed after day 29 due to drug-related adverse events. Patients who continued to show evidence of toxicity after reducing the pemetrexed dose were discontinued from the study.

**Assessments of QoL.** Pretreatment assessments included chest X-ray, electrocardiogram, blood chemistry, urinalysis, pregnancy test, creatinine clearance, functional oxygen saturation, vital signs, PS, body weight, and use of prior therapies. Tumor size was examined using X-ray, computer tomography, or magnetic resonance imaging done within 28 days before the planned day of the first treatment. This was repeated about every 4 weeks after the first examination.

**Tumor response rate.** Tumor response rate was the percentage of patients in whom complete response (CR) and partial response (PR) were confirmed based on the best overall response of the tumor response evaluation. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (20). Objective tumor responses in all responding patients were evaluated by an external review committee given no information on the treatment groups.

**Duration of overall response.** The duration of overall response was measured from the date of the first objective assessment of CR or PR until the date of progressive disease. PFS was measured from the date of registration (for the patients with histologically confirmed adenocarcinoma) until the date of progressive disease or death. One-year survival rate was defined as the percentage of patients who survived for 1 year from the registration date. Survival was measured from the registration date to the date of death (regardless of cause).

**Statistical analysis.** Efficacy measurements were analyzed according to the guidelines for clinical evaluation methods of antineoplastic drugs. Efficacy analysis was done on patients who met all selection criteria and received at least one dose of pemetrexed. Safety analysis was done on patients who received at least one dose of pemetrexed. Statistical tests were done to establish a pemetrexed response rate of >5%; 90% confidence intervals (CI) for the objective response rate were calculated for each arm. All survival curves for time-to-event variables were estimated using the Kaplan-Meier method, and 95% CIs were calculated for each arm. Response rate, response duration, and PFS were compared between the two arms using the χ² test. Cox multiple regression analysis was done on all evaluable patients from two combined arms to
identify significant prognostic factors for survival. Covariates evaluated were pemetrexed dose, gender, age, PS, disease stage, histology, interval from prior chemotherapy to registration for the first treatment course, the number of prior chemotherapeutic regimens, and use of prior platinum chemotherapy. For the QoL analysis, distributions of subscales were summarized for each arm using descriptive statistics (mean, SD, minimum, median, and maximum). As a retrospective analysis for safety, major grade 3 to 4 drug-related adverse events were compared between the two arms using the χ² test.

**Results**

**Patient disposition and characteristics.** From October 2004 to October 2005, a total of 244 Japanese patients with advanced NSCLC were enrolled at 28 centers. Of the 244 patients enrolled, 226 were randomly assigned (114 to the P500 arm and 112 to the P1000 arm) at least 1 week before treatment after receiving folic acid and vitamin B₁₂ supplementation. A total of 225 patients (114 in the P500 arm and 111 in P1000 arm) were evaluable for safety. Of these patients, 216 (108 in each arm) were evaluable for efficacy. Gender, age, PS, histology, stage, and prior platinum chemotherapy were well balanced across the two arms (Table 1).

**Efficacy evaluation.** Objective tumor response rates and durations of overall response are shown in Table 2. Of the 108 patients evaluable for efficacy in the P500 arm, 20 achieved PR for an objective response rate of 18.5% (90% CI, 12.6-25.8%); the median duration of response was 4.9 months (95% CI, 3.8-8.7 months). Of the 108 patients evaluable for efficacy in the P1000 arm, 16 achieved PR for an objective response rate of 14.8% (90% CI, 9.5-21.6%); the median duration of response was 3.0 months (95% CI, 2.8-6.1 months). As seen above, the lower limits of the 90% CI in both arms were >5%, showing a statistically significant objective response rate >5% in each of the arms. The differences between arms in response rate and response duration were not statistically significant (P = 0.5839 and 0.1740).

By October 2006, 125 of the 216 evaluable patients had died. The MST and 1-year survival rate were 16.0 months and 59.2% in the P500 arm and 12.6 months and 53.7% in the P1000 arm (P = 0.1463, log-rank test for survival; Fig. 1). Median PFS was 3.0 months (95% CI, 2.0-3.5 months) in the P500 arm and 2.5 months (95% CI, 1.8-3.2 months) in the P1000 arm (P = 0.7139, log-rank test).

Cox multiple regression analysis indicated that pemetrexed dose was not a significant prognostic factor; however, gender (female), PS (0), disease stage (III), histologic type (non-squamous cell carcinoma), and longer intervals from prior chemotherapy were shown to be good prognostic factors (Fig. 2). Of note, patients with non-squamous cell carcinoma had a longer MST compared with those with other histologic types (16.0 versus 9.3 months; P = 0.00264, Cox regression analysis). Pretreatment QoL assessments in both arms were relatively high and showed neither worsening nor improvement following pemetrexed treatment (Table 3).

**Safety evaluation.** A total of 225 patients (114 for P500 and 111 for P1000) were evaluable for safety. Leukopenia, neutropenia, lymphopenia, anemia, elevation of AST/ALT, lactate dehydrogenase, and rash were commonly reported; however, no grade 4 leukopenia or febrile neutropenia was observed (Table 4). Other grade 4 toxicities were uncommon. Gastrointestinal toxicities such as nausea, vomiting, and anorexia were mostly mild and more frequently reported in the P1000 arm. As a retrospective analysis for safety, major grade 3 to 4 drug-related adverse events were compared

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>P500</th>
<th>P1000</th>
</tr>
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<tbody>
<tr>
<td>Patients who were given at least one dose of pemetrexed</td>
<td>114</td>
<td>111</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>61.0 (37-74)</td>
<td>62.0 (26-74)</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>1</td>
<td>63</td>
<td>68</td>
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<tr>
<td>2</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Histology</td>
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<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
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<td>26</td>
</tr>
<tr>
<td>Others</td>
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<td>3</td>
</tr>
<tr>
<td>Disease stage</td>
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<td></td>
</tr>
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<td>III</td>
<td>22</td>
<td>22</td>
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<td>IV</td>
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<td>Prior platinum chemotherapy</td>
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<td>104</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Interval from prior chemotherapy to registration for the first course starts (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>45</td>
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</table>
between the two arms using the χ² test. Grade 3 or 4 anorexia was reported more frequently in the P1000 arm (10.8% versus 2.6%; \( P = 0.0284 \)). Drug-related rash was observed in 67.5% and 80.2% of the patients treated with P500 and P1000, respectively. However, all severities were grade 1 or 2. Five of the P500 patients and 3 of the P1000 patients developed interstitial lung disease related to pemetrexed treatment that resulted in the death of one patient (P500 arm). The other 7 patients recovered from their illness after discontinuing the study drug. A total 16 (14.0%) patients in the P500 arm and 26 (23.4%) patients in the P1000 arm discontinued the treatment because of drug-related adverse events.

**Dose administration.** The median number of treatment courses completed in both arms was 3 (range, 1-24+). Eleven percent of patients in the P500 arm and 8% in the P1000 arm completed at least 10 courses. Dose reduction occurred in 20 (17.5%) patients in the P500 arm and 27 (24.3%) patients in the P1000 arm. The most frequent cause of dose reduction was ALT elevation. Relative dose intensities were 89.6% in the P500 group and 89.8% in the P1000 group.

**Discussion**

This phase II, randomized study is the first report on the efficacy and safety of a higher dose of pemetrexed (1,000 mg/m²) in pretreated Japanese patients with NSCLC. Most patients (>50%) received two courses of prior chemotherapy, and the vast majority or patients (>90%) received prior platinum-based chemotherapy. The response data indicate promising tumor reduction activity and are noteworthy in pretreated patients. The survival data are also promising and better than those reported in second- and third-line settings and comparable with those reported in first-line settings (3, 24, 25). In the phase III study (3) comparing pemetrexed with docetaxel, the response

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**Table 2. Objective tumor response and median response duration**

<table>
<thead>
<tr>
<th>Variable</th>
<th>P500 (n = 108)</th>
<th>P1000 (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective tumor response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Stable disease</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>Response rate (90% CI), %</td>
<td>18.50 (12.6-25.8)</td>
<td>14.80 (9.5-21.6)</td>
</tr>
<tr>
<td>Median response duration (95% CI), mo</td>
<td>4.9 (3.8-8.7)</td>
<td>3.0 (2.8-6.1)</td>
</tr>
</tbody>
</table>

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Fig. 1. Kaplan-Meier curve showing the overall survival for each arm. Asterisk, upper limit could not be calculated because of the censoring at the end of study period.
rate and median survival in the pemetrexed arm were 9.1% and 8.3 months, respectively.

Both P500 and P1000 with folic acid and vitamin B$_{12}$ supplementation were similarly active in previously treated patients with NSCLC. All efficacy measures were similar in both arms as shown by the response rate, survival, and PFS, suggesting that doubling the standard dose of pemetrexed does not show superior efficacy. In addition, Cox multiple regression analysis showed that the difference of pemetrexed dose did not influence survival. Overall, toxicity was more frequent at the higher dose, although toxicity in both arms was mild.

Cullen et al. reported a randomized trial of 500 versus 900 mg/m$^2$ pemetrexed in patients with advanced NSCLC treated previously with platinum-based chemotherapy (26). The response rate, median PFS, and median survival were 7.1%, 2.6 months, and 6.7 months in patients treated with 500 mg/m$^2$ and 4.3%, 2.8 months, and 6.9 months in patients treated with 900 mg/m$^2$ pemetrexed, respectively. The higher dose did not improve survival more than the lower dose.

Dose intensification is not always accompanied by higher efficacy, such as in the case of docetaxel and cisplatin. One possible explanation for this in pemetrexed is that either the intracellular transport of pemetrexed is maximal at 500 mg/m$^2$ or the inhibition of target enzymes is saturated above this dose; however, there are as yet no in vitro data to support either mechanism. Although the mechanism still needs to be elucidated, the wide therapeutic window of pemetrexed makes it unique and safe for patients.

Of interest, our subgroup analysis identified some prognostic factors. The subgroups that were identified as good prognostic factors, gender (female), good PS, early-stage disease, and longer intervals from prior chemotherapy are well known as good prognostic factors for NSCLC. Of particular note, the MST

Table 3. Summary for Functional Assessment of Cancer Therapy for Lung Cancer Lung Cancer Subscale

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean (SD)</th>
<th>Min</th>
<th>Med</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P500 (n = 108)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before course 1</td>
<td>107</td>
<td>71.5 (18.81)</td>
<td>32.1</td>
<td>71.4</td>
<td>100</td>
</tr>
<tr>
<td>Before course 2</td>
<td>101</td>
<td>74.3 (16.68)</td>
<td>39.3</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Before course 3</td>
<td>84</td>
<td>74.3 (18.08)</td>
<td>35.7</td>
<td>78.6</td>
<td>100</td>
</tr>
<tr>
<td>Registration of course 1 + 3 mo*</td>
<td>59</td>
<td>76.3 (18.1)</td>
<td>32.1</td>
<td>78.6</td>
<td>100</td>
</tr>
<tr>
<td><strong>P1000 (n = 108)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before course 1</td>
<td>107</td>
<td>69.6 (18.52)</td>
<td>25</td>
<td>67.9</td>
<td>100</td>
</tr>
<tr>
<td>Before course 2</td>
<td>98</td>
<td>73.5 (17.21)</td>
<td>32.1</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Before course 3</td>
<td>72</td>
<td>71.4 (18.4)</td>
<td>28.6</td>
<td>71.4</td>
<td>100</td>
</tr>
<tr>
<td>Registration of course 1 + 3 mo*</td>
<td>61</td>
<td>74.3 (18.62)</td>
<td>28.6</td>
<td>71.4</td>
<td>100</td>
</tr>
</tbody>
</table>

*Three months ±2 weeks after the day of registration for one course.
Table 4. Hematologic and nonhematologic toxicity evaluated by Common Terminology Criteria for Adverse Events version 3.0

|                           | P500 (n = 114) | P1000 (n = 111) | P  
|---------------------------|----------------|----------------|------
|                           | Grade (%)      | Grade (%)      |      
|                           | 2  3  4  3/4/5 | 2  3  4  3/4/5 |      
| Leukopenia                | 32.5 14.9 0 14.9 | 38.7 21.6 0 21.6 | 0.2582  
| Neutropenia               | 25.4 17.5 3.5 21.1 | 27.9 19.8 4.5 24.3 | 0.6695  
| Lymphopenia               | 28.9 9.6 2.6 12.3 | 30.6 16.2 1.8 18 | 0.31  
| Anemia                    | 19.3 7 0.9 7.9 | 34.2 9 0.9 9.9 | 0.7667  
| Thrombocytopenia          | 0 0 0 0 | 8.1 0.9 0 0.9 | NA  
| Febrile neutropenia       | * 0 0 0 | * 0 0 0 | NA  
| Nausea                    | 14 0 0 0 | 14.4 2.7 0 2.7 | NA  
| Vomiting                  | 7 0 0 0 | 11.7 1.8 0 1.8 | NA  
| Anorexia                  | 16.7 2.6 0 2.6 | 15.3 10.8 0 10.8 | 0.0284  
| Fatigue                   | 3.5 0 0 0 | 1.8 0.9 0 0.9 | NA  
| Diarrhea                  | 2.6 0.9 0 0.9 | 1.8 1.8 0 1.8 | 0.9815  
| Constipation              | 1.8 0.9 0 0.9 | 5.4 0 0 0 | NA  
| Rash                      | 49.1 2.6 0 2.6 | 63.1 4.5 0 4.5 | 0.6930  
| Alopecia                  | 0 * * * | 0 * * * | NA  
| Pneumonitis               | 1.8 1.8 0 2.6† | 0 2.7 0 2.7 | 1  
| AST                        | 21.9 7.9 0 7.9 | 25.2 4.5 0 4.5 | 0.4375  
| ALT                        | 17.5 16.7 0 16.7 | 32.4 7.2 0.9 8.1 | 0.8143  

NOTE: Major grade 3 to 4 drug-related adverse events were compared between two arms using χ² test.
*Not indicated in Common Terminology Criteria for Adverse Events version 3.0.
†One patient died of drug-induced pneumonitis.

of patients with non-squamous cell carcinoma was significantly longer compared with that in patients with squamous cell carcinoma (16.0 versus 9.3 months; P = 0.00264). Pemetrexed induces its antitumor activity by inhibiting key enzymes related to the folate metabolism, such as thymidylate synthase. Studies of the tumor histology of adenocarcinoma progressive disease have reported lower-level expression of thymidylate synthase than squamous cell carcinoma (27). Good survival benefit in patients with non-squamous cell carcinoma by pemetrexed may be explained by lower levels of thymidylate synthase. Because MST was the subject of a subgroup analysis and survival was not a primary endpoint of this study, this finding should be considered exploratory requiring independent confirmation. However, if this finding of superior effectiveness in non-squamous cell carcinoma could be substantiated in future studies, it would be very useful. Indeed, histology could be a simple means of tailoring chemotherapy treatment.

In conclusion, although the recommended dose is P1000 with folic acid and vitamin B₁₂ supplementation for Japanese patients, it has similar efficacy and safety with P500, the recommend dosage in rest of the world. These results support the use of P500 as a second- or third-line treatment of NSCLC.

Disclosure of Potential Conflicts of Interest

Authors have conflicts with Eli Lilly and company.

Acknowledgments

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