Phase II Study of Gefitinib as a First-line Therapy in Elderly Patients with Pulmonary Adenocarcinoma: West Japan Thoracic Oncology Group Study 0402†

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Objective: Elderly patients prefer to receive less-toxic therapy. Monotherapy using drugs such as vinorelbine, gemcitabine or docetaxel is a preferable chemotherapy in elderly patients with advanced non-small-cell lung cancer. Gefitinib shows remarkable efficacy in patients with advanced non-small-cell lung cancer, who have activating epidermal growth factor receptor mutations. Adenocarcinoma histology is related to these mutations. Therefore, we conducted a phase II study of gefitinib as a first-line therapy in elderly patients with pulmonary adenocarcinoma.

Methods: Eligible patients were 70 years or older, had pulmonary adenocarcinoma, stage IIIB or IV disease, an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ functions. Patients were treated with oral gefitinib 250 mg daily until disease progression or unacceptable toxicity.

Results: Thirty-one patients were enrolled, of whom 30 were eligible. The median age was 78.5 years. The response rate was 20%, the disease control rate was 47%, the median progression-free survival was 2.7 months and the median overall survival was 11.9 months. Narrowing it down to those who had never smoked, the response rate increased to 43%, the disease control rate increased to 57%, the median progression-free survival prolonged to 7.1 months and the median overall survival prolonged to 13.0 months. The most frequent toxicity was rash. Other major toxicities were diarrhea, anorexia, liver dysfunction and anemia. These toxicities were mild and easily managed.

Conclusions: Gefitinib as a first-line therapy is active and well tolerated in elderly patients with pulmonary adenocarcinoma, especially in those who have never smoked.

Key words: gefitinib – elderly – adenocarcinoma – non-small-cell lung cancer

INTRODUCTION
Lung cancer is a leading cause of cancer death worldwide. According to the national Surveillance, Epidemiology and End Results (SEER) database of the USA, 14% of patients with lung cancer were 80 years or older, 33% were 70–79 years and 53% were younger than 70 years (1). Thus, one-half of patients with lung cancer are elderly. Elderly patients prefer to receive less-toxic therapy because they often have comorbidity, major organ functions are deteriorated by aging, and therapy often causes severe complication and toxicity. Several reports based on the SEER database showed that only one-third of elderly patients with advanced non-small-cell lung cancer (NSCLC) actually received chemotherapy (2–4). Development of a new chemotherapy that is suitable for elderly patients is necessary.

Platinum-based doublet chemotherapy is a standard therapy in patients with advanced NSCLC; however, elderly patients are often unsuitable for this toxic chemotherapy. Two Italian randomized trials, known as ELVIS (5) and MILES (6), showed that monotherapy using drugs such as vinorelbine or gemcitabine is a preferable chemotherapy in elderly patients. A phase III trial conducted by the West Japan Oncology Group, formerly named the West Japan Thoracic Oncology Group (WJTOG), showed that docetaxel monotherapy is also a standard chemotherapy in elderly patients (WJTOG 9904) (7).

Gefitinib, one of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors, shows remarkable efficacy in patients with advanced NSCLC, who have activating (EGFR)-tyrosine kinase inhibitors, shows remarkable efficacy in patients with advanced NSCLC, who have activating EGFR mutations (8–11). Some clinical features, such as adenocarcinoma histology, a history of never smoking, female sex and Asian ethnicity, are related to these mutations (12). Lee et al. (13) reported excellent efficacies of gefitinib as a first-line therapy in patients with pulmonary adenocarcinoma, who had never smoked. They showed a response rate of 69%, a median progression-free survival (PFS) of 7.6 months and a 1-year rate of overall survival (OS) of 73%. However, as the median age was 51 years in Lee’s study, the efficacy and safety of gefitinib in elderly patients were unclear.

Therefore, we conducted a phase II study of gefitinib as a first-line therapy in elderly patients with pulmonary adenocarcinoma (WJTOG 0402).

PATIENTS AND METHODS
PATIENT SELECTION
Eligible patients were 70 years or older, had histologically or cytologically proved pulmonary adenocarcinoma, stage IIIB that was unsuitable for radical thoracic radiation or stage IV disease, an Eastern Cooperative Oncology Group performance status of 0–2, no prior chemotherapy, measurable lesions and adequate organ functions [white blood cell (WBC) $\geq 3000/\mu l$, hemoglobin $\geq 9$ g/dl, platelet $\geq 100 000/\mu l$, aspartate aminotransferase and alanine aminotransferase $\leq 100$ IU/l, total bilirubin $\leq 1.5$ mg/dl, creatinine $\leq 1.5$ mg/dl, arterial partial pressure of oxygen $\geq 60$ mmHg]. Patients with interstitial pneumonitis or pulmonary fibrosis detected by computed tomography (CT) of chest were excluded.

All patients gave written informed consent.

TREATMENT
Patients were treated with oral gefitinib 250 mg daily until disease progression or unacceptable toxicity. If grade 3 toxicity was observed, gefitinib was interrupted up to 14 days and then resumed at 250 mg every other day, i.e. dose reduction, after improvement of the toxicity. If grade 1 or worse interstitial lung disease (ILD), or other grade 4 toxicity was observed, gefitinib was stopped.

RESPONSE AND TOXICITY EVALUATION
Before treatment, a complete medical history was obtained and physical examination was performed. The following examinations were conducted: complete blood count (CBC) with differential WBC count, blood chemistry, arterial blood gas analysis, pulse oximetry and electrocardiography. Staging procedures consisted of chest X-ray, CT of chest and upper abdomen, magnetic resonance imaging (MRI) or CT of brain, and bone scintigraphy. During treatment, CBC with differential WBC count, blood chemistry, pulse oximetry and chest X-ray were examined every 2 weeks, and CT and/or MRI for response evaluation once a month.

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (14). Extramural review of eligibility and response of all patients were performed. Toxicity was evaluated in accordance with the National Cancer Institute-Common Toxicity Criteria, version 2.0 (15).

STATISTICAL ANALYSIS
The primary endpoint of this study was response rate. The secondary endpoints were disease control rate, PFS, OS and toxicity. The survival curves were drawn using the Kaplan–Meier method (16).

Assuming that a response rate of 30% would indicate potential usefulness, whereas a rate of 10% would be the lower limit of interest and with $\alpha = 0.05$ (one side) and $\beta = 0.20$, 24 patients were required. Allowing for a 20% loss to follow-up, enrollment of a total of 30 patients was planned.

STUDY DESIGN
This study was a multi-institution, prospective and single-arm phase II study. The study protocol was approved by the WJTOG and the institutional review boards at each participating institution. Patient registration, data monitoring and data analysis were performed at the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases.
RESULTS

PATIENT CHARACTERISTICS

From December 2004 to December 2005, 31 patients were enrolled in this study from eight institutions. One patient was ineligible because of IIIA disease. The following analyses were based on 30 eligible patients.

Patient characteristics are listed in Table 1. More than half of the patients (53%) were female, the median age was 78.5 years and 14 patients (47%) had never smoked. All patients had adenocarcinoma histology including one bronchioloalveolar carcinoma feature. As we could not analyze EGFR mutation practically during the study period, EGFR mutation status was unknown in all patients.

TREATMENT ADMINISTRATION

The median treatment duration was 1.6 months with a range of 0.4–29.9 months. At the data cut-off (July 2007), one patient had been receiving gefitinib for 29.9 months. Dose reduction was done in six patients. Causes of stopping gefitinib were disease progression in 19 patients, no benefit over toxicity decided by the treating physician in 5 patients and patient request in 5 patients.

Chemotherapy after gefitinib was as follows: re-administration of gefitinib in five patients, docetaxel in four, carboplatin plus paclitaxel in three, paclitaxel in one and S-1 in one. No chemotherapy was administered in 15 patients.

RESPONSE, DISEASE CONTROL AND SURVIVAL

We observed no complete response, six partial responses and eight stable diseases. So the response rate [95% confidence interval (CI)] was 20% (8–39%) and the disease control rate (95% CI) was 47% (28–66%). As all six partial responders had never smoked, we performed subset analysis according to the smoking history. There were 6 partial responses and 2 stable diseases in 14 patients who had never smoked, and 0 and 6 in 16 smokers, respectively. So the response rate (95% CI) and the disease control rate (95% CI) were 43% (18–71%) and 57% (29–82%) in those who had never smoked, and 0 and 38% (15–65%) in smokers, respectively.

The median follow-up duration was 21.7 months with a range of 2.9–29.9 months. The survival curves are shown in Fig. 1. The median PFS (95% CI) was 2.7 (0–5.7) months and the median OS (95% CI) was 11.9 (7.8–16.0) months. We also performed same subset analysis. The median PFS

Table 1. Patient characteristics (n = 30)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>47</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>78.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>70–87</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>28</td>
<td>93</td>
</tr>
<tr>
<td>Smoking history</td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>14</td>
<td>47</td>
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<td>12</td>
<td>40</td>
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<td>23</td>
<td>77</td>
</tr>
<tr>
<td>Resection</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Radiation</td>
<td>4*</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics (n = 30)

ECOG, Eastern Cooperative Oncology Group.

*Including gamma knife in two patients.
Recently Mok et al. (17) conducted a phase III trial of gefitinib compared with carboplatin plus paclitaxel in previously untreated patients who had advanced pulmonary adenocarcinoma and who had never smoked or were former light smokers in East Asia (IPASS). The IPASS reported that the median PFS and the 1-year rate of progression that were 5.7 months and 25% in the gefitinib arm, and 5.8 months and 7% in the carboplatin/paclitaxel arm, respectively, and showed that gefitinib compared with carboplatin plus paclitaxel in previously treated patients with advanced NSCLC. The IPASS, only 42% (437/1038) of patients who gave their consent for mutation analysis could know their mutation status. More than half of patients were unable to know their mutation status. We should decide to treat such patients with gefitinib or with other drugs depending on clinical features, such as histological type and smoking history. Nowadays, it becomes possible to analyze EGFR mutation using cytological samples (18,19). Needless to say, we must analyze that if possible.

This study showed the response rate was 20%, the median PFS was 2.7 months and the median OS was 11.9 months in eligible patients. Narrowing it down to those who had never smoked, the response rate increased to 43%, the median PFS prolonged to 7.1 months and the median OS prolonged to 13.0 months. Even if EGFR mutation status is unknown, patients who have adenocarcinoma histology and a history of never smoking are candidates for gefitinib treatment. Comparing with median OS of 11.9 months, the median treatment duration of 1.6 months seemed short. Chemotherapy after gefitinib was given in 14 patients; however, we do not have clear explanation about the influence of that.

Elderly patients prefer to receive less-toxic therapy. There were two randomized trials, known as V-15–32 (20) and INTEREST (21), of gefitinib compared with docetaxel in previously treated patients with advanced NSCLC. Both trials reported fewer grade 3 or 4 toxicities in the gefitinib arm than in the docetaxel arm (41 versus 82% in V-15–32, 9 versus 41% in INTEREST). Furthermore, Crino` et al. (22) conducted a randomized trial of gefitinib compared with vinorelbine in previously untreated, elderly patients with advanced NSCLC (INVITE). The INVITE also reported fewer grade 3 or 4 toxicities in the gefitinib arm than in the vinorelbine arm (13 versus 42%). These results support our results: the toxicities of gefitinib were mild and easily managed. Gefitinib is suitable for elderly patients.

Ebi et al. (23) conducted a phase II study of gefitinib as a first-line therapy in elderly patients with advanced NSCLC. They treated 49 patients: the median age was 80 years, 82% of patients had adenocarcinoma and 61% of patients had never smoked. The response rate was 25%, the median PFS was 4 months and the median OS was 10 months. These results also support our outcomes. They reported that 4 (8.2%) of 49 patients developed ILD, while there was no ILD in our study. One of the possible reasons was that we strictly excluded patients with interstitial pneumonitis or pulmonary fibrosis detected by CT. Previously the WJTOG reported a retrospective survey of ILD in 1976 patients treated with gefitinib (24). There were 70 cases of and 31 deaths from the ILD identified, corresponding to a prevalence of 3.5% and mortality of 1.6%. The ILD was significantly associated with male sex, a history of smoking and coincidental interstitial pneumonitis. With respect to ILD,

Table 2. Toxicity (n = 30)

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>9</td>
<td>14</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2  (7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2  (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>Cardiac infarction</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>ILD</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0  (0%)</td>
</tr>
<tr>
<td>AST</td>
<td>18</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2  (7%)</td>
</tr>
<tr>
<td>ALT</td>
<td>18</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2  (7%)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>26</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1  (3%)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0  (0%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>17</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>4  (13%)</td>
</tr>
</tbody>
</table>

ILD, interstitial lung disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

(95% CI) and the median OS (95% CI) were 7.1 (0–14.2) months and 13.0 (7.2–18.8) months in those who had never smoked, and 1.9 (0.3–3.5) months and 9.7 (5.5–14.0) months in smokers, respectively.

**TOXICITY**

Toxicities are listed in Table 2. The most frequent toxicity was rash. Other major toxicities were diarrhea, anorexia, liver dysfunction and anemia. These toxicities were mild and easily managed.

One patient developed grade 4 cardiac infarction. This patient received percutaneous transluminal coronary angioplasty and coronary stenting, and soon recovered.

There was no ILD and no treatment-related death.

**DISCUSSION**

Recently Mok et al. (17) conducted a phase III trial of gefitinib and coronary stenting, and soon recovered.

Vinorelbine arm (13 versus 42%). These results support our results: the toxicities of gefitinib were mild and easily managed. Gefitinib is suitable for elderly patients.

There was no ILD and no treatment-related death.
patient selection by clinical feature is important. Patients who have never smoked have a low risk of ILD.

In conclusion, gefitinib as a first-line therapy is active and well tolerated in elderly patients with pulmonary adenocarcinoma. If EGFR mutation status is unknown, this treatment may be a choice of treatment characterized by less toxicity in this population, especially in those who have never smoked.

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Conflict of interest statement

None declared.

References