Gefitinib as a First-Line Therapy of Advanced or Metastatic Adenocarcinoma of the Lung in Never-Smokers

Dae Ho Lee, Ji-Youn Han, Hong Gi Lee, Jae Jin Lee, Eun Kyoung Lee, Hyae Young Kim, Hark Kyun Kim, Eun Kyung Hong, and Jin Soo Lee

Abstract

Purpose: A subset of patients with adenocarcinoma of the lung who had never smoked cigarettes showed excellent tumor responses to gefitinib therapy. To evaluate the efficacy of gefitinib as a first-line therapy in this subgroup of patients, we conducted a phase II study.

Experimental Design: Eligible patients had no smoking history, stage IIIB or IV adenocarcinoma, Eastern Cooperative Oncology Group performance status 0 to 2, and adequate organ functions. Treatment consisted of daily oral administration of 250 mg gefitinib for 28 days until disease progression. Responses were assessed after every two cycles of therapy.

Results: Of 37 patients enrolled, 36 were assessed for response. Twenty-five patients (69%) had partial response, 4 (11%) had stable disease, and 7 (19%) had progressive disease. Of 10 patients with evaluable brain metastases, 7 had objective responses in both intracranial and extracranial lesions, 1 had stable disease in the brain and dramatic response in the extracranial lesions, and 2 had progressive disease in both sites. After a median follow-up of 48 weeks (range, 4-70 weeks), 26 patients had disease progression, with median progression-free survival of 33 weeks, and 9 patients died, all due to disease progression. The median survival time has not been reached yet but the estimated 1-year survival rate was 73%. Common toxicities were skin rash and mild diarrhea but there was no significant hematologic toxicity.

Conclusions: Gefitinib showed very dramatic antitumor activity, even in the brain, with unprecedented survival outcome in never-smoker adenocarcinoma patients. These data support the use of gefitinib as a first-line therapy in this particular subgroup.

During the last decade, several combination chemotherapy regimens that included more active new chemotherapeutic agents, such as taxanes, gemcitabine, vinorelbine, and irinotecan, have shown therapeutic superiority to cisplatin alone or old cisplatin-based regimens for non–small cell lung cancer (NSCLC; refs. 1–3). However, no particular regimen was shown to be superior to the others. It seemed to have reached the therapeutic plateau with objective response rates of 30% to 40%, median survival time of 8 to 10 months, and 1-year survival rate of 30% to 40% (4, 5). With advances in molecular biological research, a molecular-targeted therapy using epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor emerged as a potential breakthrough for the treatment of NSCLC (6, 7). Two phase II trials of gefitinib monotherapy showed antitumor activity in previously treated NSCLC patients with objective responses reported in 9% to 19% (8, 9). Erlotinib, another EGFR tyrosine kinase inhibitor, also showed significant antitumor activity and improved the survival of NSCLC patients who failed after the first- or second-line chemotherapy (10). However, phase III randomized trials failed to show any therapeutic advantage of combining gefitinib or erlotinib with combination chemotherapy for the treatment of chemo-naive patients with advanced NSCLC (11–14). Despite these disappointing results, rather rapid and dramatic responses were observed in a small subset of patients. Subsequent analysis disclosed that patients with adenocarcinoma or bronchioloalveolar carcinoma histology and no smoking history tended to respond better to gefitinib and erlotinib therapy (15, 16). We wondered if this subgroup of patients would further benefit when gefitinib is given as a first-line therapy.

In Korea, lung cancer has become the leading cause of cancer death since 2000, and continues to increase in both men and women. The female lung cancer mortality rate, in particular, has increased more than 4-fold over the last two decades (17). Unlike most western countries, the majority of Korean female lung cancer patients had never smoked cigarettes in their lifetime (18), and their predominant histology is adenocarcinoma, which provides an ideal situation to evaluate the efficacy of gefitinib as a frontline therapy. We therefore conducted a phase II study to evaluate the efficacy of gefitinib as a first-line therapy in never-smokers with advanced or metastatic adenocarcinoma of the lung.
Patients and Methods

Patient selection. Eligibility criteria included lifetime never smoker, pathologically confirmed adenocarcinoma of the lung, stage IIIB (with pleural effusion) or IV disease, age 18 to 75, and Eastern Cooperative Oncology Group performance status of 0 to 2. Patients were also required to have bidimensionally measurable lesion(s) on computed tomography scan with adequate bone marrow, hepatic, and renal functions, defined as WBC ≥ 4.0 × 10^9/L, neutrophils ≥ 2.0 × 10^9/L, platelets ≥ 100 × 10^9/L, hemoglobin ≥ 10 mg/dL, alanine aminotransferase or aspartate aminotransferase ≤ 2.5 times the upper normal limit, serum bilirubin ≤ 1.2 mg/dL, and serum creatinine ≤ 1.5 mg/dL. No patients had received any prior chemotherapy or molecular-targeted therapy. Brain metastasis was allowed provided that there were no clinically significant neurologic symptoms or signs. All patients gave a written informed consent approved by the Institutional Review Board and the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design. Gefitinib in a dose of 250 mg was administered orally once a day until disease progression, unacceptable toxicity, or patient’s refusal. Each cycle consisted of 28 days of therapy and administration could be interrupted for a maximum of 14 days.

As a baseline, all patients underwent a complete history and physical examination, including documentation of concomitant medications, performance status and history of smoking, laboratory tests (complete blood count, biochemistry profile, and urinalysis), and electrocardiogram within 14 days before the study entry. Chest X-ray, computed tomography scans of the chest (including upper abdomen), magnetic resonance imaging of brain, and radionuclide bone scan were done within 4 weeks before the study entry. Because of the suggestion that BAC histology was an independent predictor of tumor response (15), all pathology slides and cytology slides were prospectively reviewed by a referee pathologist (E.K.H.) to identify two subgroups of adenocarcinoma, those with BAC histology and those without, as proposed by Ebright et al. (19).

Efficacy and toxicity evaluation. The primary end point of the study was response rate, which was assessed according to the WHO criteria (20) after each cycle by chest X-ray and every two cycles by computed tomography scans and magnetic resonance imaging where appropriate. The responses in brain lesions were also assessed using the same diagnostic technique done in baseline assessment and compared with the response in the extracranial sites. Complete response was defined as disappearance of all known disease for at least 4 weeks with no new lesion appearing. Partial response was defined as at least 50% decrease in the sum of the products of bidimensional diameters for at least 4 weeks without the appearance of new lesions. Stable disease was defined as failure to observe a partial response or complete response, with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the products of bidimensional diameters of any measurable lesion or the appearance of new lesions. Patients were evaluated weekly for toxicity during the first cycle and then every 4 weeks thereafter using the National Cancer Institute Common Toxicity Criteria version 2.0 (21). Duration of response was defined as the interval between the date of documented response and the date of documented disease progression. Progression-free survival was defined as the interval between the start of treatment and the date of documented disease progression or death from any cause. Overall survival was defined as the interval between the date of the start of treatment and the date of death due to any cause. If a patient was lost to follow-up, that patient was censored at the last date of contact. All patients who were enrolled and received drug were included in the toxicity analysis. Data were updated as of December 31, 2004.

Statistical considerations. Simon’s two-stage minimax design was used to determine the sample size and decision criteria for this phase II study (22). With the target activity level of 40% and the lowest response rate of interest set at 20%, we needed 33 evaluable patients with an 80% power to accept the hypothesis and a 5% significance level to reject the hypothesis. Allowing for a 10% loss to follow-up rate, a total of 37 patients were enrolled. Confidence intervals were calculated using binomial confidence intervals and comparisons of results were done with χ² test. Overall and progression-free survival and duration of response were calculated using the Kaplan-Meier method.

Results

Patients. Between August 2003 and March 2004, a total of 37 patients were enrolled and the patients’ characteristics are shown in Table 1. No patient received any prior systemic chemotherapy or targeted therapy or radiotherapy to the primary tumor. Four patients had curative resection of the primary tumor and then were enrolled in this trial after recurrence. Twelve patients had brain metastases on initial presentation. Two patients had received palliative therapy for the brain metastases: one received radiation therapy to the brain and the other surgical resection of the brain lesion. For the remaining 10 patients, who were asymptomatic except for one having mild headache, gefitinib was given as the primary modality of treatment for the brain metastasis without brain irradiation. Pleural

<table>
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<th>Characteristic</th>
<th>n (%)</th>
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<tr>
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<td>37</td>
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<tr>
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<tr>
<td>Median</td>
<td>51</td>
</tr>
<tr>
<td>Range</td>
<td>40-74</td>
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<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (8)</td>
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<tr>
<td>Female</td>
<td>34 (92)</td>
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<tr>
<td>Eastern Cooperative Oncology Group status</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>25 (68)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3 (8)</td>
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<tr>
<td>Histology</td>
<td></td>
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<tr>
<td>Adenocarcinoma only</td>
<td>30 (81)</td>
</tr>
<tr>
<td>Adenocarcinoma with BAC histology</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>1 (3)</td>
</tr>
<tr>
<td>IV</td>
<td>36 (97)</td>
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effusion, pericardial effusion, or both were noted in 12 patients. One patient declined further treatment after completing only one cycle of therapy without disease progression. This patient was excluded from response assessment but included in the toxicity assessment and survival analysis.

**Objective responses.** Of the 36 assessable patients, 25 achieved objective responses (all partial response) for an overall response rate of 69% (95% confidence interval, 52-84%), whereas 4 (11%) had stable disease and 7 (19%) had progressive disease as the best response (Table 2). All four stable disease patients showed minor tumor responses, defined as 25% or greater but less than 50% reduction in the sum of the products of diameters of all measurable lesions. By gender, 24 of 33 female patients (73%; 95% confidence interval, 54-87%) achieved objective tumor responses and 4 (12%) had minor responses, whereas only 1 of 3 (33%) male patients showed partial response and 2 (67%) had progressive disease. These results suggest that female patients tend to respond better to gefitinib than male patients ($P = 0.09$). The disease control rate (partial response + stable disease) was 81% of all patients and 85% of female patients. There was very prompt symptom relief, usually within 1 or 2 weeks of therapy. In addition, 21 of 25 responders showed radiographic responses within one cycle of gefitinib therapy, as evidenced by remarkable reductions in the size of measurable lesions and/or significant reduction in the tumor burden on chest X-ray as assessed by two physicians.

**Response by histology.** In this study, seven patients had BAC histology (i.e., adenocarcinoma with BAC features). There was no pure BAC histology. Of those seven patients, three achieved partial responses with a response rate of 43% (Table 2). This response rate tended to be lower than that for the patients with adenocarcinoma without BAC features (22 of 29, 76%) but the difference was not statistically significant ($P = 0.16$).

**Response of metastatic brain lesions.** Of the 10 patients who had evaluable brain metastases, seven had objective tumor responses both in the extracranial and intracranial lesions. One patient had stable disease in the brain lesions and partial response in the extracranial sites. The remaining two patients showed disease progression both in the intracranial and the extracranial sites.

**Progression-free and overall survival.** At the time of this analysis, with a median follow-up time of 48 weeks, a total of 26 patients had disease progression, including the 7 patients who had primary resistance, 2 of 4 patients who had stable disease, and 17 of 25 patients who showed initial responses. Median progression-free survival was 33 weeks (range, 4 to 54+ weeks) and median duration of response was 30 weeks (range, 11 to 49+ weeks). To date, 9 patients died, all due to disease progression, and 26 patients are still alive, 8 of whom are in remission state. Two patients who were lost to follow-up, one after one cycle of therapy and the other after two cycles of therapy with progression, were censored at the last follow-up of 4 and 8 weeks, respectively. The median overall survival has not been reached yet but the estimated 1-year survival rate was 73% (Fig. 1).

**Adverse events.** All thirty-seven patients were included in the toxicity evaluation (Table 3). Common toxicities were dermatologic, which included acneiform skin rash, dry skin, and paronychia. Of 35 patients who developed skin toxicity, 2 patients were required to withhold therapy for 1 week because of grade 2 paronychia and 2 patients did so for 2 weeks because of grade 3 skin rash.

**Second-line treatment after progression.** Of the 26 patients who had disease progression, 19 received second-line treatment, 15 non-platinum-containing chemotherapy regimens (i.e., gemcitabine/vinorelbine), and 4 platinum-based regimens (i.e., two with gemcitabine/vinorelbine/cisplatin, one with gemcitabine/cisplatin, and one with irinotecan/cisplatin). Only 2 of 17 evaluable patients responded to the second-line chemotherapy, one to non-platinum-containing gemcitabine/vinorelbine regimen and the other to the platinum-based regimen, whereas 7 had stable disease and 8 had progressive disease.

**Discussion**

In this phase II trial, we observed a very promising objective response rate of 69% as a first-line therapy of adenocarcinoma of the lung in never-smokers. The survival outcome (i.e., progression-free survival of 33 weeks and the estimated 1-year survival of 73%) is also unprecedentedly remarkable as compared with the results of standard first-line treatments for NSCLC patients, for which median progression-free survival and overall survival were reported to be 4 to 6 months and 8 to 10 months at best, respectively (4, 5). These data confirm that gefitinib is very active in a selected subgroup of NSCLC patients who had adenocarcinoma histology and had never smoked cigarettes. In addition, the tumor responded so rapidly and dramatically that disease-related symptoms improved within 1 to 2 weeks of therapy and radiologic improvement was often documented within 1 cycle of gefitinib therapy by plain chest X-ray. On the other hand,

### Table 2. Tumor responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Adenocarcinoma with BAC histology ($n = 7$)</th>
<th>Adenocarcinoma without BAC histology ($n = 29$)</th>
<th>Total ($N = 36$)</th>
</tr>
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<tbody>
<tr>
<td>PR</td>
<td>3 (43)</td>
<td>22 (76)</td>
<td>25 (69)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (29)</td>
<td>2 (7)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (29)</td>
<td>5 (17)</td>
<td>7 (19)</td>
</tr>
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Abbreviation: BAC, bronchioloalveolar carcinoma; PR, partial response; SD, stable disease; PD, progressive disease.
obtained by percutaneous needle aspiration biopsies. Many of BAC or its element using a limited biopsy samples possibility is the difficulty of establishing the firm diagnosis may well be due to the small study population. Another of those without BAC histology. The reason is unclear but it

subtypes of adenocarcinoma, we found that the response rate without. In a prospectively collected data set on histologic patients with BAC histology might respond better than those

response and survival of gefitinib-treated patients included female gender in addition to the adenocarcinoma or BAC histology and no smoking history (8, 9, 15). In the current study, female never-smokers tended to have a better response rate than the male counterpart. However, we had only three male patients in this study, which makes it difficult to draw any firm conclusion regarding the gender difference in gefitinib responses in NSCLC.

At the initial stage of study design, we postulated that patients with BAC histology might respond better than those without. In a prospectively collected data set on histologic subtypes of adenocarcinoma, we found that the response rate of patients with BAC histology tended to be lower than that of those without BAC histology. The reason is unclear but it may well be due to the small study population. Another possibility is the difficulty of establishing the firm diagnosis of BAC or its element using a limited biopsy samples obtained by percutaneous needle aspiration biopsies. Many of our patients had percutaneous needle aspiration biopsy of the lung lesions rather than open surgical biopsies, which made it difficult to establish the firm diagnosis of BAC histology in our series. In fact, we could not see any case of pure BAC. To evaluate the true efficacy of gefitinib in patients with pure BAC histology, we need a separate study. The case is the same with the male never-smoker patients with adenocarcinoma.

In this study, we observed gefitinib had antitumor effects on the brain lesions, which indicates that the so-called blood-brain barrier does not interfere with therapeutic efficacy of gefitinib for the metastatic brain lesions. Based on our data and previous experience with systemic chemotherapy (23, 24), it seems reasonable to use gefitinib for the treatment of brain metastases before considering palliative radiotherapy or surgery if there is no or minimal neurologic symptom. We also observed remarkable tumor response of brain metastases even in patients with significant surrounding edema and neurologic symptoms due to large brain metastases, who were treated in a non-protocol setting. Given the magnitude and promptness of response, gefitinib can be considered as a primary treatment for brain metastasis in an appropriate subset of patients even if there are neurologic symptoms or signs related to the brain metastases.

Gefitinib was initially developed to target EGFR, which is expressed more on tumor cells. Subsequent studies, however, found that the EGFR expression status itself did not correlate with the gefitinib responsiveness. Recently, two provoking studies reported that EGFR mutation, not simply the status of its expression, predicts the responsiveness of gefitinib (25, 26). Lynch et al. (25) reported that mutations in the EGFR gene, which were clustered near the ATP cleft of the tyrosine kinase domains, correlate with the clinical responsiveness to gefitinib. Paez et al. (26) reported that those EGFR mutations were more frequently observed in adenocarcinoma than in other NSCLCs, in women than in men, and in patients from Japan than in those from United States. The highest frequency of EGFR mutations (8 of 14, 57%) was observed in Japanese women with adenocarcinoma (26). Another study reported by Pao et al. (27) also showed similar types of EGFR gene alterations in 7 of 10 gefitinib-sensitive tumors and in 5 of 7 erlotinib-sensitive tumors. Interestingly, no EGFR mutations were found in 8 gefitinib-refractory and 10 erlotinib-refractory tumors (27). Collectively, these data indicate that adenocarcinomas arising in never-smokers comprise a distinct subset of lung cancer, frequently containing mutations within the tyrosine kinase domain of EGFR. Therefore, it would be very interesting to know the EGFR mutation status of the tumors of our patients. Unfortunately, however, we have only limited access to a dozen of tissue samples, on which EGFR mutation study is in progress.

To assess the potential effect of the second-line chemotherapy on survival outcome, we carefully reviewed the outcome of second-line chemotherapy in our patients. Only 2 objective tumor responses were noted in 17 assessable patients. Argiris and Mittal (28) reported a similar result; only 1 of 7 patients achieved partial response after a second-line chemotherapy following gefitinib therapy. These results suggest that the second-line chemotherapy had insignificant effect on the overall survival of patients enrolled in the current study. On the other hand, Niho et al. (29) reported that when platinum-containing regimens

19% of patients showed primary resistance to gefitinib therapy, which was confirmed by computed tomography scan within one or two cycles.

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![Fig. 1. Kaplan-Meier estimates of progression-free survival and overall survival for all patients from start of treatment. Tick marks indicate censored data. A, progression-free survival. B, overall survival.](www.aacrjournals.org)
were given as a second-line chemotherapy, 9 of 23 (39%) patients achieved objective tumor responses. Therefore, whether the resistance to gefitinib can affect the responsiveness to subsequent chemotherapy remains to be seen, particularly to the non-platinum-containing regimens.

In conclusion, gefitinib monotherapy showed very promising antitumor activity against adenocarcinoma of the lung arising in never-smokers and good toxicity profile. These data support the use of gefitinib as a first-line therapy in this particular subgroup of NSCLC patients.

References


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Clinical Cancer Research

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