Erlotinib in First-line Therapy for Non-small Cell Lung Cancer: A Prospective Phase II Study

DAE RO CHOI, DAE HO LEE, CHANG-MIN CHOI, SANG-WE KIM, CHEOLWON SUH and JUNG-SHIN LEE

Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, 388-1, Pungnap-2 dong, Songpa-gu, 138-736 Seoul, Korea

Abstract. Background: This phase II study evaluated efficacy of first-line erlotinib therapy for chemo-naive patients with non-small cell lung cancer (NSCLC) by their clinicopathological and/or molecular characteristics. Patients and Methods: Eligible patients received erlotinib 150 mg daily until disease progression, followed by a gemcitabine/carboplatin doublet. By clinicopathological characteristics, the patients were categorized as squamous cell carcinoma (SQCC group), ever-smoker with adenocarcinoma (ever-smoking ADCC group), or never-smoker with adenocarcinoma (never-smoking ADCC group). Epidermal Growth Factor Receptor (EGFR) mutations were prospectively assessed by a direct sequencing method and confirmed retrospectively by the Scorpion amplified refractory mutation system (ARMS). Results: Seventy-five patients participated in this study. The direct sequencing method detected 18 EGFR mutations while ARMS detected an additional 3 EGFR mutations and 1 second EGFR T790M mutation. The objective response rates (ORR) were 71.7% in never-smoking ADCC, 25.0% in ever-smoking ADCC, but no response in SQCC, while those of the patients with EGFR mutant and wild-type were 85.7% and 10.0%, respectively. Even in never-smoking ADCC, the EGFR mutants responded better, with ORR of 89.9% and survived longer, with median survival time of 25.4 months, than those with wild-type EGFR with ORR of 25.0% and median survival time of 16.6 months (p<0.05). ORR for gemcitabine and carboplatin was 16.1%. Conclusion: The decision to administer first-line erlotinib should be decided by molecular characteristics, if known, but can be made by clinicopathological characteristics as second best policy.

Erlotinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) accepted as one of the standard treatments for previously treated patients with advanced/metastatic non-small cell lung cancer (NSCLC) (1). It has a favorable efficacy and toxicity profile, when compared with the standard cytotoxic chemotherapy, that is, platinum doublets, prompting us to consider it as a good candidate for first-line treatment for chemotherapy-naive patients with advanced/metastatic NSCLC. However, the concurrent therapy of erlotinib and a platinum doublet failed to show benefit in unselected patients (2, 3). On the other hand, there are already well-known predictors of responsiveness to EGFR TKIs, including molecular predictors, activating EGFR mutations, especially exons 19 and 21, and clinical predictors, adenocarcinoma histology, and never-smoking history (4-6). Recently, two phase III studies of gefitinib have shown its superiority in never or light smokers with adenocarcinoma (7, 8). However, some might still argue that the results of gefitinib studies cannot be extrapolated directly into erlotinib therapy, considering the different results of two studies, the BR21 study of erlotinib (1) and the ISEL study of gefitinib (9).

Based on those findings, an explorative phase II study of single-agent erlotinib therapy was conducted in chemo-naive Asian NSCLC patients, in order to obtain preliminary information for further investigation comparing erlotinib with standard cytotoxic chemotherapy and hopefully to set a temporary guideline of erlotinib therapy.

Patients and Methods

Patient eligibility. Patients were required to have histologically documented NSCLC, stage IIB with malignant pleural or pericardial effusion or stage IV, and no history of prior cancer treatment including chemotherapy or radiotherapy. The other inclusion criteria were: Eastern Cooperative Oncology Group PS of 0-2; at least one uni-dimensionally measurable lesion and adequate organ functions (WBC 3,000/μL, platelets 100,000/μL, hemoglobin 9.0 g/dL, serum creatinine 1.5x the upper limit of normal [ULN], bilirubin 1.25x ULN, and serum aminotransferases 2.5x ULN). Brain metastases were also allowed if they were asymptomatic or controlled by supportive care. However, those patients with severe co-morbid conditions, other active
malignancies or uncontrolled brain metastases were excluded. The study was approved by the institutional review board of the Asan Medical Center and written informed consent was obtained from all the enrolled patients. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design and treatment. This was an open-label, single-institution, phase II study. Patients received erlotinib 150 mg once daily until disease progression, intolerable toxicity, or withdrawal of consent. The treatment could be interrupted for a maximum of 21 days. Prior to treatment, all the patients had complete history and physical examinations, a complete blood count (CBC) with differential cell analysis, laboratory tests including chemistry, electrolytes, glucose, liver and renal function tests, a staging chest and upper abdominal computed tomography (CT) scan, brain magnetic resonance imaging (MRI) and positron emission tomography or bone scan. Analysis of activating EGFR mutations from available tumor samples was conducted using direct sequencing (exons 18, 19 and 21) before starting the treatment, but the result of the analysis did not affect commencement of the treatment. The Scorpions Amplified Refractory Mutation System (ARMS) method (E746 A750del and L858R) was also used to identify the mutations retrospectively in collected tumor tissues. After failure of erlotinib, all the patients received a platinum doublet, consisting of gemcitabine 1000 mg/m² D1 and 8 and carboplatin AUC 5 D1 every 3 weeks, if they were still eligible for cytotoxic chemotherapy.

Endpoint and study assessment. The primary end-point was objective tumor response rate (ORR). Response assessments were performed 4±1 weeks after the commencement of erlotinib therapy and then after every 8±1 weeks unless clinically indicated, according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0 (10). For patients with a documented complete response (CR) or partial response (PR), a confirmatory evaluation was performed at least after 4 weeks. Disease control was defined as the best tumor response of CR, PR, or stable disease (SD) that was confirmed and sustained for 8 weeks or longer. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

Statistical consideration. Before starting the treatment, the patients were categorized into 3 groups based on their clinicopathological characteristics: those who had squamous cell carcinoma histology (SQCC group), those who smoked or had ever smoked and had adenocarcinoma histology (ever-smoking ADCC group), and those who had never smoked and had adenocarcinoma histology (never-smoking ADCC group). The SQCC group was not divided further by their smoking history because their tumor samples were not available or insufficient for the analysis.

Simon’s two-stage optimal design was chosen for each group. A response rate of 40% was set as the target activity level and 20% as the lowest objective response rate of interest, with 80% power to accept the hypothesis and 5% significance to reject the hypothesis. For each group, a total of 43 patients would be enrolled. If there were 3 or fewer responses during the first stage of 13 patients, the study for that group would stop early, and if 12 or fewer responses were observed by the end the study, no further investigation of the drug for that group would be warranted. Loss to follow-up would be allowed up to 15%. Progression-free survival (PFS) was defined as the interval between the starting date of the treatment and the date of documented disease progression or death from any cause. Overall survival (OS) was defined as the interval between the starting date of the treatment and the date of death from any cause. Patients lost to follow-up were censored at the last date of contact. Kaplan Meier estimates of OS and PFS and log-rank tests were used to compare survival distributions between the groups. The data were updated on March 20, 2011.

Results

Patient characteristics. Between October 2006 and January 2009, a total of 75 patients entered into the study and all were assessable for response and toxicity: 6 in the SQCC group; 16 in the ever-smoking ADCC group, and 53 in the never-smoking ADCC group. Their characteristics are shown in Table I. Eighteen patients had brain metastases. EGFR mutation status was identified in only 31 patients (41.3%), among whom 18 patients were found to have an EGFR mutation by direct sequencing before starting treatment and an additional three patients were identified by the Scorpion ARMS. One second mutation of T790M was also identified by the Scorpion ARMS. The mutation status of the other 44 patients was not known because their tumor samples were not available or insufficient for the analysis.

Patient enrollment. Although the number of patients in the SQCC group did not reach that of the first-stage, the decision to stop early was made, considering that no response was observed in the 6 patients, the lack of response in another concurrent study (11) and the treating physicians’ opinion. Among the 16 ever-smoking ADCC patients participating in the study, the fourth response was observed in the fifteenth patient, and therefore, the

### Table I. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SQCC (N)</th>
<th>Ever-smoking ADCC (N)</th>
<th>Never-smoking ADCC (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrolled</td>
<td>6</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td>Age (yr) Median</td>
<td>62 (53-70)</td>
<td>59 (47-75)</td>
<td>58 (39-73)</td>
</tr>
<tr>
<td>ECOG Performance Score</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Present*</td>
<td>0</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>7</td>
<td>31</td>
</tr>
</tbody>
</table>

*Three patients’ mutation was identified retrospectively by the Scorpions Amplified Refractory Mutation System method. ADCC: adenocarcinoma; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; SQCC: squamous cell carcinoma.
study had to stop early according to the protocol because only 3 responses were observed out of the first 13 patients.

Response and survival outcome by clinicopathologic characteristics. There was no response in the SQCC group and 4 responses (25.0%, 95% confidence interval [CI], 7.2 to 52.4%) in the ever-smoking ADCC group. Of note, 38 PRs were observed out of 53 patients in the never-smoking ADCC group as well as 6 SDs, giving a response rate of 71.7% (95% CI, 57.7 to 83.2%) and a disease control rate of 83.0% (95% CI, 70.2 to 91.9%) (Table II). With a median follow-up time of 44 months, median PFS for the never-smoking ADCC and the ever-smoking ADCC groups were 8.3 months (95% CI, 6.4 to 10.1 months) and 1.9 months (95% CI, 0.7 to 3.0 months), respectively (log-rank \( p < 0.0001 \), Figure 1a). The median survival times were 24.5 months (95% CI, 18.3 to 30.6 months) for the never-smoking ADCC group, 11.1 months (95% CI, 3.5 to 18.6 months) for the ever-smoking ADCC group, and 3.7 months (95% CI, 1.9 to 5.5 months) for the SQCC group (log-rank \( p < 0.0001 \) Figure 1b).

Response and survival outcome by molecular characteristics. By \( EGFR \) mutation status, there were 18 PRs out of the 21 patients with an \( EGFR \) mutation, giving a response rate of 85.7% (95% CI, 63.7 to 97.0%), while only 1 out of the 10 patients without an \( EGFR \) mutation, who was a never-smoking woman with adenocarcinoma, reached a PR or a response rate of 10.0% (95% CI, 0.3 to 44.5%). The median PFS and OS for those with an \( EGFR \) mutation were 11.5 months (95% CI, 2.6 to 20.5 months) and 25.4 months (95% CI, 15.4 to 35.3 months), respectively, while the same figures for those without an \( EGFR \) mutation were 1.0 months (95% CI, 0.8 to 1.3 months) and 5 months (95% CI, 0.0 to 21.0 months), respectively (Figure 1c and 1d). In the ever-smoking ADCC group, 2 out of the 3 patients with the \( EGFR \) mutation did reach a PR while the other did not. Interestingly, the non-responder had a second mutation of T790M. In the never-smoking ADCC group, 16 (88.9%, 95% CI, 66.0 to 98.1%) patients reached a PR. Even in patients with the same characteristics, there were differences in terms of survival time as well as response rate. In the never-smoking ADCC group,
EGFR mutant patients had a median survival time of 25.4 months, compared to EGFR wild type with median survival time of 16.6 months (log-rank p=0.021). On the other hand, in those patients with EGFR wild type, never-smokers survived longer with a median OS of 16.6 month than ever-smokers with median OS of 3.5 months (log-rank p=0.042). However, the median OS of EGFR mutant patients in the never-smoking ADCC group was numerically longer but not statistically different than that in the ever-smoking ADCC group (25.4 months vs. 13.8 months, log-rank p=0.733) (Figure 2).

**Toxicity profile.** The most common toxicities were skin rash (37.5%) and pruritus (37.5%). Severe or grade 3 toxicity included mucositis recorded in 2 patients, elevated liver enzyme in 2 patients, and skin rash in 1 patient. No grade 4 toxicity was observed.

**Post-erlotinib treatment.** After the failure of erlotinib therapy, 58 patients were eligible for platinum-doublet treatment and 56 patients received gemcitabine-carboplatin as planned, while 1 received pemetrexed-cisplatin and 1 declined any chemotherapy at all. Among the 56 patients, only 9 patients showed a PR while there were 16 SDs and 31 PDs, giving a response rate of 16.1% (95% CI, 7.6 to 28.3%). According to the prior response to erlotinib therapy, 6 (18.2%) out of the 33 having a PR and 2 (22.2%) out of the 9 patients with SD reached a PR, while only one (7.1%) out of the 14 patients with PD reached a PR. According to the mutation status, 1 (6.7%) out of the 15 patients with an EGFR mutation showed a PR while 2 (22.2%) out of the 9 patients without the mutation showed a PR.

**Discussion**

In the current study, a high response rate of 71.7% and good survival outcome with median PFS of 8.3 months and OS of 24.5 months was observed in the never-smoking patients with adenocarcinoma histology. However, even in the patients with the same clinicopathological characteristics, according to their
molecular characteristics their survival outcomes as well as response rate were different. In the never smoking ADCC group, median survival time of 25.4 months in those with EGFR mutation was longer than the 16.6 months in those with EGFR wild-type, which was statistically significant. The survival outcomes of those with EGFR mutation by smoking status were not different, although the small sample size limited the findings. The molecular criteria were thus a better indicator for predicting the outcome than the clinicopathological ones and the identification of EGFR mutations was more important for choosing erlotinib as first-line therapy.

On the other hand, the response rate of 16.1% to a platinum doublet after failure of erlotinib was slightly higher than those of about 10% to second-line chemotherapy treatment (12, 13) even though the patients were not exposed to cytotoxic chemotherapy before, suggesting that the sequence of the treatment might not affect the overall outcomes, which was also consistent with the results reported in two other studies (7, 8). However, some of the present patients had no opportunity of receiving possibly effective cytotoxic treatment due to the rapid deterioration of performance status during the frontline erlotinib therapy. Actually, 6 (25%) out of the 24 patients with PD could not receive chemotherapy at all. In contrast, some patient’s performance status improved noticeably and rapidly after erlotinib therapy. Some still argue that our study could not support the use of first-line erlotinib therapy, even in patients having favorable molecular predictors because they might also respond better to cytotoxic chemotherapy. However, considering not only the higher response rate but also the more favorable toxicity profile and convenience of the treatment, although the current study had some limitations, such as small sample size and single arm study, many patients and clinicians might prefer erlotinib therapy to cytotoxic chemotherapy.

Identification of molecular predictors is very important but some obstacles are yet to be overcome. The most important issue is the acquisition of sufficient tumor tissue. Interestingly, while sufficient tissue enough for EGFR mutation analysis was obtained from all the tumor biopsies taken in our hospital, the 44 patients without sufficient tumor samples were all referred from a primary clinic. This might have been due to concerns of severe complications which might occur during invasive procedure to get more tissue under suspicious but not definite diagnosis of lung cancer. However, unless sufficient tumor tissue is obtained at the time of suspicion of lung cancer, especially as molecular mechanisms of oncogenesis, such as EML4-ALK fusion gene (14-16) as well as EGFR mutation, become better known, repeated tumor biopsy might have to be considered. Additionally, more sensitive but easier and cheaper methods of identifying such molecular predictors also need to be developed. Actually, the more sensitive method, the Scorpion ARMS method, aided identification of EGFR mutation and T790M second mutation, but, disappointingly, this method could not be used prospectively and not helpful for us to make a decision.

The clinicopathological findings are helpful for establishing both diagnosis and treatment plans. The incidence rate of EGFR mutation and clinicopathological criteria to erlotinib therapy could be considered before deciding to perform or repeat invasive procedures to obtain tumor tissues for mutation analysis. Even though the molecular characteristics were identified in less than half of the present patients (31/75 or 41.3%), a high response rate of 71.7% in the never smoking patients with adenocarcinoma was observed, suggesting that choosing treatment based on a patient’s clinicopathological characteristics might be the second best policy.

In conclusion, first-line single-agent erlotinib therapy should be given to patients with an EGFR mutation and might also be given to patients with favorable clinicopathological predictors, that is, never-smoker with adenocarcinoma as the second best policy.

---

Table II. Tumor responses.

<table>
<thead>
<tr>
<th>Response</th>
<th>According to clinicopathological characteristics</th>
<th>According to EGFR mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SQCC (n=6)</td>
<td>Ever-smoking ADCC (n=16)</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>PD</td>
<td>6</td>
<td>100.0</td>
</tr>
<tr>
<td>ORR</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>DCR</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

ADCC: adenocarcinoma; CR: complete response; DCR: disease control rate; EGFR: epidermal growth factor receptor; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease; SQCC: squamous cell carcinoma.
Conflict of Interest

We declare that we have no conflict of interest.

Acknowledgements

This study was supported by Asan Institute for Life Science, Seoul, Korea [07-432 to D.H.L., 08-432 to D.H.L].

References


Received June 26, 2011
Revised August 3, 2011
Accepted August 5, 2011