Comparison of Clinical Outcomes Following Gefitinib and Erlotinib Treatment in Non–Small-Cell Lung Cancer Patients Harboring an Epidermal Growth Factor Receptor Mutation in Either Exon 19 or 21

Sung Hee Lim, MD, Ji Yun Lee, MD, Jong-Mu Sun, MD, PhD, Jin Seok Ahn, MD, PhD, Keunchil Park, MD, PhD, and Myung-Ju Ahn, MD

Background: Gefitinib and erlotinib, small-molecule kinase inhibitors that block epidermal growth factor receptor (EGFR) signaling, have demonstrated a dramatic response rate and prolonged progression-free survival (PFS) in patients harboring an activating EGFR mutation. We compared the clinical outcomes in gefitinib- and erlotinib-treated patients harboring EGFR mutations who had recurrent or metastatic non–small-cell lung cancer (NSCLC).

Methods: A total of 375 patients with recurrent or metastatic stage IIIB/IV NSCLC, who had either exon 19 deletion or the L858R mutation in exon 21, and had received either gefitinib (n = 228) or erlotinib (n = 147), were included in the study. A matched-pair case-control study design was implemented in the analysis, where 121 pairs of gefitinib-treated and erlotinib-treated patients were matched according to sex, smoking history, Eastern Cooperative Oncology Group performance status, and types of EGFR mutation.

Results: The median age of all patients was 58 years (range, 30–84), and more than half of patients had never been smokers (63.6%). Most patients had adenocarcinoma (98.3%) and good Eastern Cooperative Oncology Group performance status (0, 1) (90.9%). The median number of cycles of EGFR tyrosine kinase inhibitor (TKI) treatment was 12.7 in the gefitinib group and 10.8 in the erlotinib group. Of the 242 patients, 63 (26%) received EGFR TKI as first-line therapy. The overall response rates and disease control rates in the gefitinib- or erlotinib-treated groups were 76.9% versus 74.4% ($p = 0.575$) and 90.1% versus 86.8%, respectively ($p = 0.305$). There was no statistically significant difference with regard to PFS (median, 11.7 versus 9.6; $p = 0.056$) between the gefitinib- and erlotinib-treated groups. For patients receiving EGFR TKI as the first-line treatment, there was no significant difference between the two treatment groups in overall response rates (76.7% and 90.0%) ($p = 0.431$) and median PFS (11.7 versus 14.5 months) ($p = 0.507$).

Conclusion: In NSCLC patients harboring EGFR mutation, treatment with gefitinib and erlotinib resulted in similar effectiveness.

Key Words: Non–small-cell lung cancer, Gefitinib, Erlotinib, Epidermal growth factor receptor mutation.

(*J Thorac Oncol*. 2014;9: 506–511)

Somatic mutations in the epidermal growth factor receptor (EGFR) gene have been associated with sensitivity to EGFR tyrosine kinase inhibitors (TKIs) in non–small-cell lung cancer (NSCLC). Gefitinib and erlotinib are commonly used in metastatic NSCLC patients with EGFR mutations.[1]

Gefitinib yielded an 18.4% objective tumor response and a 40.3% symptom improvement rate in randomized phase II trials conducted in a broad spectrum of patients being treated for advanced NSCLC.[2] However, the IRESSA Survival Evaluation in Lung Cancer phase III study showed no significant improvement in median survival with gefitinib in the overall population of refractory NSCLC patients.[3] Subsequent preplanned subset analysis from IRESSA Survival Evaluation in Lung Cancer which included never-smoking patients from Asia only showed a significant survival benefit compared with placebo.[4]

Gefitinib, as a first-line therapy in NSCLC, demonstrated significantly superior outcomes in progression-free survival (PFS) compared with carboplatin plus paclitaxel within a cohort of East Asian NSCLC patients who had never smoked or were former light smokers.[5] A preplanned biomarker study showed a significant prolongation of PFS in the gefitinib group compared with the chemotherapy group among EGFR-mutant NSCLC patients. In contrast, gefitinib treatment resulted in worse outcomes in patients with wild-type EGFR. Several randomized phase III studies reported consistent improvement in PFS in NSCLC patients with an EFGR mutation who were treated with gefitinib compared with those with combination chemotherapy.[6,7] The response rate and PFS of gefitinib in these studies ranged from 62.1% to 73.7% and from 9.2 to 10.7 months, respectively.

Similarly, erlotinib has been studied as a first-line therapy and in combination chemotherapy in EGFR-mutant NSCLC

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Myung-Ju Ahn, MD, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong Gangnam-gu, Seoul 135–710, Korea. E-mail: silkahn@skku.edu or silk.ahn@samsung.com

ISSN: 1556-0864/14/0904-0506

patients.[8] OPTIMAL trial (Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation–positive NSCLC: multicenter, open-label, randomized phase III study),[9] a study conducted in China comparing erlotinib and platinum doublet treatment in EGFR-mutant NSCLC patients, demonstrated significantly longer PFS with erlotinib treatment. Another phase III trial comparing erlotinib versus standard chemotherapy as a first-line treatment for European patients with advanced EGFR mutation–positive NSCLC also reported erlotinib to result in significantly longer PFS. The PFS was 13.1 months in the OPTIMAL study compared with 9.7 months of PFS in the EURTAC study (Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation–positive NSCLC: a multicenter, open-label, randomized phase III study).[10]

Although both agents have similar structures and exemplify similar efficacy, there is a paucity of comparative data on the efficacy and safety of gefitinib and erlotinib in advanced NSCLC patients with EGFR mutation. Previously, we have reported that two agents showed similar outcomes in terms of response rate, disease control rate, PFS, and overall survival (OS) in unselected patients with advanced NSCLC in whom prior platinum-based chemotherapy was failed.[11] Another prospective, randomized phase II study demonstrated that both TKIs were effective in antitumor activity with similar tolerable toxicity profiles as second-line treatment for a clinically selected population of NSCLC.[12]

The present study sought to compare the clinical outcomes of gefitinib-treated and erlotinib-treated patients with advanced/metastatic or recurrent NSCLC harboring an EGFR mutation in either exon 19 or 21.

MATERIALS AND METHODS

Study Population

We retrospectively reviewed medical records of 375 NSCLC patients (>18 years) who had either exon 19 deletion or L858R mutation on exon 21 and had received gefitinib (n = 228) or erlotinib (n = 147) therapy at Samsung Medical Center, Seoul, Korea, between August 2007 and December 2011. A matched-pair case-control study design aimed to minimize bias was used to analyze 375 patients who were consecutively selected to account for significant variables such as sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), and EGFR mutation types.

All patients had clinically proven recurrent or advanced/metastatic stage IIIB/IV NSCLC and EGFR mutations confirmed by DNA-directed sequencing. Patients with brain metastasis who underwent whole-brain radiotherapy or stereotactic radiosurgery were not excluded from this study. The gefitinib group was defined as patients who had been treated with gefitinib as first-line treatment or those who had received it as second- or higher-line treatment after failure of cytotoxic chemotherapy and had not been treated previously with erlotinib. The erlotinib group was defined as patients who had never been treated with gefitinib but were treated with erlotinib as first-line treatment or as second- or higher-line treatment after failure of prior cytotoxic chemotherapy. Clinical parameters collected at the time of EGFR TKI treatment were as follows: age, sex, smoking status, ECOG PS, prior systemic chemotherapy regimens, stage, surgery, and sites of metastasis. None of the patients received any concurrent chemotherapy or other experimental agents during gefitinib or erlotinib treatment. Gefitinib was administered daily at a dose of 250 mg/day orally and erlotinib at a dose of 150 mg/day orally, and the cycle was repeated every 28 days. Treatment continued until progressive disease, unacceptable toxicity, or patient refusal. Response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines,[13] and evaluation was performed by dynamic, contrast-enhanced computed tomography every 8 weeks of EGFR TKI treatment.

In total, 121 pairs of gefitinib- or erlotinib-treated patients were matched using random number tables according to sex (men versus women), smoking history (never versus ever/current), ECOG PS (0–1 versus ≥2), and the type of EGFR mutation (exon 19 deletion versus L858R point mutation). This study was approved by the e-Institutional Review Board of Samsung Medical Center.

EGFR Mutation Analysis

Tumor samples for each patient in this study were obtained via either diagnostic or surgical procedures. Ninety-nine patients among the total 375 patients underwent a second tissue biopsy to reassess whether an EGFR mutation was present. Four patients initially documented as having wild-type EGFR gene were determined to have an EGFR mutation after the second biopsy suggesting the disease had progressed since the systemic chemotherapy. Samples consisted of either fresh-frozen tumor specimens or paraffin-embedded material. Exons 18 to 21 were amplified by polymerase chain reaction and analyzed by direct sequencing to detect somatic mutations in the EGFR gene.

Statistical Analysis

Treatment outcomes included response rate, disease control rate, PFS, and OS. Tumor response to EGFR TKI was assessed based on the Response Evaluation Criteria in Solid Tumors 1.1. OS was calculated from the time of EGFR TKI treatment to the date of death resulting from any cause. PFS was defined as the time elapsed between EGFR TKI treatment and disease progression or death from disease progression. If the complete survival time of a patient was unknown or the disease did not progress, patients status was assumed with the last known survival and/or contact date.

Response and disease control rates were calculated using McNemar's test. PFS and OS were estimated using the Kaplan–Meier method. Differences between the groups were compared using the Stratified Cox regression model. Baseline characteristics were compared between the groups by chi-square and Fisher's exact tests (when there were fewer than 5 expected counts in the contingency table). We also used McNemar's test to assess the relationship between the EGFR TKI group and each of the potentially influential factors, except for matching variables. Cox regression analysis was used for univariate and multivariate analyses to identify

significant prognostic factors for survival in all patients treated with EGFR TKI. Tests were two-sided, and p values less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Two hundred twenty-eight NSCLC patients harboring EGFR mutation who had been treated with gefitinib were identified in our institution between August 2007 and December 2011. The number of patients who received erlotinib treatment was less (n = 147) mostly likely due to different approval time for the drugs in Korea (gefitinib in 2003 versus erlotinib in 2006). By using computed random number tables for the matching selection process, 131 pairs were matched with four variables: sex, smoking status, ECOG PS, and EGFR mutation. Ten matched pairs were excluded because of a double mutant in EGFR (exon 19 deletion with missense mutation in exon 20) in one pair and previous exposure to EGFR TKI in nine pairs. As a result, 121 pairs were included in the final analysis.

The median age of all patients was 58 years (range, 30–84) and 26% were 65 years of age or older. Baseline characteristics of matched pairs of patients according to four variables (sex, smoking history, ECOG PS, and EGFR mutation) are shown in Table 1. The two groups were comparable with respect to demographic and disease characteristics. Most patients had adenocarcinoma (98.3%), good ECOG PS (0–1) (90.9%), and more than half of patients (63.6%) never smoked. Approximately 70% of patients were found to have exon 19 deletion in the EGFR gene. Of the 242, 63 (26%) received EGFR TKIs as first-line treatments, whereas the remaining 179 (74%) received at least one prior cytotoxic chemotherapy before receiving EGFR TKIs. Because gefitinib and erlotinib were approved in Korea for the first-line therapy in 2010 and 2011, respectively, the proportion of patients treated with more than one systemic chemotherapy before EGFR TKI treatment was higher in the erlotinib group (p = 0.001). The most common sites of metastasis in both groups at the time of EGFR TKI treatment were lung, followed by bone, the central venous system, pleural effusion, and the intra-abdominal region.

TABLE 1. Baseline Characteristics of 121 Matched Pairs of Patients Treated with Gefitinib and Erlotinib

Characteristics	Total (N = 242)	Gefitinib Group (N = 121) (%)	Erlotinib Group (N = 121) (%)	p
Age				
Median (range)		58 (29–85)	58 (30–84)	
≥65	64	32 (26.4)	32 (26.4)	NA
<65	178	89 (73.6)	89 (73.6)	
Sex				
Men	106	53 (43.8)	53 (43.8)	NA
Women	136	68 (56.2)	68 (56.2)	
ECOG PS				
0–1	220	110 (90.9)	110 (90.9)	NA
≥2	22	11 (9.1)	11 (9.1)	
EGFR mutation				
Exon 19 deletion	170	85 (70.2)	85 (70.2)	NA
L858R mutation	72	36 (29.8)	36 (29.8)	
Histology				
Adenocarcinoma	236	119 (98.3)	117 (96.7)	0.408
Nonadenocarcinoma	6	2 (1.7)	4 (3.3)	
No. of prior systemic chemotherapy				
0	63	43 (35.5)	20 (16.5)	0.001
1	147	65 (53.7)	82 (67.8)	
≥2	32	13 (10.7)	19 (15.7)	
Smoking				
Never	154	77 (63.6)	77 (63.6)	NA
Current or ever	88	44 (36.4)	44 (36.4)	
Stage of disease				
IIIB	3	1 (0.8)	2 (1.7)	NA
IV	178	90 (74.4)	88 (72.7)	
Recurred	61	30 (24.8)	31 (25.6)	
Metastasized region				
CNS	70	33 (27.7)	37 (30.6)	0.628
Lung to lung	99	46 (38.0)	53 (49.5)	0.36
Pleural effusion	73	39 (32.2)	34 (28.1)	0.484
Intra-abdominal	24	11 (9.1)	13 (10.7)	0.667
Bone	83	46 (38.0)	37 (30.8)	0.241

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NA, not applicable; CNS, central nervous system.

Efficacy and Clinical Outcomes of EGFR TKIs

The median number of cycles of EGFR TKI treatment was 12.7 (range, 0–41.6; 95% confidence interval [CI], 12.2–15.7) in the gefitinib group and 10.8 (range, 0–38.0; 95% CI, 10.9–14.2) in the erlotinib group. The overall response rate was 76.9% in the gefitinib group and 74.4% in the erlotinib group (p = 0.575), with no complete response in either group. The median PFS from EGFR TKI treatment in the gefitinib and erlotinib group was 11.7 months (95% CI, 9.4–13.9) and 9.6 months (95% CI 8.1–11.1), respectively (Fig. 1). Although there was a favorable trend in PFS for the gefitinib group compared with the erlotinib group, it did not reach statistical significance by exploratory analysis (p = 0.056). PFS was analyzed in the two groups of patients with respect to various clinicopathologic characteristics. Univariate and multivariate analyses revealed that ECOG PS of 2 or more, nonadenocarcinoma histology, presence of central nervous system (CNS) metastasis, and intra-abdominal metastasis were independent risk factors associated with poor PFS (Table 2). Here, we defined intra-abdominal metastasis as liver and/or adrenal gland, intra-abdominal lymph nodes, kidney, pancreas metastasis. Among 24 patients with intra-abdominal metastasis, the number of patients with liver metastasis was 15 and adrenal gland metastasis was found in 10 patients. Intra-abdominal lymph nodes, kidney, or pancreas metastasis was found in a few cases, thus we included them as intra-abdominal metastasis category. And a previously reported study also demonstrated that the presence of intra-abdominal metastasis

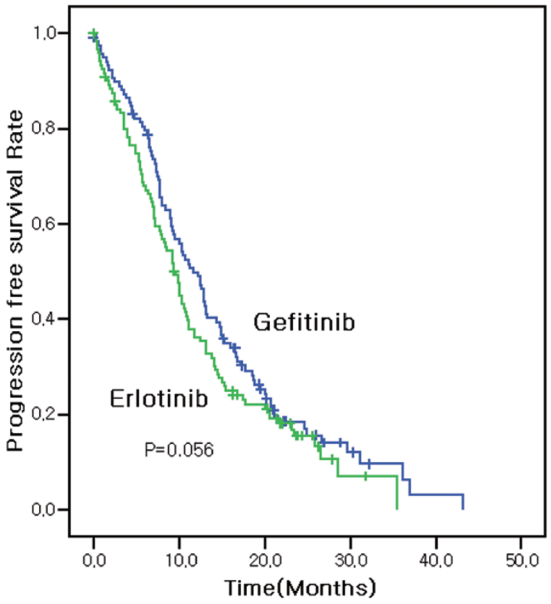

FIGURE 1. Kaplan–Meier plots suggesting progression-free survival within the treatment groups.

was correlated with poor prognosis in NSCLC patients treated with erlotinib as salvage therapy.[14]

In univariate analysis, patients treated with EGFR TKI as first-line treatment seemed to have a longer PFS than those with prior cytotoxic chemotherapy before EGFR TKI treatment. However, longer PFS trend associated with first-line EGFR TKI treatment was diminished in then multivariate analysis (hazard ratio, 1.32; 95% CI 0.92–1.88; $p = 0.135$).

First-Line EGFR TKIs

For subgroup analysis, 63 patients (26%) treated with first-line EGFR TKIs were analyzed with regard to response rate, PFS, and OS in both groups. The response rates in the gefitinib- and erlotinib-treated groups were 76.7% and 90.0%, respectively ($p = 0.431$). There was no significant difference between the two treatment groups in median PFS (11.7 months; 95% CI, 6.7–16.7 versus 14.5 months; 95% CI, 8.7–20.4) ($p = 0.507$) (Fig. 2). The median OS was 24.5 months (95% CI, 8.6–40.4) in the gefitinib group, whereas in the erlotinib group, the median OS had not been reached at the time of the analysis. Using univariate and multivariate analyses for PFS in patient subgroups, smoking ($p = 0.009$) and the presence of CNS metastasis ($p = 0.002$) were found to be independent predictors for poor PFS.

Safety and Dose Adjustment of EGFR TKIs

EGFR TKI treatment was generally well tolerated, and only a small number of patients required dose adjustment. Twenty-two patients treated with erlotinib required dose reduction from 150 to 100 mg/day, whereas one patient with gefitinib needed dose reduction from 250 mg once a day to 250 mg every other day due to grade 3/4 skin rash and diarrhea. Neither interstitial lung disease (ILD)-like events nor toxic death was observed in either group.

DISCUSSION

In the present matched-pair case-control study, the clinical effectiveness of gefitinib and erlotinib was similar in selected patients with advanced/metastatic or recurrent NSCLC harboring activating EGFR mutation. Brain metastasis is a well-known important prognostic factor for all NSCLC as also shown in our study (Table 2). However, in this study, EGFR TKIs were treated as first-line or second- or higher-line of therapy; therefore, most of the patients were not screened for the presence of brain metastasis by brain magnetic resonance imaging at the time of EGFR TKI treatment. Therefore, the four matching variables (sex, smoking history, ECOG PS, and type of EGFR mutation) which are considered as generally acceptable variables were selected in this study.

The response rates and disease control rates in the gefitinib- and erlotinib-treated groups in this study were 76.9% versus 74.4% ($p = 0.575$) and 90.1% versus 86.8% ($p = 0.305$), respectively, which are consistent with previous studies.[5–7,9] The response rates and disease control rates of erlotinib were reported to be up to 82% and 96%, respectively, in patients with NSCLC with EGFR mutations,[9] and the response rate of gefitinib ranged from 70% to 80%[5–7] in EGFR-mutated NSCLC patients. A previously reported prospective phase II study conducted at our institution also demonstrated[12] that both gefitinib and erlotinib showed similar antitumor activity as second-line treatment for clinically selected patients without known EGFR mutation status.

Until now, comparative studies on gefitinib and erlotinib have not been investigated in NSCLC patients positive for EGFR mutations. In an Iressa Pan-Asia Study (IPASS) study, a subgroup analysis of patients with EGFR mutations demonstrated that the PFS of patients treated with first-line gefitinib was 10.7 months compared with 6 months for those treated with chemotherapy.[5] The PFSs of gefitinib-treated patients in the NEJ002 and WJTOG3405 studies were 10.4 and 9.2 months, respectively.[6,7] Regarding erlotinib, the PFSs of erlotinib-treated patients in OPTIMAL and EURTAC studies were 13.1 and 9.7 months, respectively.[9,10] Indirect comparisons of these two EGFR TKIs resulted in inconsistency with regard to PFS.

Statistically, it is very complicated to adjust various types of chemotherapy and/or periods of use for each chemotherapeutic agent, and this issue is difficult to overcome. Therefore, the primary endpoint of this study for comparing the efficacy of both TKIs is mainly focused on PFS, not on OS. In this study, the median PFS in the gefitinib-treated group was 11.7 months (95% CI, 9.4–13.9) and 9.6 months (95% CI 8.1–11.1) for the erlotinib-treated group. We did not find any statistical difference in PFS between the two groups. In the subgroup analysis of patients treated with EGFR TKIs as a first-line therapy, no significant difference in PFS was noted between the two groups (11.7 months for gefitinib; 95% CI, 6.7–16.7 versus 14.5 months for erlotinib; 95% CI, 8.7–20.4) ($p = 0.507$), suggesting that these two EGFR TKIs have similar effectiveness in terms of PFS. However, due to the small number of first-line EGFR TKI–treated patients (N = 63), the analysis is limited in determining better therapy. Further preplanned and large-scale studies are warranted.

TABLE 2. PFS in NSCLC Patients Treated with EGFR TKI According to Clinical Characteristics

Characteristics	Patient No. (%) Total N = 242	Median PFS (mo)	Univariate *p*	Multivariate HR (95% CI)	Multivariate *p*
Age					
<65	178 (84)	10.4			
≥65	64 (26)	9.9	0.509	0.79 (0.55–1.12)	0.785
Sex					
Women	136 (56)	10.7			
Men	106 (44)	9.1	0.176	0.99 (0.65–1.50)	0.953
ECOG PS					
0–1	220 (91)	10.4			
≥2	22 (9)	7.0	0.007	2.61 (1.53–4.44)	0.001
Smoking					
Never	154 (64)	11.1			
Current or ever	88 (36)	7.8	0.012	1.48 (0.96–2.27)	0.077
EGFR mutation					
Exon 19 deletion	170 (70)	10.6			
L858R mutation	72 (30)	9.2	0.293	1.21 (0.88–1.67)	0.250
Histology					
Adenocarcinoma	236 (98)	10.4			
Nonadenocarcinoma	6 (2)	3.3	0.001	3.62 (1.51–8.69)	0.004
No. of prior systemic chemotherapy					
0	63 (26)	12.9			
≥1	179 (74)	9.9	0.031	1.32 (0.92–1.88)	0.135
Metastasized region					
CNS	70 (29)	9.5	0.069	1.50 (1.10–2.10)	0.020
Lung to lung	99 (41)	10.6	0.632	1.07 (0.78–1.48)	0.677
Pleural effusion	73 (30)	10.7	0.512	1.35 (0.94–1.93)	0.10
Intra-abdominal	24 (10)	6.9	0.101	1.71 (1.03–2.82)	0.037
Bone	83 (34)	10.1	0.279	1.04 (0.75–1.44)	0.797
EGFR TKI					
Gefitinib	121 (50)	11.7			
Erlotinib	121 (50)	9.6	0.139	1.14 (0.85–1.52)	0.386

NSCLC, non–small-cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system.

We also found that the PFS for patients treated with EGFR TKI (either gefitinib or erlotinib) as first-line therapy was 13.1 months (95% CI 8.7–17.5), compared with 10.1 months (95% CI, 8.7–11.5) ($p = 0.082$) for patients who received the treatment as a second- or higher-line of therapy. Previously, Rosell et al. reported that in a group of 217 EGFR-mutant NSCLC patients, PFS was similar for patients receiving first-line (n = 113) (14.0 months; 95% CI, 9.7–18.3) or second-line therapy (n = 104) (13.0 months; 95% CI, 9.7–16.3; $p = 0.62$). Our results are consistent with this previous study, highlighting that EGFR-mutant lung cancer is a distinct class of lung cancer, and EGFR TKIs can induce durable and high responses irrespective of the line of therapy.[15]

Given the retrospective nature of this study, toxicity profiles were not always complete. However, we observed that dose reduction due to adverse events were more frequent in the erlotinib-treated group. This result is in line with a previous study[16] in that the plasma concentration of erlotinib is higher than that of gefitinib in standard dosage. Nevertheless, both drugs were well tolerated, and no treatment-related mortality was found. No occurrence of ILD or an ILD-like event was noted in this cohort, confirming that the incidence rate of ILD in Korean patients is very rare compared with the rate in Japan, where a 3% to 4% incidence rate has been reported.[17]

To the best of our knowledge, this is the first matched-pair case-control study in comparing the effectiveness of gefitinib and erlotinib in EGFR mutation–positive, advanced NSCLC patients. The study however has several limitations. Although four important baseline variables with baseline characteristics were matched between two groups, the number and types of chemotherapy regimens administered before or after treatment were varied and were not accounted for. This difference may have introduced potential bias, which in turn might have affected the study outcomes particularly the PFS and OS. The treatment responsiveness was evaluated by contrast computed tomography scan every two cycles of EGFR

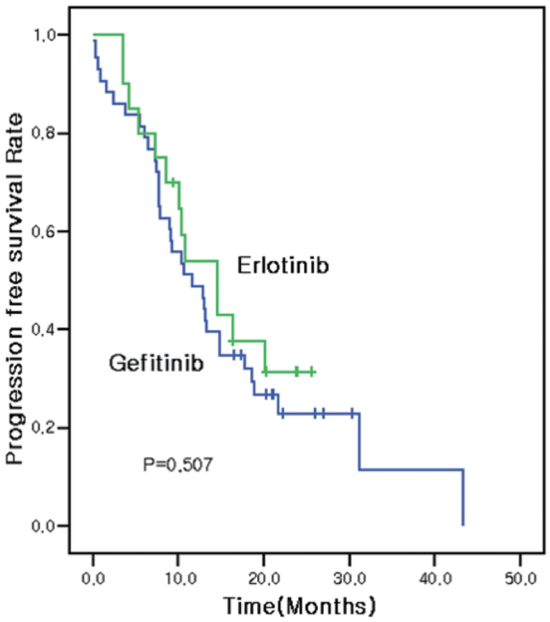

FIGURE 2. Kaplan–Meier plots for subgroup analysis. First-line EGFR TKI treatment. Progression-free survival within the treatment groups. EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

TKI in this study. However, brain magnetic resonance imaging or bone scan was not routinely checked but was performed only when clinically indicated, which may have affected the evaluation of PFS. Moreover, due to the retrospective nature of the study, other unmeasured confounding factors may have been introduced to the treatment groups. Timely and interestingly, a prospective, randomized trial of erlotinib versus gefitinib in advanced NSCLC with exon 21 mutation is currently ongoing,[18] which may address limitations of the current study and further strengthen the growing body of evidence on the treatment efficacy of EGFR TKI.

In conclusion, the present study demonstrated that both gefitinib and erlotinib are well tolerated and have similar effectiveness in NSCLC patients harboring EGFR mutation.

ACKNOWLEDGMENTS

This study was supported in part by Samsung Biomedical Research Institute Grant (GE1-B3-081-1).

REFERENCES

1. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat Rev Cancer* 2010;10:760–774.
2. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol* 2003;21:2237–2246.
3. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527–1537.
4. Chang A, Parikh P, Thongprasert S, et al. Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006;1:847–855.
5. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
6. Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–128.
7. Maemondo M, Inoue A, Kobayashi K, et al; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
9. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735–742.
10. Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group in Collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–246.
11. Kim ST, Lee J, Kim JH, et al. Comparison of gefitinib versus erlotinib in patients with nonsmall cell lung cancer who failed previous chemotherapy. *Cancer* 2010;116:3025–3033.
12. Kim ST, Uhm JE, Lee J, et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012;75:82–88.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
14. Kim ST, Lee J, Sun JM, et al. Prognostic model to predict outcomes in non-small cell lung cancer patients with erlotinib as salvage treatment. *Oncology* 2010;79:78–84.
15. Rosell R, Moran T, Queralt C, et al; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–967.
16. Yoshida T, Yamada K, Azuma K, et al. Comparison of adverse events and efficacy between gefitinib and erlotinib in patients with non-small-cell lung cancer: a retrospective analysis. *Med Oncol* 2013;30:349.
17. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–2556.
18. ClinicalTrials.gov NCT01024413. Available at: http://clinicaltrials.gov/ct2/show/NCT01024413?term=NCT01024413&rank=1. Accessed July 29, 2013.

