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Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy☆

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ABSTRACT

Purpose: Gefitinib and erlotinib are potent EGFR TKIs, with antitumor activity. In this randomized, single-center, non-comparative phase II trial, the efficacy and safety of gefitinib and erlotinib was evaluated as the second-line therapy for advanced non-small cell lung cancer (NSCLC).
Patients and methods: Patients with locally advanced, metastatic stage IIIB/IV NSCLC who failed first-line chemotherapy and had either EGFR mutation or at least two out of three clinical factors associated with higher incidence of EGFR mutations (female, adenocarcinoma histology, and never-smoker) were eligible.
Results: A total of 96 (48 per arm) patients were randomly assigned to gefitinib- or erlotinib-arm, respectively. Baseline characteristics were well-balanced between the two arms. The response rates (RR) were 47.9% in the gefitinib arm and 39.6% in the erlotinib arm. Median PFS was 4.9 months (95% CI, 1.3–8.5) in the gefitinib arm and 3.1 months (95% CI, 0.0–6.4) in the erlotinib arm. The most common grade 3/4 toxicity was skin rash. Exploratory analyses showed that there was no significant difference in RR and PFS in the gefitinib arm compared to the erlotinib arm (RR (%) 47.9 vs. 39.6, $p = 0.269$; median survival (months) 4.9 vs. 3.1, $p = 0.336$). There was no significant difference in QOL between the two arms.
Conclusion: Both gefitinib and erlotinib showed effective activity and tolerable toxicity profiles as second-line treatment for the selected population of NSCLC. We may consider conducting a phase III trial to directly compare the efficacy and toxicity between gefitinib and erlotinib in an enriched patient population.

1. Introduction

Lung cancer is a leading cause of cancer-related deaths worldwide, with a 5-year survival of less than 15%, because most patients are diagnosed with advanced stage disease [1–4]. Several meta-analysis of randomized clinical trials have demonstrated that platinum-based combination chemotherapy is able to induce a modest but significant survival advantage over the best supportive care alone in patients with untreated advanced non-small cell lung cancer (NSCLC) [4–6]. However, most patients with advanced disease will eventually progress after standard platinum-based combination chemotherapy. As the number of patients receiving first-line chemotherapy increases, the need for effective second- or even third-line therapy has been increasing.

Docetaxel and pemetrexed are FDA (Food and Drug Administration)-approved cytotoxic agents for patients who failed first-line therapy [7–9]. Docetaxel improved survival and quality of life compared with best supportive care and compared with an alternative single agent treatment, i.e. vinorelbine or ifosfamide [8]. Pemetrexed showed a similar median survival of 8.3 months as compared with 7.9 months for docetaxel when used as second-line chemotherapy [9]. Although both agents are approved for advanced NSCLC in many countries as monotherapy in the pre-treated setting, there is still much room for improvement in terms of efficacy as well as toxicity. Selective targeting of signaling pathways that contribute to the development and progression of NSCLC has the potential to provide antitumor efficacy with reduced toxicity compared with the conventional cytotoxic agents.

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Representative molecularly targeted agents as a new approach for improving the outcomes in NSCLC are epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) [10–12]. The small molecule EGFR TKIs, gefitinib and erlotinib, have both demonstrated antitumor activity as a single agent in the treatment of patients with advanced NSCLC. Recently, reported phase III studies, INTEREST (IRESSA in NSCLC Trial Evaluating Response and Survial vs. Taxotere) and V-15-32 (comparing gefitinib with docetaxel in pretreated advanced NSCLC), have demonstrated equivalence or similar efficacy in terms of overall survival [13,14]. More recently, ISTANA (IRESSA as Second-line Therapy in Advanced NSCLC-Korea) showed longer PFS and a significantly improved ORR compared with docetaxel in Korean patients [15].

The BR.21 trial demonstrated that erlotinib monotherapy was an effective treatment compared to placebo for patients with advanced NSCLC that had relapsed or recurred after prior chemotherapy and not eligible for further chemotherapy [10]. This is the only placebo-controlled trial that have shown an increase in survival with an EGFR inhibitor in advanced NSCLC. Although in ISEL study gefitinib did not demonstrate improvement of overall survival, preplanned subgroup analyses showed significantly longer survival in the gefitinib groups than the placebo group for never-smokers and patients of Asian origin [16]. Based on the results of several large randomized clinical trials, the EGFR TKIs [10,13,16,17], gefitinib or erlotinib can be considered as valid treatment options for pretreated patients with advanced NSCLC and are registered in many countries for this indication.

Although both agents have similar structures and appear to show similar efficacy, the comparison of gefitinib and erlotinib in terms of efficacy and other clinical outcomes in patients with NSCLC who have failed prior chemotherapy has not been performed yet. In this randomized, single-center, non-comparative phase II trial, the efficacy and safety of gefitinib and erlotinib was evaluated as the second-line therapy for advanced non-small cell lung cancer (NSCLC).

2. Patients and methods

2.1. Eligibility

The main eligibility criteria were histologically confirmed stage IIIB or IV NSCLC including recurrent or metastatic disease after failure of first-line chemotherapy, age ≥18 years, a WHO performance status of 0–2, and a life expectancy ≥12 weeks. Patients were eligible if they either had an activating EGFR mutation or at least two out of three clinical factors associated with higher incidence of EGFR mutations (female, adenocarcinoma histology, and never-smoker). Brain metastasis was permitted if treated at least 4 weeks before entry and clinically stable without steroid treatment for 1 week. Adequate organ function and at least one measurable lesion as RECIST criteria were required. Patients with gastrointestinal (GI) illness that might affect oral absorption or any other serious medical condition that might impair their ability to receive protocol therapy were not eligible. Patients with any previous treatment with EGFR signaling inhibitors and radiation therapy within the preceding 4 weeks were not eligible. This study was approved by the institutional review board at Samsung Medical Center. All patients signed informed consent.

2.2. Study design and treatment plan

This trial was designed as a prospective open-label randomized non-comparative parallel study in a single institute. To improve the balance of prognostic factors between two arms, patients having either an activating EGFR mutation or favorable clinical factors were selected. Patients were randomly assigned in a 1:1 ratio to gefitinib (250 mg orally once daily) or erlotinib (150 mg orally once daily) administered every 4 weeks. Random assignment was performed by an independent provider not involved in this study and was stratified by EGFR mutation versus at least two among three factors: female-gender, adenocarcinoma histology, and never-smoker. The response evaluations were performed at 4 weeks from treatment initiation for the first assessment, and every 8 weeks after then. Treatment continued until progressive disease, unacceptable toxicity, or withdrawal of consent. Patients who progressed from gefitinib or erlotinib were treated at the discretion of each physician. Toxicity was assessed every 28-day cycle using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0. Specific dose reduction management plans were in place for skin toxicity and gastrointestinal toxicity as well as a general dose reduction scheme for any CTC grade 3 or 4 adverse event.

2.3. Quality of life measurement

Health-related quality of life (QOL) was assessed with the use of a cancer-specific, 30-item score questionnaire (QLQ-C30-Version 3.0) developed by the European Organization for Research and Treatment of Cancer (EORTC). The EORTC QLQ-C30 included five functional scales (physical, role, cognitive, emotional, and social), four symptom related scales (fatigue, pain, nausea, and vomiting), one scale to assess global health and general QOL, several questions regarding symptoms that are commonly reported at patients with cancer and additional questions regarding the perceived financial impact of the disease. Patients completed the questionnaire before receiving the first dose of treatment as baseline, on day 1 of each subsequent 28-day cycle, and at the end of the study.

2.4. EGFR mutation testing

Paraffin-embedded tumor tissues were collected for the molecular analysis of EGFR gene mutation. Tumor cell region was microdissected and EGFR gene mutation (exon 18–21) was analyzed by DNA directed sequencing as previously described [18].

2.5. Statistical analysis

The primary objective of this prospective open-label randomized phase II study was to evaluate the response rate for each arm compared to a historical control independently (Fig. 1). Exploratory analyses were also planned to compare clinical outcomes between two arms. The sample size was calculated independently for each arm by use of a two-stage optimal Simon's design to control the type I error at 5% for the null hypothesis that, for each arm, the true response was 10% or below and to have 80% of power if the true response was 25% or higher. For each arm, eighteen patients were to be treated in the first stage. If at least three responses were observed in the first stage, 25 additional patients were to be entered onto the second stage. RR is reported with its exact 95% CI.

Secondary endpoints were disease control rate (DCR) including complete response (CR), partial response (PR) and stable disease (SD), progression free survival (PFS), overall survival (OS), toxicity profile, QOL, and a molecular correlation. PFS was defined as the time from random assignment until the first day of progression or death in the absence of progression. OS was calculated as the time from random assignment until date of death resulting from any cause. If a patient was known not to have died, its survival time was censored at the last known alive date. All patients who received gefitinib or erlotinib over one day were analyzed for RR,

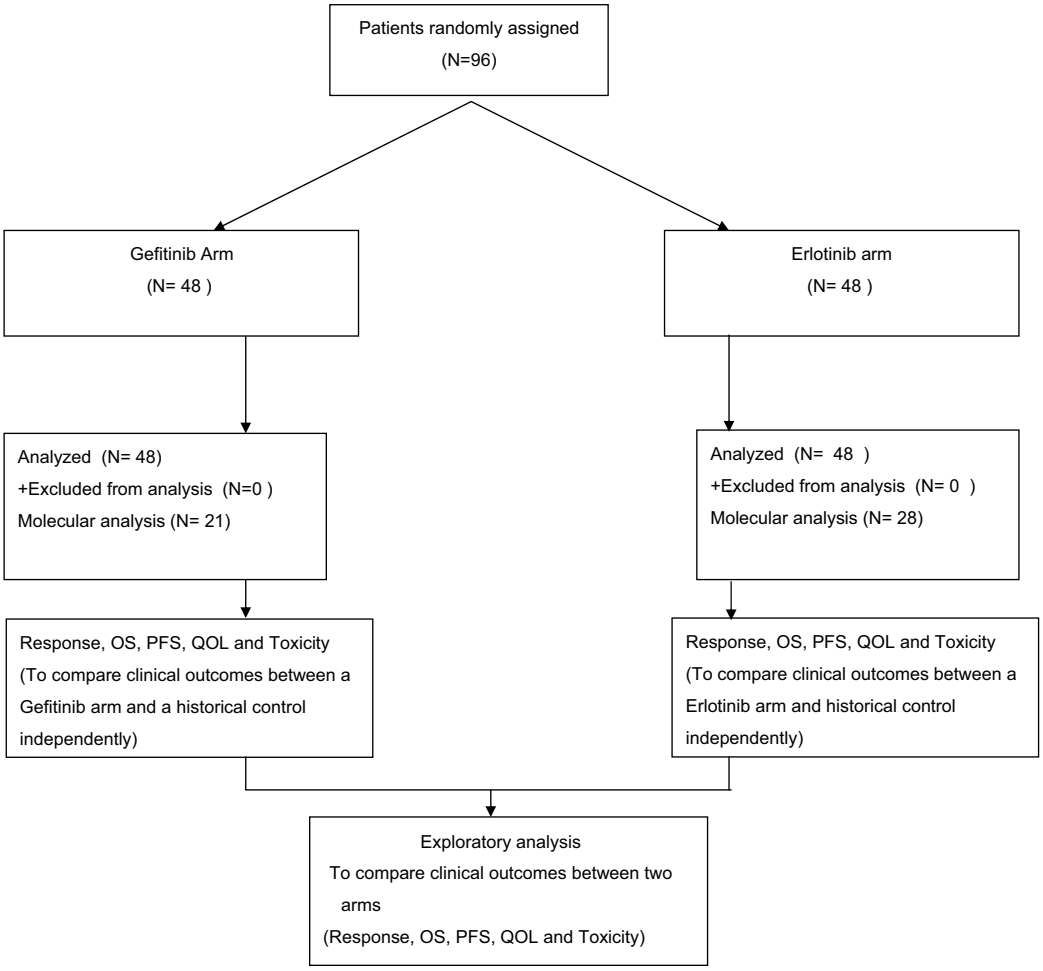

Fig. 1. CONSORT diagram. (+) With the exception of the primary end point (based on the first 48 patients per protocol in each arm) and the molecular analysis (based on 49 patients—gefitinib arm; 21 and erlotinib arm; 28—who had complete molecular information).

PFS, OS and toxicities. Median time to event and 95% CI were estimated from the Kaplan–Meier curves. Cox regression analyses were used to estimate hazard ratios. The exploratory analyses comparing the RR and toxicity rate between two arms were conducted using the chi-squared test. The log-rank test was used to evaluate the difference between two treatment arms with respect to the time to survival endpoints.

Numbers of patients with QOL measurements are summarized at each measurement over 2 years of period. For each QOL subscale, the mean trend is plotted over time for each arm, and the slope of time trend is compared between two treatment arms using generalized estimating equation method with working independence correlation structure [19,20].

3. Results

3.1. Patients characteristics

A total of 96 patients were randomly assigned between August 2007 and October 2008 to the gefitinib ($n = 48$) or erlotinib ($n = 48$) arm. The two arms were well-balanced with respect to demographic and disease characteristics (Table 1). Eighty-five percent of patients had recurrent or stage IV disease, and 16% were 70 years of age or older. Most patients (96.9%) received platinum-based doublet as the first-line chemotherapy. There was no significant difference in prior doublet regimens between patients with gefitinib and with erlotinib.

3.2. Efficacy

The median numbers of treatment cycles was 5 (range, 0.5–24) (6 cycles for gefitinib, range, 0.5–24 and 4 cycles for erlotinib, range 0.5–20). A total of 674 cycles were administered. The overall response rates (ORR) were 47.9% (95% CI, 33.8–62.0%) in the gefitinib arm and 39.6% (95% CI, 25.7–53.4%) in the erlotinib arm (Table 2) with one complete response for each arm. Although there was a favorable trend for RR in the gefitinib arm, it did not reach statistical significance by exploratory analysis. There was no significant difference in RR between adenocarcinoma and non-adenocarcinoma histology in all enrolled patients with EGFR-TKIs. In both the gefitinib and the erlotinib arms, the RR was higher in patients with skin rash of any grade ($N = 65$, RR: 55.4%) compared with patients experiencing no skin rash ($N = 31$, RR: 19.4%) ($p < 0.05$). Median PFS was 4.9 months (95% CI, 1.3 months–8.5 months) in the gefitinib arm and 3.1 months (95% CI, 0.0–6.4 months) in the erlotinib arm. Although there was a favorable trend in PFS for the gefitinib arm compared to the erlotinib arm ($p = 0.336$), it did not reach statistical significance (Fig. 2). For all patients ($N = 96$), univariate analysis revealed that adenocarcinoma histology and EGFR mutation status were significant factors associated with longer PFS. The median PFS for adenocarcinoma and activating EGFR gene mutation was 6.3 months and 12.9 months respectively, compared to 0.9 months for squamous histology and 2.8 months for wild type EGFR, respectively. However, a multivariate analysis revealed that adenocarcinoma histology was the

Table 1
Patients' characteristics.

Characteristics		All patients (n = 96, %)	Gefitinib group (n = 48, %)	Erlotinib group (n = 48, %)
Age (years)	Median	59	60	56
	Range	32–83	37–83	32–81
Sex	Male	14 (14.6)	7 (14.6)	7 (14.6)
	Female	82 (85.4)	41 (85.4)	41 (85.4)
ECOG PS	1	82 (85.4)	41 (85.4)	41 (85.4)
	2	14 (14.6)	14 (14.6)	14 (14.6)
Stage	IIIB	12 (12.5)	7 (14.6)	5 (10.4)
	IV	69 (71.9)	35 (72.9)	34 (70.8)
	Recurred	13 (13.5)	6 (12.5)	7 (14.6)
Histology	Adenocarcinoma	87 (90.6)	44 (91.7)	43 (89.6)
	Squamous cell carcinoma	6 (6.3)	3 (6.3)	3 (6.3)
	Others	3 (3.1)	1 (2.1)	2 (4.1)
Surgery	Lobectomy	14	5	9
	Bilobectomy	1 (1.0)	1 (2.1)	0 (0)
	None	81 (84.3)	42 (87.5)	39 (81.3)
Prior treatment	Neoadjuvant CCRT	2 (2.1)	1 (2.1)	1 (2.1)
	Adjuvant CCRT	3 (3.1)	2 (2.1)	1 (2.1)
	Adjuvant chemotherapy	5 (5.2)	2 (4.2)	3 (6.3)
	Definitive CCRT	3 (3.1)	2 (4.2)	1 (2.1)
	Platinum chemotherapy	93 (96.9)	45 (93.8)	48 (100)
Smoking status	Current or former smoker	6 (6.2)	4 (8.3)	2 (4.2)
	Never smoker	90 (93.7)	44 (91.7)	46 (95.8)

Table 2
Best response rate and disease control rate of treatment groups.

	Gefitinib (n = 48)		Erlotinib (n = 48)	
	N	%	*N*	%
CR	1	2.1	1	2.1
PR	22	45.8	18	37.5
SD	12	25.0	13	27.1
PD	12	25.0	15	31.3
NE	1	2.1	1	2.1
ORR	23	47.9	19	39.6
DCR	35	72.9	32	66.7

Numbers of treatment cycles: median 5 (range, 0.5–24), sum = 674. Gefitinib group: median 6 (range, 0.5–24), sum = 373. Erlotinib group: median 4 (range, 0.5–20), sum = 301.

only independent predictor affecting prolongation of PFS (hazard ratio [HR] = 3.32; 95% CI, 1.44–7.64; p = 0.003). Patients with skin rash of any grade had improved PFS with EGFR-TKIs as compared with patients experiencing no skin rash (median PFS: no reached vs. 13.3 months, p = 0.011). Median OS for both arms has not been reached yet with a median follow-up of 16.3 months (range: 7.4–25.9 months) (Fig. 2).

3.3. Molecular analysis

Of 96 patients, 49 patients (51%) had adequate tissue samples for EGFR mutation test. Among 49 patients, 17 patients (34.6%) had activating EGFR mutations; 14 with exon 19 deletion and 3 with L858R. Of 21 patients in the gefitinib arm, 9 patients (43%) have EGFR mutation compared to 8 of 28 patients (29%) in the erlotinib arm. The RR for gefitinib arm in patients with activating EGFR mutation was 66.7% compared 62.5% in erlotinib arm. The overall RR of patients with EGFR mutation was 76.5% (13/17), compared with 25% (8/32) in patients with wild type EGFR (p = 0.001). The median PFS for EGFR mutation patients was 11.9 months compared only 2.8 months for wild type (p = 0.086) (Fig. 3). Among 47 patients with unknown status of EGFR mutation, the RR and PFS was 37% and 4.3 months for the gefitinib arm and 55% and 3.1 months for erlotinib arm, respectively.

3.4. Quality of life

QOL data were repeatedly measured over a maximum of 2 year period. The number of patients with QOL measurements was monotonically decreasing, but did not show a significant difference between two arms over the study period. The time trend of each

Table 3
Non-hematological treatment-related adverse events.

	Gefitinib Toxicity grade				Erlotinib Toxicity grade			
	1	2	3	Total	1	2	3	Total
Skin rash	25 (52.1)	4 (8.3)	1 (2.1)	30	14 (29.2)	16 (33.3)	5 (10.4)	35
Dry skin	8 (16.7)	0 (0)	–	8 (16.7)	9 (18.8)	1 (2.1)	–	10 (20.9)
Paronychia	4 (8.3)	1 (2.1)	–	5 (10.4)	4 (8.3)	0 (0)	–	4 (8.3)
Diarrhea	8 (16.7)	8 (16.7)	–	16 (33.4)	14 (29.2)	3 (6.3)	–	17 (35.5)
Mucositis	1 (2.1)	2 (4.2)	–	3 (6.3)	4 (8.3)	1 (2.1)	–	5 (10.4)
Fatigue	0 (0)	0 (0)	–	0 (0)	5 (10.4)	3 (3.1)	–	8 (16.7)
Anorexia	7 (14.6)	0 (0)	–	7 (14.6)	4 (8.3)	1 (2.1)	–	5 (10.4)
Nausea	3 (6.3)	–	–	3 (6.3)	2 (4.2)	–	–	2 (4.2)
Vomiting	1 (2.1)	–	–	1 (2.1)	0 (0)	–	–	0 (0)
Alopecia	3 (6.3)	–	–	3 (6.3)	1 (2.1)	–	–	1 (2.1)
Peripheral neuropathy	2 (4.2)	2 (4.2)	–	4 (8.4)	3 (6.3)	0 (0)	–	3 (6.3)
Infection	–	–	1 (2.1)	1 (2.1)	–	–	1 (2.1)	1 (2.1)
ILD	–	–	–	–				

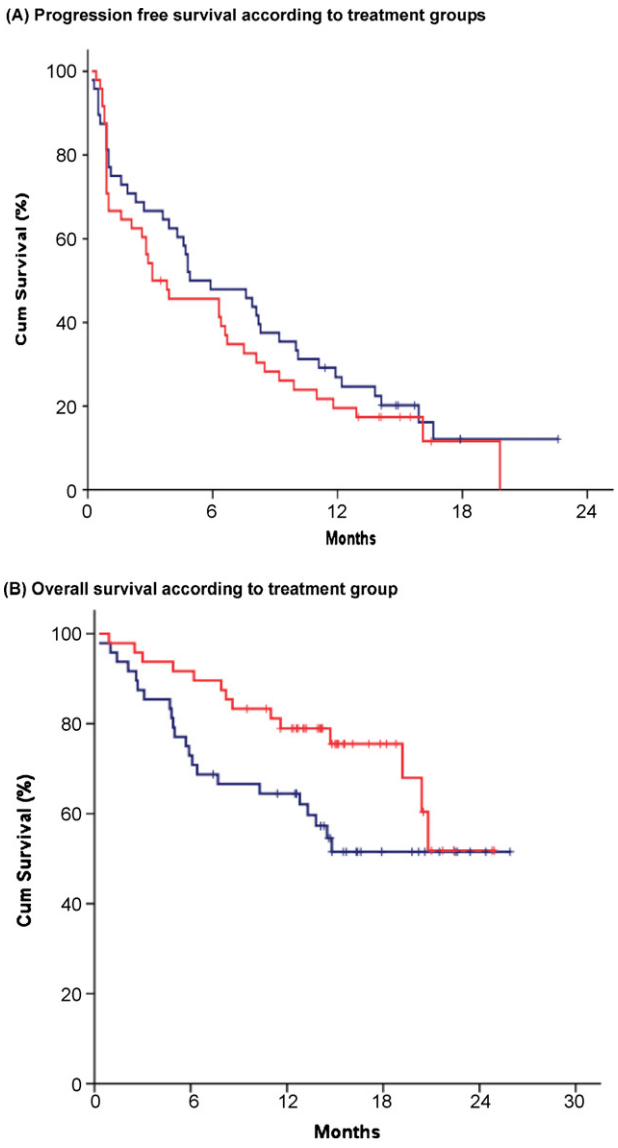

Fig. 2. Kaplan–Meier plots. (A) Progression free survival according to treatment groups. Gefitinib (blue): median 4.9 months (95% CI, 1.3–8.5) and erlotinib (red): median 3.1 months (95% CI, 0.0–6.4). $p = 0.336$. (B) Overall survival according to treatment group. Gefitinib (blue) and erlotinib (red). $p = 0.194$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

QOL subscale, QLQ-C30 and QLQ-L13 seems to have a linear trend, so that the slope is compared between two treatment arms. It is shown that all QOL subscales have similar slopes between two arms except for peripheral neuropathy ($p = 0.0349$).

3.5. Safety

Treatment-related grade 3/4 adverse events in both the gefitinib- and the erlotinib-arm were noted in 4.2% and 12.4% of patients, respectively (Table 3). In the gefitinib arm, grade 3/4 events included skin rash in one patient (2.1%) and infection in one patient (2.1%). In the erlotinib arm, five patients (10.4%) experienced skin rash of grade 3 and one (2.1%) patient had infection of grade 3. The most common grade 3/4 adverse event was skin rash. Although more patients in the erlotinib arm showed grade 3/4 skin rash, the number of patients requiring dose reduction of each arm was similar between two arms (4 in the gefitinib arm and 6 in the

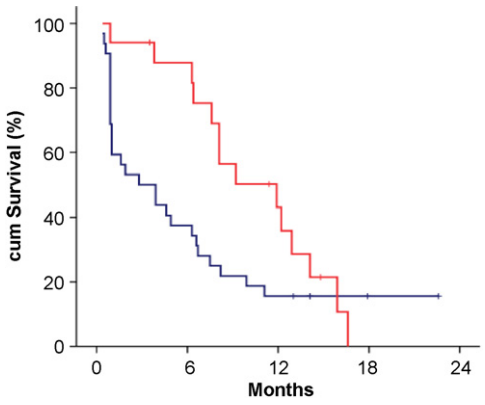

Fig. 3. Progression free survival according EGFR mutation status. Median PFS of EGFR mutant (red): 11.9 months (95% CI, 4.9–19.0) and median PFS of EGFR wild type (blue): 2.8 months (95% CI, 0.0–6.0). p-Value = 0.086. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

erlotinib). Any grades of skin rash were developed in 60–70% of patients in two groups. There were slightly more grade 2–3 skin rash (43.7% vs. 10.4%) in the erlotinib arm. Also, more patients of erlotinib group suffered from fatigue (16.7% vs. 0%). Two patients of gefitinib group and 1 patient of erlotinib group died due to pneumonia. However, there was no interstitial lung disease confirmed.

4. Discussion

The present study is the first prospective randomized phase II trial to evaluate clinical efficacy of gefitinib or erlotinib independently compared to a historical control as the second-line therapy in patients with NSCLC who have failed prior chemotherapy. To minimize heterogeneity of study population and to improve the balance of prognostic factors between two arms, patients with either EGFR mutation or at least two out of three factors, were selected. Given that the enriched population of NSCLC which has been known to show favorable clinical outcomes with EGFR TKIs has been selected, the response rate for both arms was quite high (47.9% vs. 39.6%, respectively). The median PFS was 4.9 months (95% CI, 1.3–8.5 months) in the gefitinib arm and 3.1 months (95% CI, 0.0–6.4 months) in the erlotinib arm, respectively, which are also longer than those from previous studies on unselected patent population. We conducted exploratory analyses to compare clinical outcomes between two arms. Although a favorable trend for RR and PFS was seen in the gefitinib arm, they did not reach statistical significance. The favorable trend of RR and PFS in gefitinib arm may be attributed to the difference in the incidence of EGFR mutation between two arms. However, considering the nature of exploratory analysis and small numbers of patients enrolled, the current study has limitation. Therefore, the direct comparison between gefitinib and erlotinib remains as an evolving question, awaiting prospective studies with large number of patients.

We also found that histology and EGFR mutation status were significant factors associated with PFS. Treatment with EGFR-TKIs has been known to be most effective in females, patients who have never smoked, patients with pulmonary adenocarcinomas and patients of Asian origin [10,16,21]. However, in our analysis, female gender and never smokers were not independent predictors affecting prolongation of PFS. These findings may be explained by the fact that small number of male gender and smokers were enrolled in this study.

Both treatment regimens were well tolerated. Rash and diarrhea were the frequent toxicities seen in both the two arms which

are consistent with previous reports [22–25] Although grade 2–3 skin rash was more frequently observed in the erlotinib arm (43.7% vs. 10.4%) and more patients of the erlotinib group suffered from fatigue (16.7% vs. 0%), these differences in side effects did not affect the difference in dose intensity or QOL between the two arms. Although the number of patients suffering from peripheral neuropathy was similar between the two treatment arms, QOL subscales showed that more patients in the gefitinib arm had felt uncomfortable due to peripheral neuropathy ($p = 0.0349$). Given that peripheral neuropathy is considered as very rare side effect from EGFR TKIs, this symptom is most likely to be the sequela of previous platinum-based chemotherapy.

The correlation between clinical efficacy of EGFR-TKI therapy and the occurrence of skin rash has been reported in other TKI trials [22–24,26]. Lilenbaum et al. [26] the result from a randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced NSCLC and a performance status of 2. An analysis of this study indicated that the PFS was substantially better for patients who developed moderate to severe skin rash on erlotinib compared with those who had mild or no rash.

It is of note that, these correlations were more prominent in the erlotinib arm ($p < 0.001$), however, not retained in the gefitinib arm ($p = 0.109$). Until now, there is not enough evidence to support the significance of skin rash as a surrogate marker for EGFR inhibition and clinical benefit with gefitinib. A phase II study (IDEAL) showed that increasing doses of gefitinib increased the incidence of rash, but not the response rate [11]. Thus, it has been shown that gefitinib accumulates significantly more in tumor tissue than in plasma compared to that of erlotinib [25]. This pharmacokinetic difference might partly explain why it would be possible to achieve maximum clinical efficacy with gefitinib at doses lower than maximal tolerated dose [27].

The molecular analysis was available for 49 (51%) of all patients. Among 49 patients, 17 patients (34.6%) had activating EGFR mutations. Considering the enrollment of enriched population for high probability of activating EGFR mutation [28,29], the frequency of EGFR mutation was relatively low. Moreover, the RR in patients with unknown EGFR mutation status was 44.7% and the DCR was 68.1%, which is high. Also, RR in EGFR mutation negative is 25% which is much higher than expected. In contrast, the biomarker study of IPASS (Iressa Pan-Asia Study) trial for clinically selected NSCLC patients in East Asia demonstrated that 261 of 437 samples (59.7%) were positive for an EGFR mutation [30]. The high response rate in EGFR negative patients in our study can be explained by the use of direct DNA sequencing method which has low sensitivity and requires a high ratio of tumor-to-normal tissue DNA for optimal results [30]. It is of note that there was no significant difference in RR or PFS between the gefitinib and erlotinib arms according to known EGFR mutation status or unknown status, suggesting that both agents have similar efficacy in this population of patients irrespective of EGFR mutation status. Given the small number of patients analyzed for molecular study for each arm, caution should be exercised and a prospective study with large numbers of tumor analysis will be needed.

In summary, this study demonstrated that both gefitinib and erlotinib showed effective anti-tumor activity and tolerable toxicity profiles as second-line treatment for selected population of NSCLC. Further study with inclusion of both gefitinib and erlotinib in a properly conducted and powered phase III trial in an enriched patient population that would directly compare their efficacy and toxicity is warranted.

Conflicts of interest

The authors declared no conflicts of interest.

Contributors

Seung Tae Kim, Ji Eun Uhm, and Myung-Ju Ahn wrote the report, which was approved by all authors. Keunchil Park, Sin-Ho Jung and Myung-Ju Ahn reviewed and modified this report. Seung Tae Kim, Ji Eun Uhm, Insuk Sohn, Seon Woo Kim, Sin-Ho Jung and Myung-Ju Ahn analyzed and interpreted the data. Jeeyun Lee, Jong-mu Sun, Seon Woo Kim, Sin-Ho Jung, Yeon Hee Park, Jin Seok Ahn, Keunchil Park, and Myung-Ju Ahn were responsible for the conception and design of this study. Seung Tae Kim, Ji Eun Uhm, Jeeyun Lee, Jong-mu Sun, Yeon Hee Park, Jin Seok Ahn, Keunchil Park, and Myung-Ju Ahn collected and assembled the data.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.lungcan.2011.05.022.

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