Erlotinib Monotherapy for Stage IIIB/IV Non-small Cell Lung Cancer

A Multicenter Trial by the Korean Cancer Study Group

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Background: Erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY) is an oral, epidermal growth factor receptor tyrosine kinase inhibitor that has antitumor activity and good tolerability in non-small cell lung cancer (NSCLC). In particular, higher response rates have been reported in Asian patients than in Western patients. The aim of this study conducted by the Korean Cancer Study Group was to evaluate the efficacy and tolerability of erlotinib monotherapy as a palliative treatment for advanced NSCLC patients in Korea.

Patients and Methods: Patients with histologically or cytologically confirmed stage IIIB or IV NSCLC including recurrent or metastatic disease, with performance status from 0 to 3, were eligible either if they had received any anticancer treatment except epidermal growth factor receptor inhibitors or if they were unsuitable for chemotherapy because of poor performance status. Enrolled patients were treated with oral erlotinib at a dose of 150 mg daily until disease progression or development of intolerable toxicity.

Results: A total of 120 patients were enrolled between January 2005 and May 2006. Forty-four patients (36.7%) were female and 72 patients were current or former smoker. Fifty percent of patients had received one prior palliative chemotherapy regimens and 34.2% had two or more prior palliative regimens. The overall tumor response rate was 24.2% (95% confidence interval [CI], 16.8–32.8%) with 4 complete responses and 25 partial responses, and the disease control rate was 56.7%. The favorable clinical variables for tumor response were female ($P = 0.001$), never smokers ($P = 0.041$), and adenocarcinoma ($P = 0.001$). The most common adverse event was skin rash (78% of which grade 3 or 4 skin rash occurred in 13.3% of the patients). With a median follow-up of 23.6 months, the median time to progression was 2.7 months (95% CI, 2.2–3.2), and the median overall survival was 12.9 months (95% CI, 6.9–18.8). By multivariate analysis, female and development of skin rash were significantly associated with longer time to progression and overall survival.

Conclusion: Erlotinib monotherapy showed significant antitumor activity and an acceptable tolerability profile as a palliative treatment in advanced NSCLC patients in Korea, especially in females, never smokers, and patients with adenocarcinoma histology.

Key Words: Erlotinib, Non-small cell lung cancer, Korean.

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in Korea and in Western countries. Recent advances in understanding of the molecular mechanism of the disease have translated into the launch of molecularly targeted therapy.

Platinum-based combination regimens as a first-line palliative chemotherapy for advanced NSCLC offer a modest survival advantage over best supportive care, but these agents are commonly associated with nephrotoxicity, neurotoxicity, and myelosuppression.[1] Such toxicities may preclude the use of these regimens in elderly patients or those with poor

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performance status (PS), although some data suggest that elderly patients can benefit from platinum-based chemotherapy doublets.[2] On the other hand, response to first-line therapy is generally short lived, and disease progression frequently occurs 4 to 6 months after the treatment is discontinued.[3] Because a great majority of these patients continue to have a good PS, they are candidates for second-line therapy. Although docetaxel, pemetrexed, and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as erlotinib are recommended as salvage chemotherapy for patients with good PS, the effort has been required to determine the effective and well-tolerated antitumor agents for patients who failed to first-line platinum-based chemotherapy.[4–7]

Erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY), an oral human EGFR TKI, was approved by the U.S. Food and Drug Administration in November 2004 and by the European Commission in September 2005 for patients with advanced or metastatic NSCLC who have failed at least one prior chemotherapy regimen. The previous phase III trial (BR.21) of erlotinib monotherapy showed survival benefit for previously treated advanced NSCLC. Of particular interest, exploratory analysis demonstrated favorable response and prolonged survival in Asian patients.[7] Gefitinib, which is another EGFR TKI used for NSCLC, also showed survival benefit in Asian patients.[8–10] In support of this, a recent analysis of 1974 patients indicated that the EGFR TKI response was significantly dependent on ethnicity (Caucasian 10% versus East Asians 33%).[11]

Given the favorable treatment outcome from EGFR TKIs in Asian NSCLC patients, the Korean Cancer Study Group conducted a multicenter prospective study to evaluate the efficacy and tolerability of erlotinib monotherapy as a palliative treatment for advanced NSCLC patients in Korea.

PATIENTS AND METHODS

Eligibility Criteria

Eligibility for the present clinical trial required histologically or cytologically proven stage IIIB (only the cases with malignant pleural effusion or pleural seeding)/IV, advanced or metastatic NSCLC patients who have failed standard treatment, patients who cannot receive other cytotoxic anticancer therapy, or patients who are not medically suitable for systemic chemotherapy. Other inclusion criteria included age 18 years or older with a life expectancy of 3 months or longer; measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST); Eastern Cooperative Oncology Group PS 3 or lower; adequate function of the bone marrow (absolute neutrophil count $\geq 1.5 \times 10^9$/liter, platelet count $\geq 100 \times 10^9$/liter), kidney (serum creatinine $\leq 1.5 \times$ upper normal limit (UNL) or creatinine clearance ≥ 60 ml/min), and liver (total bilirubin $\leq 1.5 \times$ UNL, aspartate transaminase and alanine aminotransferase $< 2 \times$ UNL (or $< 5 \times$ UNL, in case of liver metastasis). Females of childbearing potential had to have a negative pregnancy test. Patients were excluded if they had unstable systemic disease (active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within 1 year, and serious cardiac arrhythmia requiring medication), any other malignancies within 5 years except for adequately treated carcinoma in situ of the cervix, or basal or squamous cell skin cancer. Patients with brain metastases were allowed in the study if there was no evidence of progression in the brain after local treatment and in the absence of corticosteroid treatment. Patients with significant eye disorders were excluded (severe dry eye syndrome, Sjogren syndrome, severe exposure keratinitis, and any other eye disorder likely to increase the risk of corneal epithelial lesions). Signed informed consent was required for all patients. The study was conducted according to the latest version of the Declaration of Helsinki, and the protocol was approved by the independent Ethics Committee and the Review Board from each participating institution.

Treatment and Assessments

Erlotinib 150 mg tablets were given orally daily, in the morning with 200 ml of water, and at least 1 hour before or 2 hours after ingestion of food or medication. Treatment was continued until disease progression, patient refusal, or intolerable toxicity. Dose adjustment, in 50-mg decrements, was done if grade 3 or 4 toxicity was encountered.

Before treatment, all patients underwent a complete medical history and physical examination, chest radiography, chest and upper abdominal computed tomography (CT) scan, and electrocardiogram. A brain CT or magnetic resonance imaging scan and radionuclide bone scan were optionally performed to document the extent of the disease. Laboratory tests included complete blood cell counts with differential counts of white blood cell, liver function tests, serum electrolytes, serum creatinine, blood urea nitrogen, and urinalysis.

The physical examination, laboratory tests, and chest radiography were performed every 4 weeks. Tumor measurements were assessed at first 4th week after treatment and then every 8 weeks using chest and upper abdominal CT scans. Additional assessments with CT scans were performed at next 4th week in cases of response to treatment to confirm tumor response. Response assessment was according to the Response Evaluation Criteria in Solid Tumors (RECIST).[12] A minimum duration of 4 weeks was required to document a response and the best response was recorded for each patient. Drug-induced toxicity was assessed every 4 weeks and was classified in accordance with National Cancer Institute Common Toxicity Criteria, version 2.0. The worst data for each patient across all course of treatment were used in the toxicity analysis.

Statistical Methods

The primary end point of the study was the response rate, and secondary objectives were disease control rate (DCR), time to disease progression, survival, and safety. Efficacy and safety was evaluated from the basis of intent-to-treatment. The association between tumor responses and each of the interest variables was measured using Pearson's χ^2 or Fisher's exact tests. Baseline factors found to be significant by univariate analysis were included in logistic regression multivariate models to identify baseline factors that might independently predict response and disease con-

trol. Statistical significance was defined as $p < 0.05$. Survival and time to progression (TTP) were calculated from day 1 of treatment. Survival curves were constructed using the Kaplan-Meier method, and survival was compared using the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio.

RESULTS

Patient Characteristics

Between January 2005 and May 2006, 120 patients were enrolled from 12 medical centers in Korea. Table 1 summarizes the baseline characteristics of the patients. The median age was 61 years (range, from 33 to 83). Forty-four patients (36.7%) were female. Most patients had a good PS of 0 or 1, but 13 (10.8%) had PS of 2 or 3. Sixteen patients (13.3%) had stage IIIB disease, and 104 (86.7%) had stage IV disease at study entry. Histologically, 74 patients (61.7%) had adenocarcinoma (including 4 bronchioloalveolar carcinomas), 31 (25.8%) squamous cell carcinoma, and 15 other histologic types. Sixty patients (50.0%) had failed one prior chemotherapy regimen, 41 (34.1%) failed to respond to at least two prior regimens, and 19 (15.8%) were treated with erlotinib as first-line therapy. Seventy-two (60.0%) of them were current smokers or ever smokers.

TABLE 1. Patients Characteristics

	n = 120	
Characteristics	**No. of Patients**	**%**
Age (yr)		
Median	61	
Range	33–83	
Sex		
Male	76	63.3
Female	44	36.7
ECOG PS		
0	7	5.8
1	100	83.3
2	10	8.3
3	3	2.5
Stage		
IIIB	16	13.3
IV	104	86.7
Histology		
Adenocarcinoma	74	61.7
Squamous cell carcinoma	31	25.8
Others	15	12.5
Prior chemotherapy		
None	19	15.8
One regimen	60	50.0
Two or more regimens	41	34.2
Smoking status		
Current or former smoker	72	60.0
Never smoker	48	40.0

ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy Response

All enrolled patients received erlotinib monotherapy, but 109 patients were assessable for efficacy and safety. Five patients died before first evaluation because of disease progression, another five patients were not assessable because of patients' refusal for further treatment, and one patient was lost to follow-up. The objective best response rate was 24.2% (29 of 120, 95% confidence interval [CI], 16.5–31.9) with 4 complete responses and 25 partial responses. In addition, 39 patients had stable disease, producing an overall DCR of 56.7% (95% CI, 47.7–65.7). Female, never smokers, and patients with adenocarcinoma were significantly more responsive to erolotinib than male, smokers, and patients with nonadenocarcinoma histology, respectively; and superior DCR was achieved in female and never smokers (Table 2). The type of prior chemotherapeutic regimen did not affect response rate or DCR. The occurrence of skin rash was significantly associated with treatment response to erlotinib ($p = 0.047$). Of note, only 7 patients of 27 patients (25.9%) with no skin rash achieved a response better than stable disease. In contrast, 54.3% (25 of 46) with grade 1 skin rash, 67.7% (21 of 31) with grade 3, and 93.8% (15 of 16) with grade 4 skin rash had response better than stable disease ($p < 0.001$).

In multivariate analyses, female (hazard ratio [HR] = 0.25; 95% CI, 0.07–0.88; $p = 0.031$) was independently associated with a better response rate, whereas female (HR = 0.15; 95% CI, 0.06–0.38; $p < 0.001$) and the presence of skin rash (HR = 0.22; 95% CI, 0.08–0.63; $p = 0.004$) were independently associated with a better DCR. Among the responders, the median duration of response was 11.6 months (range, 2.6–18.2), and the median duration of disease control was 5.8 months in patients with disease controlled (range, 1.6–18.7).

Survival

With a median follow-up duration of 23.6 months (range, 1.2–29.0), the median TTP was 2.7 months (95% CI, 2.2–3.2) and the median overall survival (OS) was 12.9 months (95% CI, 6.9–18.8) (Figure 1). The 1-year TTP and OS rates were 21.7% and 54.3%, respectively.

Univariate analysis showed that female, histology of adenocarcinoma, never smoker, good performance (Eastern Cooperative Oncology Group PS 0 to 1), and the occurrence of skin rash were significant favorable factors for prolonged TTP and OS (Table 4). In multivariate analysis, female and development of skin rash were significantly associated with longer TTP and OS (Table 4). PS 0–1 was one of the good prognostic factors for OS but not correlated with longer TTP. In contrast, age, stage, and the number of prior chemotherapy regimens did not retain statistical significance in multivariate level.

Safety

At least one drug-related adverse event was observed in 106 (86.6%) of patients, but most of them were mild (grade 1 or 2) and reversible with no grade 4 toxicity (Table 3).

Ninety-three patients (77.5%) experienced drug-related skin rash including 16 patients (13%) of grade 3, often in association with other skin-related symptoms, such as popular or pustular rash and pruritus. In patients with grade 3 skin

TABLE 2. Best Response Rate and Disease Control Rate for Erlotinib Monotherapy

	Response Rate			Disease Control Rate		
	n	%	*P*	*n*	%	*P*
Overall rate	29/120	24.2		68/120	56.7	
Age						
<60	18/53	34.0	0.026	33/53	62.3	0.271
≥60	11/67	16.4		35/67	52.2	
Sex						
Female	19/44	43.2	<0.001	37/44	84.1	<0.001
Male	10/76	13.2		31/76	40.8	
ECOG PS						
0–1	27/107	25.2	0.732	61/107	57.0	0.828
2–3	2/13	15.4		7/13	53.8	
Stage						
IIIB	5/11	31.3	0.477	10/16	62.5	0.613
IV	24/104	23.1		58/104	55.8	
Histology						
Adenocarcinoma	25/74	33.8	0.002	47/74	63.5	0.055
Nonadenocarcinoma	4/46	8.7		21/46	45.7	
Smoking status						
Never smoker	16/47	34.0	0.043	35/48	74.5	0.002
Smoker	13/73	17.8		33/72	45.2	
Erlotinib treatment						
1st line	6/19	31.6	0.411	13/19	68.4	0.260
≥2nd line	23/101	22.8		55/101	54.5	
Skin rash						
Yes	26/93	28.0	0.080	61/93	65.6	0.001
No	3/27	11.1		7/27	25.9	

ECOG PS, Eastern Cooperative Oncology Group performance status.

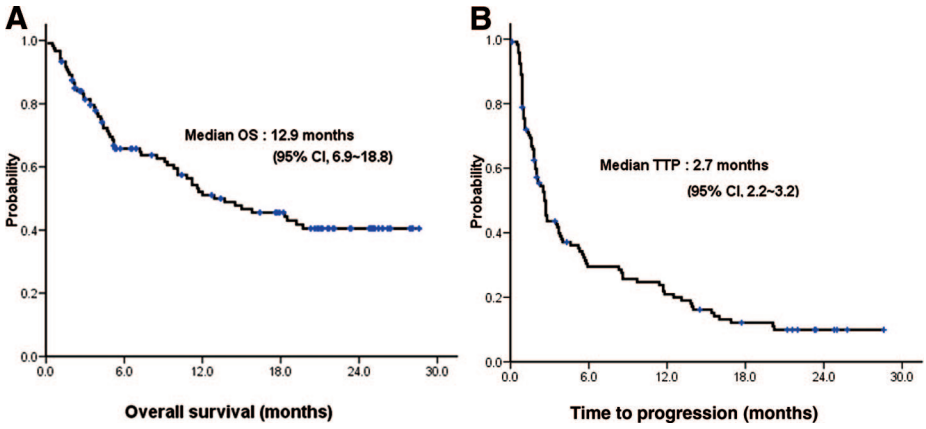

FIGURE 1. *A*, Overall survival. *B*, Overall time to progression.

toxicity, skin rash was improved after temporary interruption of drug or treatment with topical antibiotics and antihistamines. Another commonly reported adverse event was diarrhea (39.2%), which could be controlled if necessary with antidiarrheal agents such as loperamide. No clinically significant deterioration in renal or hepatic function was observed during the trial, even in patients who entered the trial with mild or moderate functional impairment. There were no grade 3 or 4 hematologic toxicities. There was one case of suspicious drug-induced interstitial lung disease that completely resolved upon conservative treatment.

Dose reduction to 100 mg/d of erlotinib was necessary in 22 patients (18.3%) because of grade 3 toxicities. Two patients required short treatment interruptions, because of prolonged grade 3 skin reaction despite dose reduction. There were no drug-related deaths.

DISCUSSION

Erlotinib is the first and the only EGFR TKI to show survival benefit in patients with previously treated advanced NSCLC in a randomized, placebo-controlled trial (BR.21),[7]

TABLE 3. Nonhematological Treatment-Related Adverse Effects

	Toxicity Grade			No. of Patients (%), Total
	1	2	3	
Skin rash	46 (38.3)	31 (25.8)	16 (13.3)	93 (77.5)
Dry skin	37 (30.8)	12 (10.0)	—	49 (40.8)
Diarrhea	33 (27.5)	9 (7.5)	5 (4.2)	47 (39.2)
Myalgia	22 (18.3)	14 (11.7)	3 (2.5)	39 (32.5)
Anorexia	25 (20.8)	10 (8.3)	1 (0.8)	36 (30.0)
Emesis	23 (19.2)	7 (5.8)	—	30 (25.0)
Fatigue	14 (11.7)	8 (6.7)	4 (3.3)	26 (21.7)
Mucositis	15 (12.5)	8 (6.7)	—	23 (19.2)
Paronychia	11 (9.2)	5 (4.2)	—	16 (13.3)
Neuropathy	13 (10.8)	2 (1.7)	—	15 (12.5)
Dyspepsia	7 (5.8)	4 (3.3)	—	11 (9.1)
Alopecia	9 (7.5)	1 (0.8)	—	10 (7.5)
Edema	5 (4.2)	1 (0.8)	1 (0.8)	7 (5.8)
Coneal injury	4 (3.3)	—	1 (0.8)	5 (4.1)
Insomnia	2 (1.7)	2 (1.7)	—	4 (3.3)
Pneumonia	—	—	2 (1.7)	2 (1.7)
ILD	—	1 (0.8)	—	1 (0.8)

There was no grade 4 toxicity.
ILD, Interstitial lung disease.

particularly in Asian patients. In salvage setting, erlotinib has similar response rate to pemetrexed or docetaxel monotherapy as second-line treatment,[6] but spares from premedication or inconvenience from intravenous administration. In this study, 24.2% response rate was observed with erlotinib monotherapy in NSCLC patients, most of who had failed to previous chemotherapy. The response rate achieved in this study (24.2%) is considerably higher than the response rate of 8.9% observed in the BR.21 study.

One of the plausible explanations for the high response rate observed in the study may be the ethnic difference in prevalence of EGFR gene mutations. We have recently conducted EGFR gene mutational analyses in the same cohort of patients and observed a superior response rate (58.3%) in the group with EGFR gene mutations as compared with the group without EGFR mutations (16.2%) ($p < 0.001$).[13] Consistent with previous reports, the incidence of EGFR mutations was higher (26.1%) in Korean patients when compared with the Western countries (<10%). Importantly, we recently showed that patients with EGFR gene mutations or gene amplification showed both better response rate (58.3% versus 16.2%, $p < 0.001$; 41.7% versus 17.3%, $p = 0.012$) and TTP (8.6 versus 2.5 months, $p = 0.003$; 5.8 versus 1.8 months, $p < 0.001$) and overall survival (not reached versus 10.8 months, $p = 0.023$; not reached versus 10.1 months, $p = 0.033$).[13] However, multivariate analysis revealed that EGFR gene mutation was an independent factor associated with prolonged TTP, but not OS, suggesting other clinical parameters such as female, adenocarcinoma histology, or never smokers may be involved in prolongation of OS.

Despite similar progression-free survival (PFS) with BR.21 trial (2.6 months of current data versus 2.2 months of BR.21), the current trial demonstrated longer overall survival (12.9 months versus 6.7 months, respectively).[7] The study population of current study might have had more indolent disease than previous studies, which includes the ethnic differences. Many clinical trials suggested the Asian ethnicity as good prognostic factor of survival as well as the clinicopathologic characteristics such as histology, PS, EGFR mutations, and smoking history.[7,8,14] The subgroup analysis of BR.21 suggested Asian ethnicity as good prognostic factors of erlotinib therapy.[7] Furthermore, better survival outcomes of Asians with EGFR TKIs also demonstrated in gefitinib trials.[8,14] However, it is unclear that Asian origins has benefits from EGFR TKIs but not cytotoxic chemotherapy or benefits from both modalities. Although recent two randomized trials of gefitinib versus docetaxel could not demonstrate superior survivals of gefitinib compared with docetaxel,[15,16] the Japanese trial reported longer overall survival than INTEREST trial, which included about 20% of Asian patients (11.5–14.0 months and 7.6–8.0 months, respectively). A small phase II trial of erlotinib monotherapy for Japanese patients as salvage treatment also demonstrated 14.7 months of median OS.[17] Although the molecular biomarkers and study designs have to be considered, the ethnic diversity as a prognostic factor remains to be solved.

Recently, Lilenbaum et al.[18] reported the result of randomized phase II trial of erlotinib or paclitaxel/carboplatin chemotherapy in patients with PS 2. As the first-line treatment for advanced NSCLC patients with PS 2, erlotinib demonstrated inferior survival outcome than standard chemotherapy of paclitaxel and carboplatin (median OS 6.5 months versus 9.7 months, respectively, $p = 0.018$). PS ≥2 as poor prognostic factor was also suggested in BR.21.[7] As compared with BR.21, current trial included only 10% of patients with PS 2 or 3, whereas BR.21 did over 30%. In addition, the subgroup of PS 2 or 3 in current study achieved only 4.7 months of median OS. Therefore, the good survival outcomes of current study have to be considered with the majority of good PS patients.

Erlotinib was generally well tolerated with the most common ≥grade 3 toxicities being skin rash and diarrhea. The correlation between clinical efficacy of EGFR TKI therapy and the occurrence of skin rash have been reported in other TKI trials.[19–22] Although skin rash may be a potentially predictive factor for clinical efficacy and may be used as a surrogate marker, its predictive capacity needs to be further validated. Patients who developed skin rash were likely to respond to erlotinib with statistical significance ($p = 0.047$). Particularly, more than 90% of the patients (15 of 16) with grade 3 skin rash achieved stable disease or better to erlotinib treatment. Its statistical significance was retained at the multivariate level (HR = 0.22; 95% CI, 0.08–0.63; $p = 0.004$) along with female (HR = 0.25; 95% CI, 0.07–0.88; $p = 0.031$) to predict favorable response. In patients with grade 3 skin toxicity, skin rash was improved after temporary drug interruption. Another commonly encountered adverse event was diarrhea, which was easily controllable with loperamide.

The adverse events of current data were overly similar with previous results of BR.21 with differences in details.[7]

TABLE 4. Prognostic Factors for Survival

	TTP				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	Median (mo)	*P*	HR (95% CI)	*P*	Median (mo)	*P*	HR (95% CI)	*P*
Age								
<60	2.6	0.656	0.816	0.335	18.3	0.293	1.07	0.809
≥60	2.7		(0.54–1.23)		11.7		(0.63–1.82)	
Sex								
Female	8.6	<0.001	0.33	<0.001	NR	<0.001	0.18	<0.001
Male	1.8		(0.21–0.51)		5.3		(0.09–0.36)	
ECOG PS								
0–1	2.6	0.352	0.52	0.052	15.0	0.005	0.21	<0.001
2–3	2.7		(0.27–1.01)		4.7		(0.11–0.43)	
Stage								
IIIB	3.8	0.301	0.58	0.072	11.7	0.604	1.32	0.489
IV	2.5		(0.32–1.05)		13.7		(0.60–2.93)	
Histology								
Adenocarcinoma	3.9	0.001	0.72	0.177	NR	0.001	0.76	0.329
Others	2.0		(0.45–1.16)		7.2		(0.43–1.33)	
Smoking								
No	5.6	0.002	0.64	0.218	NR	<0.001	0.91	0.833
Yes	1.9		(0.32–1.30)		5.3		(0.36–2.30)	
Erlotinib treatment								
1st line	4.0	0.352	0.68	0.209	19.2	0.465	0.56	0.149
≥2nd line	2.5		(0.37–1.24)		12.0		(0.25–1.23)	
Skin rash								
Yes	2.7	0.003	0.54	0.019	19.2	<0.001	0.35	<0.001
No	1.7		(0.32–0.90)		4.3		(0.20–0.63)	

TTP, time to progression; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval; NR, not reached.

The skin rash ≥grade 3 was 13.3% of this study and 9% of BR.21, whereas the grade 3 anorexia was 0.8% and 6%, respectively. Fatigue ≥grade 3 also reported less in current study than BR.21 (6.7% and 19%). Recent report of erlotinib monotherapy in Japanese patients demonstrated that all study population suffered from any adverse events. However, the adverse events ≥grade 3 seemed to be lower than current study and BR.21 in terms of 3% of skin rash, 5% of diarrhea, and 0% of fatigue.[7,17] In current study, dose reduction needed in 18.3% of patients and dose interruptions occurred in 2% of patients, which were similar dose reduction rate and lower treatment interruption rate of BR.21 (19% and 27%, respectively).[7] Although a phase II study of erlotinib in Japanese population seemed to show lower rates of serious adverse events, they needed more dose modifications including 23% of dose reduction, 48.4% of dose interruptions, and 18% of discontinuation.[17] In comparison with gefitinib, which is another EGFR TKI, previous reports of two phase II trials of gefitinib in Korean patients demonstrated less than 3% of ≥grade 3 skin rashes, anorexia, and diarrhea.[23,24] These findings of Korean population showed consistency with previous gefitinib trials such as IDEAL-1, IDEAL-2, and ISEL.[8,9,14] However, there was no randomized controlled trial of gefitinib and erlotinib. In addition, the heterogeneity of EGFR mutation status of each trial should also be considered. Therefore, it is inconclusive whether gefitinib has more tolerable toxicity profiles than erlotinib.

Three agents are currently approved by the U.S. Food and Drug Administration in the second-line setting: docetaxel, pemetrexed, and erlotinib. Phase III trial comparing standard dose docetaxel every 3 weeks with pemetrexed (500 mg/m^2 every 3 weeks) demonstrated that the two regimens were similar in clinical efficacy with lower rate of hematologic toxicities in pemetrexed alone arm.[6] Although the clinical superiority of erlotinib over docetaxel or pemetrexed has not been proven in phase III trials, erlotinib may be preferred by patient because of no premedication, no alopecia, less physician's office visits, and convenience of oral administration. Given a high response rate in Asian patients, a randomized clinical trial should be conducted to compare pemetrexed or docetaxel to erlotinib as second-line treatment even though two recent trials of docetaxel and gefitinib failed to show survival differences.[15,16] Indeed gefitinib was associated with lower rates of treatment related adverse events including serious adverse events, treatment discontinuation than docetaxel, whereas noninferiority of gefitinib was verified for overall survival (HR = 1.020; 95% CI, 0.905–1.150) in INTEREST trial.[15] Furthermore, the clinical benefit of erlotinib in terms of PFS was recently reported in first-line setting in a phase III randomized study comparing erlotinib to

standard chemotherapy (paclitaxel and carboplatin) in never smokers and Asian population (IPASS trial).[25] Although final results are pending with further survival update, PFS that was primary end points of IPASS trial was superior in erlotinib group, especially positive EGFR mutation status (HR = 0.741 of all patients, $p < 0.0001$ and 0.48 of patients with EGFR mutations, $p < 0.0001$). This study probably provides support for the role EGFR TKI as the first-line treatment in subpopulation of NSCLC patients in selected patients such as never smoker or positive EGFR mutation status.

Although gefitinib was not recommended as second-line treatment, the questions about the efficacy of gefitinib for selected patients such as female, adenocarcinoma, EGFR mutation, and Asian population still remain with debate. Even though gefitinib failed to confirm survival benefit compare with placebo in a large phase III trial (5.6 months for gefitinib and 5.1 months for placebo, $p = 0.087$), East Asian patients achieved longer survivals than other ethnical populations in subgroup analysis (HR = 0.66; $p = 0.010$).[14] The survival benefits of East Asian patients from gefitinib also observed in subset analysis of IDEAL-1.[8,26] The original results of IDEAL-1 demonstrated about 8 months of median OS, which was similar to 6–7months of IDEAL-2, whereas Japanese subset ($n = 102$) achieved 12.0 months of median OS with higher response rates (27.5% versus 10.4%, respectively, $p = 0.0023$).[8,9,26] Even though a Japanese phase III study of gefitinib and docetaxel as second-line treatments (V-15-32 trial) showed no difference of overall survival between two groups, recent presentation of Korean trial (ISTATA trial) suggested the benefit of PFS for gefitinib group than docetaxel group.[16,27] Therefore, gefitinib as second-line treatments for East Asian origin compared with single-agent chemotherapy warrants to further investigation.

In conclusion, this study indicates that erlotinib monotherapy is an effective and well-tolerated regimen for Korean patients with advanced NSCLC in salvage setting. Tumor responses and survival outcomes for erlotinib were comparable or superior to the reported results from previously tried first- or second-line chemotherapy regimens. Therefore, erlotinib monotherapy was verified as the one of salvage treatments for patients with advanced NSCLC in Korea or Asia. This study provides the supplementary evidence for randomized trial compared erlotinib with systemic chemotherapy.

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