Different Efficacies of Erlotinib and Gefitinib in Taiwanese Patients with Advanced Non-small Cell Lung Cancer

A Retrospective Multicenter Study

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Introduction: Epidermal growth factor receptor-tyrosine kinase inhibitors are used as effective first-line and salvage therapy in the treatment of advanced non-small cell lung cancer (NSCLC) patients in East Asia. The objective of this study was to compare the efficacy of gefitinib and erlotinib in Taiwanese patients with advanced NSCLC.

Methods: Clinical data of NSCLC patients treated with gefitinib or erlotinib from January 2004 to December 2008 were collected retrospectively. Five tertiary referral centers in Taiwan participated in the study.

Results: Of the 1122 patients enrolled, 506 (45%) were female, 594 (53%) were never smokers or former light smokers, and 867 (77%) were diagnosed with adenocarcinoma. Epidermal growth factor receptor-tyrosine kinase inhibitors were prescribed as first-line treatment in 465 (41%) patients and as second-line or salvage therapy in 657 patients (59%). The objective response rate was similar between the gefitinib and erlotinib treatment groups, while disease control rate was 58.9 and 65.8% ($p = 0.025$), respectively. Median progression-free survival of gefitinib and erlotinib groups was 3.6 and 4.6 months, respectively ($p = 0.027$). Median overall survival of gefitinib and erlotinib groups was 9.6 and 10.7 months, respectively ($p = 0.013$).

Conclusion: Taiwanese patients with advanced NSCLC treated with erlotinib reported higher disease control rate, longer progression-free survival, and overall survival compared with patients treated with gefitinib.

Key Words: Epidermal growth factor receptor, Tyrosine kinase inhibitors, Non-small cell lung cancer.

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Worldwide, lung cancer is the leading cause of cancer mortality.[1] Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases and is generally diagnosed at an advanced stage (stage IIIB and IV). Although platinum-based combination chemotherapy remains the first-line treatment of choice, median survival with these regimens is only 8 to 10 months.[2] Second-line chemotherapy, such as docetaxel or pemetrexed, has a modest but significant effect on symptom control and survival.[3] Major progress in understanding cancer biology and mechanisms of oncogenesis during the last decade resulted in the development of molecular targets for NSCLC treatments. Inhibition of the epidermal growth factor receptor (EGFR) pathway with tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib provides effective and promising treatment for NSCLC, either first-line or salvage therapy with added advantage of improved tolerability and quality of life against chemotherapy agents.[4–9] It has been demonstrated that a subset of patients (females, never smokers, and adenocarcinoma diagnosis in patients of East Asian origin) achieved a better response to TKIs. A higher prevalence of sensitive activating EGFR mutations (deletion in exon 19 or point mutation of L858R in exon 21) was found in these individuals.[10–12]

Gefitinib and erlotinib were each compared with placebo in phase III randomized trials (ISEL and BR.21, respectively) in which the majority of enrolled patients were Caucasian.[4,5] Different overall survival outcomes of these two drugs compared with placebo were widely debated, although gefitinib demonstrated a significant survival benefit in a subgroup of patients of Asian origin.[6] There are many possible reasons for this difference in survival. One possible reason is that the dose intensity or drug concentrations are higher in patients receiving erlotinib treatment compared with

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gefitinib treatment, because one 150 mg erlotinib tablet is equal to 2.4 to 2.8 tablets of 250 mg gefitinib (150 mg erlotinib is equal to 600–700 mg gefitinib).[13–16] To our knowledge, to date, there is no published prospective trial comparing gefitinib and erlotinib treatment. In this study, we retrospectively evaluated the difference in efficacy between these two agents in Taiwanese patients with advanced NSCLC treated at five institutions. The aim of the study was to identify clinical predictors to assist physicians in selecting gefitinib or erlotinib treatment.

PATIENTS AND METHODS

Patients

Between January 2004 and December 2008, patients who received gefitinib 250 mg daily or erlotinib 150 mg daily with assessable disease were enrolled into this retrospective study conducted at five tertiary referral centers in Taiwan. Medical charts, imaging reports, and images to evaluate treatment response were retrospectively reviewed at each center. Clinical characteristics, including patients' age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor cytohistologic type, stage, smoking history, present EGFR-TKI therapy, body surface area (BSA), best response to prior chemotherapy, and refractory to prior chemotherapy or not (defined as recurrent or progressive disease while receiving or within 90 days of last dose of chemotherapy), were recorded.[4] Smoking history was classified as nonsmokers (patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of less than 10 pack-years of smoking). The Iressa Pan-Asia Study population (IPASS population nonsmokers or former light smokers with adenocarcinoma) was also identified.[8] The date of initial diagnosis, date of starting treatment, time to disease progression, and date of death or last follow-up were also recorded.

Efficacy Evaluation

Baseline assessments were performed within 3 weeks before EGFR-TKI treatment. Chest computed tomography scan (including liver and adrenal glands) was performed within 3 weeks before starting EGFR-TKI treatment, every 2 to 3 months thereafter, or when confirmation of treatment response or disease progression was required. Treatment response evaluation was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) group criteria.[17] Time to disease progression was calculated from the date of administration of the first dose of EGFR-TKI to the date of occurrence of disease progression. Overall survival was calculated from the starting date of EGFR-TKI to the date of death. In patients for whom there were no disease progression at the time of the last follow-up visit, time to disease progression was censored at the last time point. Date for patients who were alive was censored as of the date of the last follow-up visit. This study was approved by the Joint Institutional Review Board in Taiwan (09-S-014).

Statistical Analysis

All categorical variables were analyzed with χ^2 tests. Two-sided *t*-tests were conducted for continuous variables when comparing between the two treatment groups. The objective response rate (complete response + partial response) and the disease control rate (complete response + partial response + stable disease) were compared between the two treatment groups. Median progression-free survival and overall survival was estimated by using the Kaplan-Meier method with log-rank test. Hazard ratios in the overall population and in patient subsets were calculated using the Cox proportional hazards model. All p values were two sided, and a value of $p < 0.05$ was considered to be statistically

TABLE 1. Baseline Characteristics of Patients

Variables	No. of Patient (n = 1122)	Treatment Group, N (%)		p^a
		Gefitinib (n = 715)	Erlotinib (n = 407)	
Age (yr)				<0.001
<70	658	449 (62.8)	209 (51.4)	
≥70	464	266 (37.2)	198 (48.6)	
Gender				<0.001
Male	616	337 (47.1)	279 (68.6)	
Female	506	378 (52.9)	128 (31.4)	
Smoking history				<0.001
Never or light ex-smoker	594	448 (62.7)	146 (35.9)	
Other	528	267 (37.3)	261 (64.1)	
Performance status				NS
0–1	642	413 (57.8)	229 (56.3)	
≥2	480	302 (42.2)	178 (43.7)	
Histology				<0.001
Adenocarcinoma	867	621 (86.9)	246 (60.4)	
Other	255	94 (13.1)	161 (39.6)	
Tumor stage				NS
IIIB	223	142 (19.9)	91 (22.4)	
IV	889	573 (80.1)	316 (77.6)	
Received EGFR-TKI as				NS
First line	465	309 (43.2)	156 (38.3)	
Salvage	657	406 (56.8)	251 (61.7)	
IPASS population				<0.001
Yes	529	410 (57.3)	119 (29.2)	
No	593	305 (42.7)	288 (70.8)	
BSA[b]				<0.001
≤1.64	585	406 (56.8)	179 (44.0)	
>1.64	537	309 (43.2)	228 (56.0)	
Best response to prior chemotherapy[c]				NS
CR + PR	121	78 (24.2)	43 (21.5)	
SD + PD	401	244 (75.8)	157 (78.5)	
Refractory to prior chemotherapy[c]				<0.001
Yes	366	207 (64.3)	159 (79.5)	
No	156	115 (35.7)	41 (20.5)	

[a] Pearson two-sided χ^2 test.
[b] Median body surface area of overall population.
[c] n = 522 (gefitinib 322, erlotinib 200); patients treated with EGFR-TKI as first-line treatment and those with missing data were excluded.
NS, not significant; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; BSA, body surface area; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

significant. All statistical analyses were performed by using SPSS software (version 17.0; SPSS Inc., Chicago, IL).

RESULTS

Patients

A total of 1122 patients received EGFR-TKIs treatment (715 gefitinib, 407 erlotinib). Of these patients, 464 (41.4%) were aged 70 years or older, 506 (45.1%) were female, 594 (52.9%) were never or former light smokers, 867 patients (77.3%) were diagnosed with adenocarcinoma, and 529 (47.1%) met the IPASS population criteria. There were 465 patients (41.4%) who received EGFR-TKI as first-line treatment, while the remainder used EGFR-TKI as salvage therapy after failing previous chemotherapy. More elderly patients, females, never or former light smokers, and IPASS population received EGFR-TKIs as first-line treatment, while more patients with PS 2 or higher received EGFR-TKIs as salvage therapy. Baseline demographics of the two treatment groups are shown in Table 1. There were significantly more elderly, males, and smoking patients with nonadenocarcinoma histology in the erlotinib treatment group. This group also contained significantly more patients of the non-IPASS population.

TABLE 2. Comparison of Objective Response Rate and Disease Control Rate Between Treatment Groups

	Response Rate (%)			Control Rate (%)		
	Gefitinib (n = 715)	Erlotinib (n = 407)	p^a	Gefitinib (n = 715)	Erlotinib (n = 407)	p^a
Overall	34.4	35.6	NS	58.9	65.8	0.025
Age (yr)						
<70	35.9	40.2	NS	61.2	66.5	NS
≥70	31.2	30.8	NS	54.9	65.2	0.033
Gender						
Male	23.4	27.6	NS	48.1	59.5	0.006
Female	44.2	53.1	NS	68.5	79.7	0.021
Smoking history						
Never or light ex-smoker	44.6	53.4	NS	69.9	78.1	NS
Other	17.2	25.7	0.02	40.5	59.0	<0.001
Histology						
Adenocarcinoma	38.5	43.9	NS	64.3	72.8	0.02
Other	7.4	23	0.003	23.4	55.3	<0.001
ECOG PS						
0–1	28.6	33.2	NS	71.4	73.8	NS
≥2	18.9	31.5	0.002	41.7	55.6	0.004
Stage at diagnosis						
IIIB	26.1	25.3	NS	26.1	25.3	NS
IV	36.5	38.6	NS	36.5	38.6	NS
Received EGFR-TKI as						
First line	38.4	39.8	NS	59.9	69.9	0.044
Salvage	31.5	33.1	NS	58.1	63.3	NS
IPASS population						
Yes	47.3	54.6	NS	73.2	79.8	NS
No	17.1	27.8	0.003	39.7	60.1	0.001
BSA[b]						
≤1.64	39.2	43.0	NS	61.8	72.1	0.032
>1.64	28.2	29.8	NS	55.2	61.0	NS
Best Response to prior chemotherapy[c]						
CR + PR	39.7	30.2	NS	62.8	58.1	NS
SD + PD	26.6	31.8	NS	53.3	61.8	NS
Refractory to prior chemotherapy[c]						
Yes	29.0	32.7	NS	51.2	59.7	NS
No	31.3	26.8	NS	63.5	65.9	NS

[a] Pearson two-sided χ^2 test.
[b] Median body surface area of overall population.
[c] n = 522 (gefitinib 322, erlotinib 200); patients treated with EGFR-TKI as first-line treatment and those with missing data were excluded.
NS, not significant; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IPASS, Iressa Pan-Asia Study; BSA, body surface area; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The majority of female patients were nonsmokers, and the majority of male patients were smokers. Male patients had larger BSA compared with female patients (median, 1.71 versus 1.55 m^2, $p < 0.001$). BSA in the erlotinib group was larger than the BSA in the gefitinib group (median, 1.67 versus 1.62 m^2, $p < 0.001$). PS, tumor stage, line of TKI treatment, and best response to prior chemotherapy were balanced between the two treatment groups.

Treatment Response

Objective response rate to EGFR-TKI was similar between gefitinib and erlotinib treatment groups (34.4 versus 35.6%, $p = 0.728$; Table 2). Erlotinib was statistically superior to gefitinib in terms of disease control rate (58.9 versus 65.8%, $p = 0.025$; Table 2). When analyzing subgroups of patients, the response rate was statistically higher with erlotinib treatment in current or former nonlight smokers, patients with nonadenocarcinoma, poor PS (ECOG PS ≥2), and patients from the non-IPASS population (Table 2). Disease control rate was statistically greater with erlotinib treatment in both male and female elderly patients, current or former nonlight smokers, regardless of histology type, PS ≥2, BSA ≤1.64, and non-IPASS population (Table 2).

Progression-Free Survival

Progression-free survival was longer in the erlotinib group compared with the gefitinib group (median, 4.6 versus 3.6 months; hazard ratio: 0.87; 95% confidence interval [CI]: 0.76–0.98; $p = 0.027$) in the entire study population based on the unadjusted analysis (Figure 1). Similar results were obtained from supportive Cox regression analysis adjusted for covariates, including gender, performance status, IPASS or non-IPASS population, and BSA. Among the patients' characteristics, performance status of 2 or higher and non-IPASS population coincide with shorter progression-free survival than their contraries, independent of which TKI was used (Table 3). On the other hand, progression-free survival was not influenced by the patient's age, gender, tumor stage, line of TKI treatment, and BSA. Noteworthy, erlotinib reached longer progression-free survival in both IPASS (median, 7.2 versus 5.1 months; $p < 0.001$) and non-IPASS populations (3.6 versus 2.0 months; $p = 0.002$) (Figure 2).

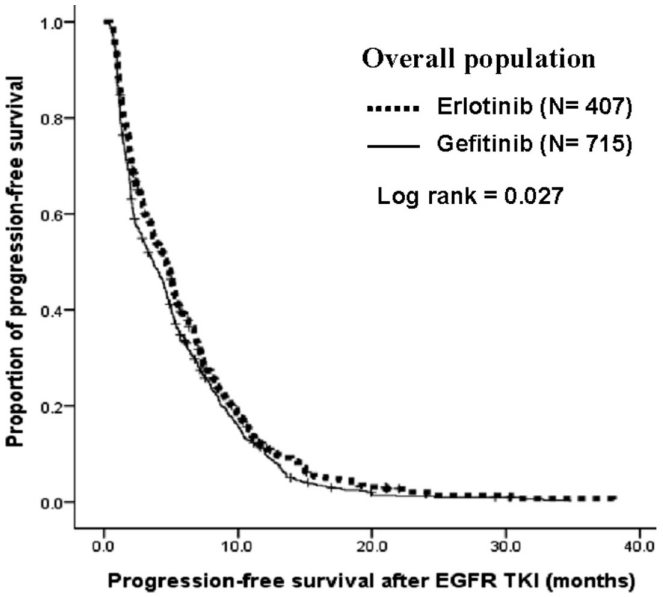

FIGURE 1. Kaplan-Meier analysis of progression-free survival after the start of EGFR-TKIs. Erlotinib treatment was associated with a longer progression-free survival compared with gefitinib treatment (median, 4.6 versus 3.6 months, $p = 0.027$).

TABLE 3. Progression-Free Survival Based on Clinical Characteristics

Factor (No. of Patient)	Median PFS (mo)	Univariate Analysis		Multivariate Analysis	
		HR	P^a	HR	P^b
Treatment group		1.151	0.027	1.265	0.016
Gefitinib ($n = 715$)	3.6				
Erlotinib ($n = 497$)	4.6				
Age		1.012	0.702		
≥70 yr ($n = 464$)	3.5				
<70 yr ($n = 658$)	4.4				
Gender		1.163	<0.001	1.232	0.113
Male ($n = 616$)	2.8				
Female ($n = 506$)	5.1				
Performance status (ECOG)		0.729	<0.001	0.489	<0.001
0–1 ($n = 642$)	5.4				
≥2 ($n = 480$)	2.1				
IPASS population		0.792	<0.001	0.725	0.009
Yes ($n = 529$)	5.5				
No ($n = 593$)	2.3				
Tumor stage		1.046	0.237		
IIIB ($n = 233$)	3.1				
IV ($n = 889$)	4.4				
Received TKI as		0.956	0.741		
First line ($n = 465$)	4.3				
Salvage ($n = 657$)	3.8				
BSA[c]		0.934	0.025	0.912	0.361
≤1.64 ($n = 585$)	4.6				
>1.64 ($n = 537$)	3.5				

[a] Kaplan-Meier analysis by log-rank test.
[b] Cox regression.
[c] Median body surface area of overall population.
ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; BSA, body surface area; IPASS, Iressa Pan-Asia Study.

Overall Survival

Overall survival was longer in the erlotinib group compared with the gefitinib group (median, 10.7 versus 9.6 months; hazard ratio: 0.84; 95% CI: 0.73–0.96; $p = 0.013$) in the entire study population based on the unadjusted analysis (Figure 3). Similar results were obtained from supportive Cox regression analysis adjusted for covariates, including gender, performance status, IPASS or non-IPASS population, and line of TKI treatment. Among the patients' characteristics, PS of 2 or higher and non-IPASS population coincide with

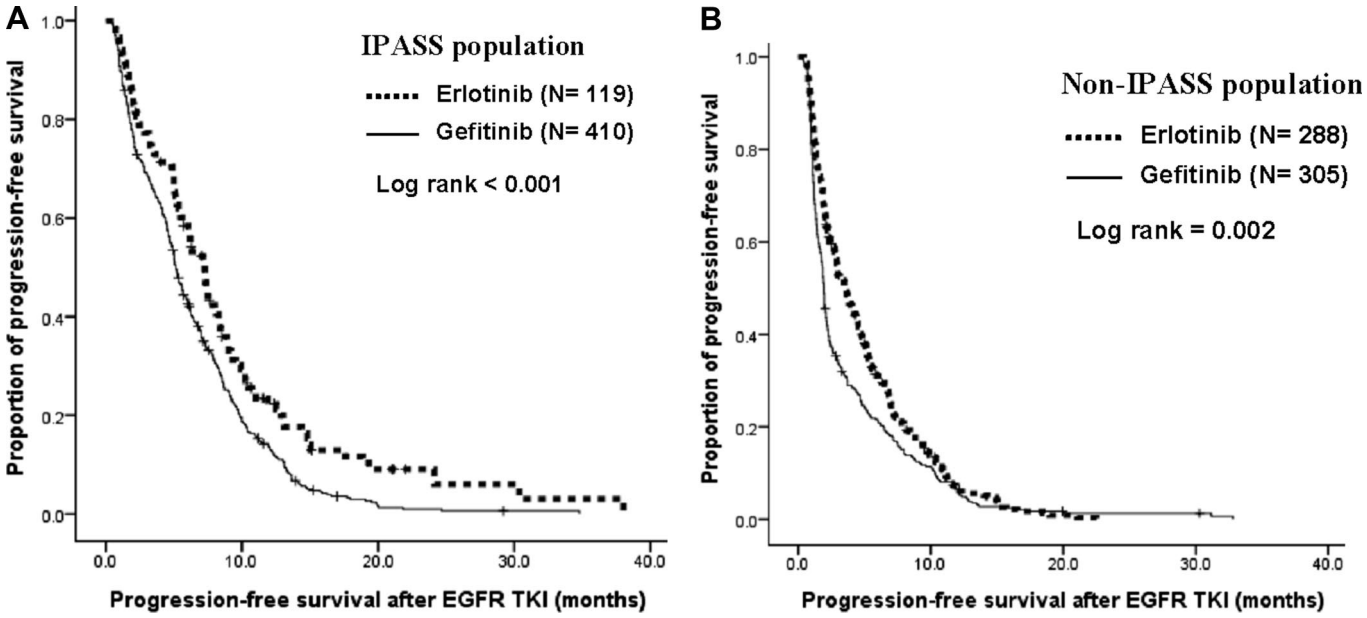

FIGURE 2. Kaplan-Meier analysis of progression-free survival after the start of EGFR-TKIs in IPASS population (*A*) and non-IPASS population (*B*). Erlotinib treatment resulted in longer progression-free survival in both the IPASS (median, 7.2 versus 5.1 months, $p < 0.001$) and non-IPASS populations (median, 3.6 versus 2 months, $p = 0.002$).

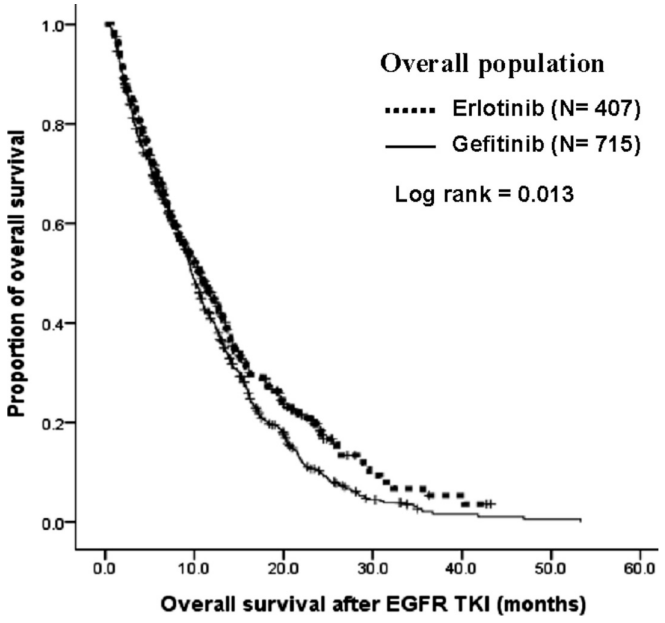

FIGURE 3. Kaplan-Meier analysis of overall survival after the start of EGFR-TKIs. Erlotinib treatment was associated with a longer overall survival compared with gefitinib treatment (median, 10.7 versus 9.6 months, $p = 0.013$).

shorter overall survival than their contraries, independent of which TKI was used (Table 4). On the other hand, overall survival was not influenced by the patient's age, gender, tumor stage, line of TKI treatment, and BSA.

The timing of two agents became commercially available in Taiwan was different, gefitinib in August 2003 and erlotinib in March 2006. To eliminate the potential effects of the difference in its availability, patients ($N = 816$) who started EGFR-TKIs treatment after March 2006, when the both agents were commercially available in Taiwan, were analyzed. There were significantly more patients with unfavorable clinical predictors for EGFR-TKI response (males, smokers, and nonadenocarcinoma histology) in the erlotinib treatment group. Consistent with the overall population, erlotinib ($N = 376$) reached longer progression-free survival and overall survival than gefitinib ($N = 440$). Median progression-free survival of gefitinib and erlotinib groups were 4.0 and 4.9 months, respectively ($p = 0.035$). Median overall survival of gefitinib and erlotinib groups were 10.0 and 11.1 months, respectively ($p = 0.034$).

IPASS or Non-IPASS Population

In the IPASS population (clinical-enriched tumor EGFR exon 19 or 21 mutated patients), there was no significant difference between the two treatments in terms of response rate and disease control rate, irrespective of gender or BSA groups. Progression-free survival was longer with erlotinib compared with gefitinib in females and both BSA groups of the IPASS population (Table 5). In the non-IPASS population, disease control rate was statistically higher and progression-free survival was longer with erlotinib than with gefitinib irrespective of gender or BSA groups. In females and patients in the lower BSA group, the response rate was statistically higher with erlotinib (Table 5).

DISCUSSION

Treatment with one of the EGFR-TKIs, gefitinib or erlotinib, has become an important option for patients with advanced NSCLC, especially in Asian patients. The tumor EGFR mutation rate is about three times more prevalent in

TABLE 4. Overall Survival Based on Clinical Characteristics

Factor (No. of Patient)	Median OS (mo)	Univariate Analysis HR	Univariate Analysis P^a	Multivariate Analysis HR	Multivariate Analysis P^b
Treatment group		1.196	0.013	1.477	<0.001
Gefitinib (n = 715)	9.6				
Erlotinib (n = 497)	10.7				
Age		1.127	0.075		
≥70 yr (n = 464)	9.2				
<70 yr (n = 658)	10.5				
Gender		1.388	<0.001	1.064	0.468
Male (n = 616)	8.0				
Female (n = 506)	12.2				
Performance status (ECOG)		0.397	<0.001	0.396	<0.001
0–1 (n = 642)	13.4				
≥2 (n = 480)	5.4				
IPASS population		0.626	<0.001	0.626	<0.001
Yes (n = 529)	12.6				
No (n = 593)	7.3				
Tumor stage		0.980	0.810		
IIIB (n = 233)	10.5				
IV (n = 889)	9.9				
Received TKI as		0.841	0.010	0.994	0.928
First line (n = 465)	11.5				
Salvage (n = 657)	9.1				
BSA[c]		0.974	0.690		
≤1.64 (n = 585)	10.3				
>1.64 (n = 537)	9.6				

[a] Kaplan-Meier analysis by log-rank test.
[b] Cox regression.
[c] Median body surface area of overall population.
ECOG, Eastern Cooperative Oncology Group; OS, overall survival; HR, hazard ratio; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; IPASS, Iressa Pan-Asia Study.

Asian patients than Caucasians. An effect on overall survival in genotypically uncharacterized NSCLC patients was observed with erlotinib (BR.21 trial),[5] but not gefitinib (ISEL trial),[4] although the response rates were similar. Several possible explanations were discussed, including the refractory, difficult-to-treat nature of the population in the ISEL study, and suboptimal dosing of gefitinib. Erlotinib was used at its maximum tolerated dose (MTD), whereas gefitinib was used at approximately one-third of its MTD.[13–16] The standard doses of erlotinib and gefitinib are not biologically equivalent. Erlotinib treatment may be more efficacious than gefitinib in wild-type EGFR lung tumors because erlotinib inhibits the activity of wild-type EGFR-TKI in tumor cells at 50% inhibitory concentration of 2 to 20 nmol/L. In contrast, for gefitinib to block wild-type EGFR signaling, several-fold higher drug concentrations are required.[18–21] This result was supported by evidence from patients lacking EGFR mutations who still achieved a benefit from erlotinib after failure of gefitinib treatment.[22] In addition, the survival impact of erlotinib was not confounded significantly by tumor cell EGFR mutation status in a recent molecular analysis of the BR.21 trial.[23] Furthermore, the SATURN trial that tested maintenance erlotinib after chemotherapy showed that progression-free survival and overall survival were prolonged in patients with or without an EGFR mutation.[24] These results indicate that erlotinib therapy is beneficial irrespective of EGFR mutation status. Our results consistently showed better response rate, disease control rate, and longer progression-free survival in current or former nonlight smokers, nonadenocarcinoma histology, and non-IPASS population patients (Table 5). These patients are considered less likely to harbor sensitive activating EGFR mutations.

In our study, more patients with unfavorable clinical predictors for EGFR-TKI response received erlotinib treatment. The most likely reasons were physicians' preference and in Taiwan, the National Health Insurance policy allowed patients with nonadenocarcinoma histology to receive only

TABLE 5. Efficacy Comparison Between Treatment Groups in IPASS and Non-IPASS Populations

IPASS Population	No. of Patient 529	ORR (%) G	ORR (%) E	ORR (%) p^a	DCR (%) G	DCR (%) E	DCR (%) p^a	Median PFS (Months) G	Median PFS (Months) E	Median PFS (Months) p^b
Male	(G 83, E 30)	39.8	50	NS	72.3	73.3	NS	5.1	7.2	0.09
Female	(G 327, E 89)	49.2	56.2	NS	73.4	82	NS	5.2	7.3	0.002
BSA										
≤1.58[c]	(G 221, E 59)	52.5	61	NS	75.1	86.4	NS	5.6	7.3	0.009
>1.58	(G 189, E 60)	41.3	48.3	NS	70.9	73.3	NS	5	7.2	0.009
Non-IPASS Population	**593**	**G**	**E**	***p***	**G**	**E**	***p***	**G**	**E**	***p***
Male	(G 254, E 249)	18.1	24.9	0.08	40.2	57.8	<0.001	2	3	0.021
Female	(G 51, E 39)	11.8	46.2	<0.001	37.3	74.4	0.001	1.9	5	0.007
BSA										
≤1.68[d]	(G 162, E 128)	16.5	28.9	0.003	34.6	58.6	<0.001	2	3.5	0.017
>1.68	(G 143, E 160)	20.3	26.9	0.226	45.5	61.3	0.008	2	3.6	0.052

[a] χ^2 test.
[b] Log-rank test.
[c] Median BSA of IPASS population.
[d] Median BSA of non-IPASS population.
ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; G, gefitinib; E, erlotinib; BSA, body surface area; IPASS, Iressa Pan-Asia Study.

erlotinib reimbursement as salvage EGFR-TKI treatment. Therefore, more patients who were refractory to prior chemotherapy subsequently received erlotinib treatment.

The higher clinical benefits with erlotinib observed in patients with lower BSA and female patients of the non-IPASS population (Table 5) may be due to the relative higher dose intensity of erlotinib compared with gefitinib. The issue of dose intensity as reflected in the differences observed in serum concentrations of erlotinib and gefitinib cannot be overemphasized. The antitumor effects in the central nervous system (CNS) may be different between the two drugs because of incomplete CNS penetration hindered by the blood-brain barrier. Treatment with erlotinib or using an increased dose of gefitinib is proven to be a reasonable strategy to circumvent the EGFR-TKI-sensitive tumor cells that are present in the CNS.[25–27] Based on these results, erlotinib may confer better CNS control compared with gefitinib because of its MTD design.

EGFR mutation pattern rather than mutation status may have implications for the selection of specific EGFR TKI.[28–30] Moreover, it is not known if both drugs are equally active for the most common, classic mutations (in-frame deletions of exon 19 and missence point mutation in exon 21 leading to L858R). The deletion in exon 19 exhibits malignant transforming abilities compared with the exon 21 point mutation (L858R), and this difference may reflect patient survival.[31,32] In a recent Spanish study, patients with exon 19 deletions had a longer PFS and overall survival compared with those carrying L858R mutations when treated with erlotinib.[9] In contrast, recent Japanese trials did not detect any difference.[33,34] On the other hand, Paz-Ares et al. reported a pooled analysis of published studies that evaluated clinical outcomes in patients with EGFR-mutated NSCLC who were treated with chemotherapy or EGFR-TKIs. The results showed that the overall median progression-free survival was 13.2 months with erlotinib, 9.8 months with gefitinib, and 5.9 months with chemotherapy.[35]

Lack of tumor EGFR genotype analysis of our patients may be a limitation of concern. Accurate EGFR genotype analysis of patient groups included in this study would assist to elucidate the true difference between these two similar EGFR-TKIs. The IPASS study confirmed that clinical-enriched patients were approximately 60% EGFR mutation positive.[36] Accordingly, we divided our patients into IPASS or non-IPASS population to clarify the efficacy relationship between these two EGFR-TKIs.

The study has several other limitations. First, this is a retrospective study with inherent potential for bias. Second, toxicity profiles are not reported in this study. It was considered that there may be some differences in the frequency of adverse effects between the two agents because of different dose intensity. Third, use of these two drugs was affected by the National Health Insurance policy in Taiwan. Physicians' preference may also be considered as limitation of the study. Although more patients in the erlotinib group exhibited non-favorable clinical characteristics for EGFR-TKI use, similar response rates and improved disease control rates were achieved compared with the gefitinib group.

In conclusion, erlotinib reached better disease control rates, longer progression-free survival, and overall survival than gefitinib in Taiwanese patients with advanced NSCLC. It is reasonable to use erlotinib in patients with unknown EGFR mutation status to achieve higher dose intensity unless unacceptable toxicities occurred. Further prospective randomized trials based on tumor EGFR genotype to compare gefitinib and erlotinib are needed.

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