Gefitinib Therapy in Patients With Advanced Non-Small Cell Lung Cancer With or Without Testing for Epidermal Growth Factor Receptor (EGFR) Mutations

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Abstract: Gefitinib is effective in treating advanced non-small cell lung cancer (NSCLC), especially in Asian patients in whom the prevalence of epidermal growth factor receptor (EGFR) mutation was high. We analyzed our gefitinib treatment use in patients for advanced NSCLC to study the influence of clinical factors on the treatment outcomes in a tertiary referral medical center in Taiwan. Clinical data and EGFR mutational status of the tumors were collected.

A total of 907 patients received gefitinib for advanced NSCLC: 466 patients (51.4%) underwent testing for EGFR mutations, and the other 441 patients did not. In the 466 patients who were tested for EGFR mutations, 272 (58.4%) had EGFR mutations, and an EGFR mutation was a prominent factor for objective response to gefitinib (67.3% vs. 18.3% in wildtype EGFR, $p < 0.001$). In the 441 patients who did not receive EGFR mutation sequencing, nonsmoker status, female sex, and adenocarcinoma cell type were predictors for better gefitinib response ($p < 0.005$). We found that testing for EGFR mutations was helpful in NSCLC patients in Taiwan to guide the use of gefitinib. In patients with positive activating EGFR mutations, gefitinib efficacy was prominent and significant. Therefore, analysis for EGFR mutation should be advocated. In those patients who have unknown EGFR mutation status, demographic and histopathology characteristics can be relied on to judge the potential efficacy of gefitinib use.

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Abbreviations: CT = computed tomography, EGFR = epidermal growth factor receptor, ISEL = Iressa Survival Evaluation in Lung Cancer, NSCLC = non-small cell lung cancer, PCR = polymerase chain reaction, TK = tyrosine kinase.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related mortality in the world, causing more than one million deaths annually.[18] Most patients with NSCLC are diagnosed at advanced stages (stage IIIb and IV), with an essentially poor prognosis. The standard first-line treatment is platinum-based chemotherapy, which has been documented to improve overall survival and quality of life.[14,19] However, platinum-based chemotherapy also has the disadvantage of toxic effects,[14] and certain patients, such as the elderly, may not be able to tolerate the potential toxicity.[7] Gefitinib (Iressa, AstraZeneca, Wilmington, DE), an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase (TK), has a favorable antitumor effect on NSCLC. In recent clinical studies, gefitinib was reported to be effective in first-, second-, or third-line regimens for patients with advanced NSCLC, with favorable tolerance of drug toxicity.[9,13,32,35]

EGFR, a transmembrane glycoprotein, is involved in cell proliferation, angiogenesis, and resistance to apoptosis. Loss of control of EGFR due to deregulation, amplification, or mutation may result in malignant changes of cells.[15,20] Effective gefitinib responsiveness has been reported to be associated with EGFR mutations.[8,26,29,33] A series of EGFR kinase domain mutations has been discovered in NSCLC, mainly in adenocarcinoma.[10,11,16] The mutations most frequently exist in exons 18–21, which encompass most of the TK binding domain of EGFR.[6] They are substitutions for G719 in the nucleotide-binding loop of exon 18, in-frame deletions within exon 19, in-frame duplication and/or insertion in exon 20, and substitutions for L858 or L861 in the activation loop in exon 21. As reported in the literature, 2 major EGFR mutations are deletions in exon 19 and L858R in exon 21.[1] These 2 mutations are the most well-documented mutations with which patients might have an effective response to gefitinib treatment.[17] EGFR mutations are more frequent in nonsmokers, in females, in adenocarcinoma than other cell types, and in Asian ethnicity compared with other ethnicities.[23] These characteristics of EGFR mutations have been reflected in the effectiveness of gefitinib in recent clinical studies. For example, in the Iressa Survival Evaluation in Lung Cancer (ISEL) study[27] composed of patients of heterogeneous ethnicities, gefitinib was superior than placebo plus supportive care in patients of Asian origin in overall outcome. However, in patients of non-Asian origin, the overall outcomes of gefitinib and placebo plus supportive care were much the same.

In the present study, we retrospectively analyzed the patients who had received gefitinib for advanced NSCLC in a tertiary medical center in Taiwan. The patient group and the proportion of patients who received testing for EGFR mutations were relatively large. We conducted the study to reveal the influence of EGFR mutations and outcomes of gefitinib treatment in Taiwanese patients. (See also the accompanying commentary on this study by A. F. Gazdar, in this issue.[4a])

MATERIALS AND METHODS

Patients

We reviewed all lung cancer patients diagnosed at the National Taiwan University Hospital between January 2004 and August 2008. We identified all patients who received gefitinib for treating stage IIIb or IV NSCLC using the records of the hospital pharmacy department.

We reviewed the patients' clinical data, including demographic information, cancer cell type, smoking status, and imaging studies. Nonsmokers were defined as those who had smoked

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fewer than 100 cigarettes in their lifetime. Date of diagnosis, all chemotherapy received, and responsiveness of chemotherapy were recorded. Lung cancer histology was defined according to the World Health Organization pathology classification.[30] Tumor specimens obtained by either surgical or needle biopsy/aspiration procedures, including primary lung tumors, malignant effusion cell blocks, and other distant metastases, were sequenced for mutational analysis. Written informed consent for the use of tissue in molecular analysis was acquired from patients when tumor specimens were procured. This study was approved by the institutional review board of the National Taiwan University Hospital.

Antitumor Chemotherapy and Evaluation of Effectiveness

The timing and order of different chemotherapy regimens depended on the physicians' discretion. Gefitinib was taken orally at a dosage of 250 mg daily. Baseline assessments were usually performed within 2 weeks before treatment. Chest radiography was routinely performed and assessed every 2–3 weeks to evaluate response after the start of treatment. A chest computed tomography (CT) scan (including liver and adrenal glands) was performed every 2–3 months as routine clinical practice and as needed to confirm the response and progression of disease. Treatment responses were defined as progressive disease, stable disease, partial response, and complete response, according to the criteria of the Response Evaluation Criteria in Solid Tumors (RECIST) group.[28] Patients with complete response or partial response were regarded as responders, and the others as nonresponders, to antitumor therapy. The disease control status included complete response, partial response, and stable disease. Overall survival was measured from the first day of gefitinib treatment until the day of death. Progression-free survival with gefitinib was measured from the first day of gefitinib treatment until the first objective or clinical sign of disease progression.

Mutational Analysis for EGFR

We retrospectively reviewed the EGFR mutation status of the lung cancer specimens. Tumor specimens, including paraffin blocks or frozen tissues of surgical specimens, fine needle biopsies, and pleural effusions, were procured for mutational analysis. These formalin-fixed and paraffin-embedded blocks were retrieved from the department of pathology, National Taiwan University Hospital. Patients tested for EGFR mutations were 1) those who underwent fine needle biopsies or thoracentesis for pleural effusions after July 2004, when consecutive recruitment for EGFR mutations was started at the hospital, 2) those whose resected tumors were retrospectively sequenced, or 3) those who were recruited for retrospective NSCLC studies.[5,24,34] The above patients underwent EGFR testing, and they were not selected by the clinical or histologic characteristics. Some patients of the study population were reported in previously published papers that focused on specific issues, such as EGFR exon 20 mutations.[34] The mutational analysis for EGFR genes has been described previously.[24] Briefly, DNA was derived from the tumors embedded in paraffin blocks using a QIAamp DNA Mini kit (Qiagen, Valencia, CA). The TK domain of the EGFR coding sequence, involving exons 18, 19, 20, and 21, was amplified, and independent polymerase chain reaction (PCR) amplifications were purified and sequenced in an automatic ABI Prism 3700 DNA Analyzer.

The frozen lung cancer tissues were obtained at surgery, immediately snap frozen in liquid nitrogen, and stored until use. Total mRNA was extracted from resected cancer tissue using an RNA extraction kit (RNeasy Mini kit; Qiagen). The 4 exons (exon 18–21) that code for the TK domain of the EGFR gene were amplified with primers and PCR conditions as previously reported.[12,34] Reverse transcription (RT)-PCR amplicons were purified and sequenced.

All sequencing reactions were performed in both forward and reverse directions, using tracings from at least 2 PCRs.

Statistical Analysis

All categorical variables were analyzed with chi-square tests, except where a small size (<5) required the use of the Fisher exact test. Otherwise, the Student t test was conducted for continuous variables for means comparisons between the 2 groups. We also constructed the dichotomized response variable using a logistic regression model. For multivariate analysis, multiple logistic regression using the stepwise method was implemented to select significant variables, which were defined as 0.05 for both the entering and removing effect in the models. Median overall survival and progression-free survival after gefitinib treatment were estimated by the Kaplan-Meier method to assess the time to death or progression. The log-rank test was used to compare cumulative survival in different groups, such as responder vs. nonresponder. All reported p values were 2-sided, and a p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (v. 13.0; SPSS Inc. Chicago, IL).

RESULTS

Patients Receiving Gefitinib for Advanced NSCLC

A total of 951 NSCLC patients received gefitinib treatment between January 2004 and August 2008. We excluded 44

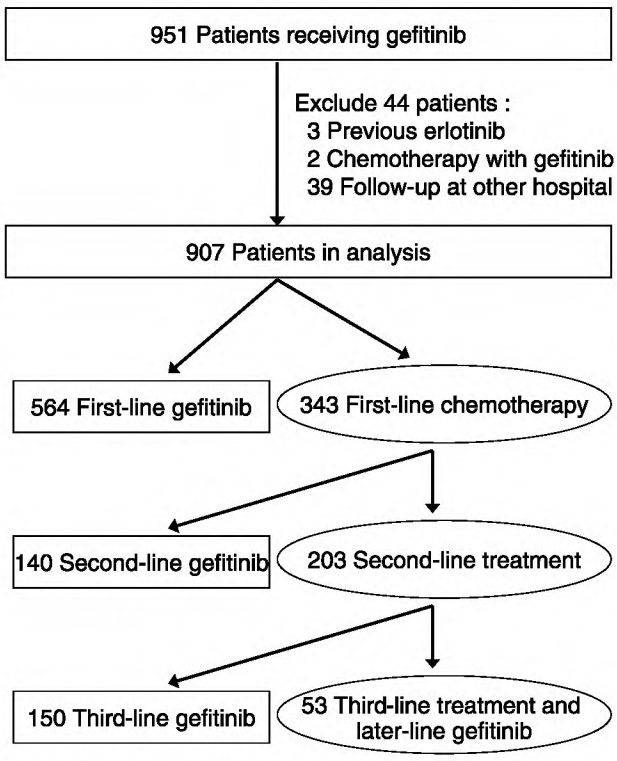

FIGURE 1. Flowchart of treatment algorithm of patients receiving gefitinib for advanced NSCLC.

TABLE 1. Clinical Data of Patients Who Received Gefitinib for Advanced NSCLC

Variable*	Total (n = 907)	With EGFR Testing (n = 466)	Without EGFR Testing (n = 441)	p
Age, mean (range), yr	65 (25–95)	64 (25–91)	65 (29–95)	0.182
Sex (F/M), No.	541/366	301/165	240/201	0.001
Smoking status (nonsmoker/smoker), No.	646/261	359/107	287/154	<0.001
Cell type (adeno/other), No.	829/78	432/34	397/44	0.150
Staging (IIIb/IV), No.	123/784	60/406	63/378	0.535
Performance status (ECOG 0–1/≥2), No.	551/356	305/161	246/195	0.003
Responders, No. (%)	404 (44.5)	218 (46.8)	186 (42.2)	0.163
Disease control, No. (%)	566 (62.4)	302 (64.8)	264 (59.9)	0.125
Gefitinib line, No.				0.319
1st line	564	300	264	
2nd line	140	70	70	
3rd or later line	203	96	107	
Progression-free duration†, median (range), mo	4.9 (0.5–62.0)	5.4 (0.5–62.0)	4.0 (0.5–60.2)	0.689
Survival duration†, median (range), mo	16.2 (0.5–64.8)	16.7 (0.5–64.8)	15.3 (0.5–60.2)	0.279

Abbreviations: adeno = adenocarcinoma, ECOG = Eastern Cooperative Oncology Group.

*See Methods section for definitions.

†After start of gefitinib.

patients: 3 patients who received erlotinib (another TK inhibitor before administration of gefitinib), 2 patients who received other chemotherapy along with gefitinib, and 39 patients who received follow-up at other hospitals after the start of gefitinib treatment in our hospital (Figure 1). Finally, 907 patients who received treatment and follow-up at the National Taiwan University Hospital were included in the analysis of this study. The demographic data of these 907 patients are shown in Table 1.

In the 907 patients, 564 patients received gefitinib as first-line anticancer treatment, 140 patients as second-line, and 203 patients as third-line or later-line treatment. The first 3 lines of treatment for the 907 patients are listed in Table 2. The cutoff date for data collection was July 31, 2009. Ninety-seven patients (10.7%) were still receiving gefitinib for advanced NSCLC at the cutoff date. Four hundred four patients (44.5%) had an objective clinical response (complete response or partial response) to

TABLE 2. First 3 Treatments of Patients Who Received Gefitinib for Advanced NSCLC

Gefitinib Line	1st-Line Treatment (No.)	2nd-Line Treatment (No.)	3rd-Line Treatment (No.)
1st-Line gefitinib (n = 564)	**Gefitinib** (564)	Cisplatin-containing treatment (121)	Cisplatin-containing treatment (27)
		Erlotinib (85)	Erlotinib (5)
		Gemcitabine (35)	Gemcitabine (23)
		Vinorelbine (18)	Vinorelbine (14)
		Taxane (8)	Taxane (44)
		Pemetrexed (8)	Pemetrexed (26)
		Cetuximab-containing treatment (2)	Cetuximab-containing treatment (4)
		No 2nd-line (287)	No 3rd-line (421)
2nd-Line gefitinib (n = 140)	Cisplatin-containing treatment (102)	**Gefitinib** (140)	Cisplatin-containing treatment (12)
	Gemcitabine (25)		Erlotinib (8)
	Vinorelbine (6)		Gemcitabine (10)
	Taxane (7)		Vinorelbine (4)
			Taxane (14)
			Pemetrexed (12)
			No 3rd-line (80)
3rd- or Later-line gefitinib (n = 203)	Cisplatin-containing treatment (161)	Cisplatin-containing treatment (42)	**Gefitinib** (150)
	Gemcitabine (29)	Gemcitabine (29)	Cisplatin-containing treatment (4)
	Vinorelbine (11)	Vinorelbine (8)	Gemcitabine (4)
	Taxane (2)	Taxane (98)	Vinorelbine (8)
		Pemetrexed (26)	Taxane (30)
			Pemetrexed (7)

TABLE 3. Clinical Data of Patients With EGFR Testing Who Received Gefitinib for Advanced NSCLC

Variable*	Mutant EGFR (n = 272)	Wildtype EGFR (n = 194)	p
Age, mean (range), yr	65 (28–91)	64 (25–89)	0.363
Sex (F/M), No.	187/85	114/80	0.026
Smoking status (nonsmoker/smoker), No.	224/48	135/59	0.001
Cell type (adeno/other), No.	260/12	172/22	0.005
Staging (IIIb/IV), No.	40/232	20/174	0.162
Performance status (ECOG 0–1/≥2), No.	169/103	136/58	0.074
Responders, No. (%)	183 (67.3)	35 (18.0)	<0.001
Disease control, No. (%)	228 (83.8)	74 (38.1)	<0.001
Gefitinib line, No.			0.392
1st line	171	129	
2nd line	37	33	
3rd or later line	64	32	
Progression-free duration†, median (range), mo	7.8 (0.5–62.0)	2.0 (0.5–46.7)	<0.001
Survival duration†, median (range), mo	19.4 (1.0–64.8)	12.4 (0.5–49.9)	0.001

Abbreviations: See Table 1.

*See Methods section for definitions.

†After start of gefitinib.

gefitinib. In the total 907 patients, the median progression-free survival was 4.9 months, and overall survival after the start of gefitinib was 16.2 months. The 12-month progression-free survival rate was 18.5%, and the 12-month survival rate was 50.6%.

EGFR Mutations and Treatment Response

In the 907 patients who received gefitinib, 466 patients were analyzed for EGFR mutations, and the other 441 patients were not. The demographic data of the patient groups who did or did not undergo EGFR mutation testing are shown in Table 1. The tissues examined for mutations included 102 surgical specimens, 202 needle biopsies (echo-guided, CT-guided, or bronchoscopic), and 162 cell block preparations of pleural effusion.

In the 466 patients who received testing, 272 (58.4%) had EGFR mutations. In the study population, the mutations were more frequent in nonsmokers than smokers (62.4% vs. 44.9%, p = 0.001), in adenocarcinomas than non-adenocarcinomas (60.2% vs. 35.3%, p = 0.005), and in female patients than in males (62.1% vs. 51.5%, p = 0.026) (Table 3). Age and clinical cancer staging were comparable between patients with mutant EGFR and patients with wildtype EGFR. In the 272 patients with EGFR mutations, 106 patients (39.0%) had deletions in exon 19, 114 patients (41.9%) had mutation L858R, 11 patients (4.0%) had mutations in exon 20, and the other 41 patients (15.1%) had other single or complex EGFR mutations.

EGFR mutations are associated with objective gefitinib efficacy. The gefitinib response rate and disease control rate were 67.3% and 83.8%, respectively, in patients with EGFR mutations, significantly better than in patients with wildtype EGFR (response rate, 18.0% and disease control rate, 38.1%). The good response rate led to a significantly longer progression-free survival and overall survival in patients with mutant EGFR (Table 3) (Figure 2 A and B). Female sex, adenocarcinoma cell

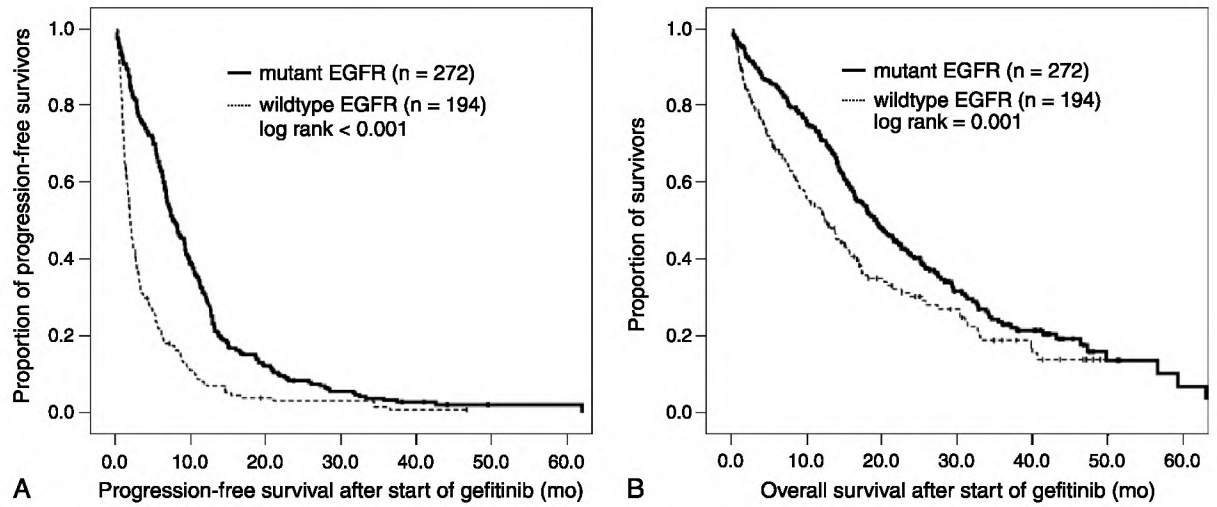

FIGURE 2. Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) after starting gefitinib in patients with mutant or wildtype EGFR.

TABLE 4. Predictive Factors Associated With Clinical Response to Gefitinib in Patients With EGFR Testing

Variable	No. of Patients (n = 466)	Responder (No.)	Response Rate (%)	Univariate Analysis, p	Multivariate Analysis, p*
Sex				0.003†	0.550
Female	301	156	51.8		
Male	165	62	37.6		
Cell type				<0.001‡	0.002
Adenocarcinoma	432	213	49.3		
Other	34	5	14.7		
Smoking status				<0.001†	0.014
Smoker	107	33	30.8		
Nonsmoker	359	185	51.5		
Age, yr				0.990†	
≤65	231	108	46.8		
>65	235	110	46.8		
Clinical staging				0.566†	
Stage IIIb	60	26	43.3		
Stage IV	406	192	47.3		
EGFR status				<0.001†	<0.001
Mutant	272	183	67.3		
Wildtype	194	35	18.0		

*Logistic regression test.
†Chi-square test.
‡Fisher exact test.

type, nonsmoker status, and EGFR mutation were associated with gefitinib objective response in univariate analysis (Table 4). After multivariate analysis by logistic regression, adenocarcinoma cell type ($p = 0.002$), nonsmoker status ($p = 0.014$), and EGFR mutation ($p < 0.001$) were independently associated with the clinical response to gefitinib.

Patients Not Tested for EGFR Mutations

Four hundred forty-one patients did not receive analysis for EGFR mutations, for the following reasons: 128 underwent tissue diagnosis for NSCLC in other hospitals, 276 received tissue diagnosis before consecutive recruitment of tissues for EGFR mutations was started at the hospital, 13 were diagnosed by cytology examination only, and 24 had tissue specimens of inadequate size for EGFR analysis.

Sex, smoking status, and Eastern Cooperative Oncology Group performance were different between patients who underwent testing for EGFR mutation and those who did not (Table 1). Other factors, such as age, histology of cancer, and clinical staging, were similar. The gefitinib response rates of patients who did and did not receive testing for EGFR mutations were not different statistically (46.8% vs. 42.2%, respectively,

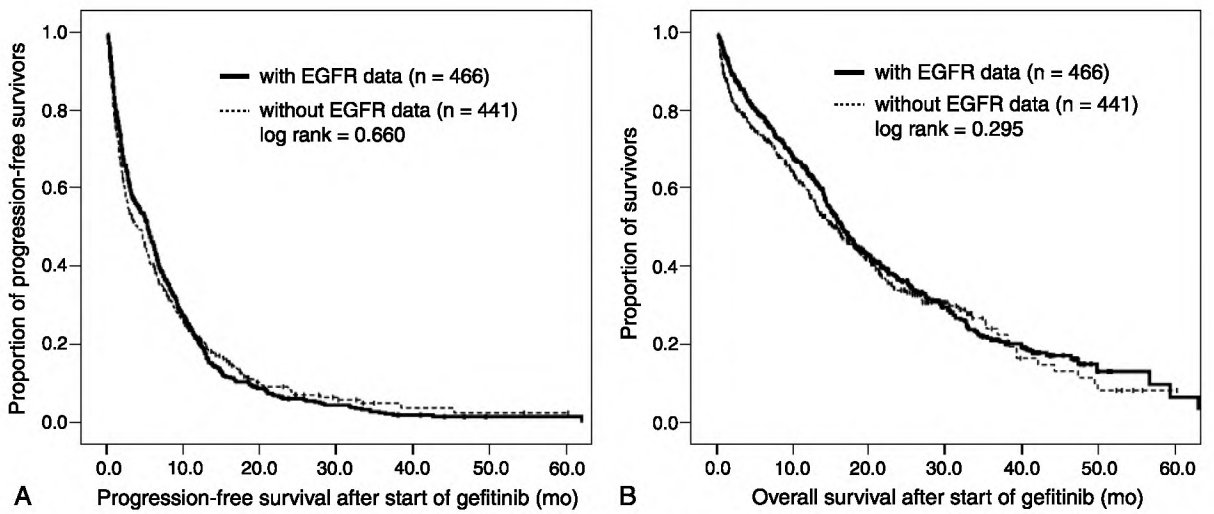

FIGURE 3. Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) after starting gefitinib in patients with or without testing for EGFR mutations.

p = 0.163). In addition, the progression-free survival (5.4 mo vs. 4.0 mo, p = 0.660) and overall survival (16.7 mo vs. 15.3 mo, p = 0.295) of the 2 groups were comparable (Figure 3A and B).

In patients who were not analyzed for EGFR mutations, female sex, adenocarcinoma cell type, and nonsmoker status tended to predict gefitinib response in univariate analysis (Table 5). After multivariate analysis by logistic regression, nonsmoker status (p < 0.001) was independently associated with clinical response to gefitinib. In the group with all 3 good predictors (female sex, adenocarcinoma cell type, and nonsmoker status) (n = 209), the progression-free survival was much better than in the group without any good predictors (n = 21) (6.3 mo vs. 1.4 mo, respectively, p < 0.001). Similarly, the overall survival was much longer in the group with all 3 good predictors compared to the group with none (21.8 mo vs. 2.0 mo, p < 0.001).

Value of EGFR Mutations Beyond the Clinical and Histologic Characteristics

To clarify the additional prediction value that EGFR mutations added to clinical and histologic characteristics, we further analyzed the subgroup of patients who were female, had adenocarcinoma cell type, and were nonsmokers in the group of patients who underwent testing for EGFR mutations. In the total 441 patients who underwent EGFR analysis, 276 patients were in this subgroup. In this subgroup, 178 patients had mutant EGFR, and 98 patients had wildtype EGFR. Gefitinib response rate and progression-free survival was better in the 178 patients with mutant EGFR than in the 98 patients with wildtype EGFR, even though all patients had favorable clinical and histologic predictors (response rate, 69.7% vs. 26.5%, and progression-free survival 7.9 mo vs. 2.5 mo, both p < 0.001). Median overall survival was longer in patients with EGFR mutation than in those with wildtype EGFR, but the difference was not statistically significant (21.6 mo vs. 17.5 mo, p = 0.762).

Furthermore, in the 441 patients who received EGFR testing, 99 patients were male and smokers. There were only 12 patients who were male, smoker, and had non-adenocarcinoma cell type; the number is too small for analysis. In the 99 male and smoking patients, 45 patients had EGFR mutations and 54 patients had wildtype EGFR. In this subgroup, gefitinib response rate (57.8% vs. 5.9%, p < 0.001), progression-free survival (6.0 mo vs. 1.5 mo, p < 0.001), and overall survival (16.4 mo vs. 5.4 mo, p = 0.002) were all better in patients with EGFR mutations than patients with wildtype EGFR.

We also compared patients who had mutant EGFR (n = 272) with patients who did not undergo testing for EGFR mutations (n = 441). Patients with EGFR mutations had more favorable outcomes after gefitinib treatment than patients who did not undergo testing for EGFR mutations, with better response rate (67.3% vs. 42.2%, p < 0.001), progression-free survival (7.8 mo vs. 4.0 mo, p < 0.001), and overall survival (19.4 mo vs. 15.3 mo, p = 0.019).

DISCUSSION

In the current study, we present the results of gefitinib treatment in patients with advanced NSCLC in a tertiary medical center in Taiwan (East Asia). Our analysis included a large population and a high proportion of patients who had EGFR mutation testing. The progression-free survival of the total 907 patients was 4.9 months, and the overall survival was 16.2 months. EGFR mutation was strongly associated with objective response to gefitinib in the patients who were analyzed for EGFR mutations. In the patients who were not analyzed for EGFR mutations, demographic and histopathologic characteristics helped to predict a good clinical response to gefitinib treatment.

Several studies have revealed obvious differences in EGFR mutation rates in NSCLC between patients of Western and Eastern ethnicities. Patients of Eastern ethnicities have been shown to have higher rates of EGFR mutations. In the study by Shigematsu et al,[23] the EGFR mutation rate was only 8% in those of non-Asian ethnicities (mainly American and Australian,

TABLE 5. Predictive Factors Associated With Clinical Response to Gefitinib in Patients Without EGFR Testing

Variable	No. of Patients (n = 441)	Responder (No.)	Response Rate (%)	Univariate Analysis, p	Multivariate Analysis, p ‡*
Sex				<0.001†	0.104
Female	240	133	55.4		
Male	201	53	26.4		
Cell type				0.037‡	0.222
Adenocarcinoma	397	174	43.8		
Other	44	12	27.3		
Smoking status				<0.001†	<0.001
Smoker	154	28	18.2		
Nonsmoker	287	158	55.1		
Age, yr				0.941†	
≤65	203	86	42.4		
>65	238	100	42.0		
Clinical staging				0.503†	
Stage IIIb	63	29	46.0		
Stage IV	378	157	41.5		

*Logistic regression test.
†Chi-square test.
‡Fisher exact test.

n = 158), while 30% of those of Asian ethnicity (mainly Japanese, n = 361) had EGFR mutations. In the study by Cortes-Funes et al,[3] including all Spanish patients (n = 83), the EGFR mutation rate was 12%. In contrast, in a study composed of only Thai patients, EGFR mutations were detected in 35 of 61 patients (57.4%).[25] In the current study population of Taiwanese patients, a large proportion of patients who took gefitinib for advanced NSCLC were analyzed for EGFR mutations, and the mutation rate was 58.4% (272/466).

The obviously different EGFR mutation rates between Asian and non-Asian populations could be the leading cause of different gefitinib efficacy in treating NSCLC. Before the prevalence of analysis for EGFR mutations was high, large-scale clinical studies disclosed the differences of gefitinib response between those of Asian and non-Asian ethnicities. In the ISEL study,[27] the overall survival after gefitinib treatment was 9.5 months in Asian patients (24% of the total study population), while overall survival for the whole study population was 5.6 months. In the INTEREST study[9] comparing gefitinib and docetaxel as second- or third-line regimens, in the gefitinib arm Asian patients had a longer survival than non-Asian patients. These differences are now considered to be the result of different EGFR mutation rates between different ethnicities. The current study is representative of general clinical practice compared to other clinical trials in Asian populations. We found that the response rate to gefitinib, progression-free survival, and overall survival were comparable with the results of Asian populations in these other clinical trials comprising patients of different ethnicity.

The large-scale clinical trial, IPASS, compared gefitinib and standard chemotherapy as first-line treatment for NSCLC.[13] The IPASS trial was composed of only Asian patients (total n = 1196, mainly from China and Japan). Of the 437 patients tested for EGFR mutations, 261 (59.7%) had mutant EGFR. The overall survival rate after first-line gefitinib was 18.6 months. The current study also included a large group of patients; we found a mutation rate of 58.4% (272/466). The patients receiving gefitinib as first-line treatment had a survival rate of 17.3 months (data not shown). From these clinical data, we suggest that Taiwanese patients have NSCLC characteristics and gefitinib treatment results similar to those of patients in the IPASS trial, even though the current study is retrospective and based on general daily practice.

Patients with mutant EGFR have much better treatment outcomes than those with wildtype EGFR, as reported in the current study and in others. Because EGFR status greatly influences the treatment outcome of gefitinib for NSCLC, there is a call for universal analysis for EGFR mutations before treating advanced NSCLC. Through such analysis, physicians can select highly active therapies, and personalized medicine can be achieved.[4] However, universal analysis for EGFR mutations is not in place at present due to technical and financial concerns. Not every patient with advanced NSCLC receives testing, and physicians can only judge possible treatment outcomes and select therapies based on the demographic and histopathology characteristics of the patients. In the current study, the patients who underwent EGFR mutation testing had a progression-free survival and overall survival comparable to those of patients who did not receive testing. For the patients who did not receive testing, factors including female sex, adenocarcinoma cell type, and nonsmoker status tended to predict gefitinib response. In Taiwan, advanced NSCLC patients with these factors can be treated with gefitinib with an expectation of better responses. Moreover, although clinical factors can predict response, our analysis revealed that EGFR status had a more useful predictive value than clinical and histologic characteristics. For example, patients with unfavorable factors, such as male sex and smoking history, can still have a favorable response to gefitinib if they have EGFR mutations. Besides, our analysis also showed that patients with mutant EGFR can have better outcomes than the whole population who did not undergo testing for EGFR mutations. EGFR testing can be performed to guide treatment for NSCLC.

That being said, EGFR mutations do not guarantee good gefitinib efficacy, and about 30% patients with mutant EGFR do not respond to gefitinib. Patients with favorable clinical and histologic factors do not definitely respond to gefitinib, either. On the other hand, some patients with wildtype EGFR do respond to gefitinib. Reasons for these phenomena are still not clear. Some new molecular findings may provide a possible hypothesis for the phenomena, for example MET and EML4-ALK genes. Amplification of MET gene and existence of EML4-ALK oncogene both are associated with poor response to TK inhibitors.[21,22] Other mechanisms for the resistance of TK inhibitors and treatment for the resistance will be the focus of future research, and will no doubt change the course of treatment for NSCLC patients.

The current study has some limitations. First, there are limitations related to the study's retrospective design. The use of gefitinib and the sequence of other chemotherapy depended on the clinical decisions of the physicians caring for the patients. Selection of gefitinib can be influenced. More female patients, patients with adenocarcinoma cell type, and nonsmoking patients received gefitinib, because they probably had EGFR mutations. There may have been bias in patient selection, and this study population does not represent the whole population of NSCLC patients. Second, the study was done in a single tertiary care center. To compensate for this limitation, we compared the gefitinib response rate and median survival of patients in hospitals in other parts of Taiwan. The response rates ranged from 30% to 56%, and median survival ranged from 7.5 months to 16.0 months.[2,31] We found that the gefitinib treatment outcomes in our study are comparable to those in other parts of Taiwan.

In conclusion, a high proportion of NSCLC patients in Taiwan and other Asian areas have favorable treatment outcomes with gefitinib, which can be taken orally and is well tolerated. In the current study of Taiwanese patients, more than half of the patients with advanced NSCLC received EGFR mutation testing. In patients with EGFR mutations, gefitinib efficacy was prominent and significant. Therefore, analysis for EGFR mutations should be advocated. In patients who do not receive EGFR analysis, demographic and histopathology factors can be used to guide the choice of gefitinib treatment.

REFERENCES

1. Chan SK, Gullick WJ, Hill ME. Mutations of the epidermal growth factor receptor in non-small cell lung cancer—search and destroy. *Eur J Cancer.* 2006;42:17–23.
2. Chang JW, Liu HP, Hsieh MH, Fang YF, Hsieh MS, Hsieh JJ, Chiu YT, Tsai HY, Chen YH, Chen YT, Hsu HY, Chen YT, Tsai SF, Chen YR, Hsi BL, Huang SF. Increased epidermal growth factor receptor (EGFR) gene copy number is strongly associated with EGFR mutations and adenocarcinoma in non-small cell lung cancers: a chromogenic in situ hybridization study of 182 patients. *Lung Cancer.* 2008;61:328–339.
3. Cortes-Funes H, Gomez C, Rosell R, Valero P, Garcia-Giron C, Velasco A, Izquierdo A, Diz P, Camps C, Castellanos D, Alberola V, Cardenal F, Gonzalez-Larriba JL, Vieitez JM, Maeztu I, Sanchez JJ, Queralt C, Mayo C, Mendez P, Moran T, Taron M. Epidermal growth

factor receptor activating mutations in Spanish gefitinib-treated non-small-cell lung cancer patients. *Ann Oncol.* 2005;16:1081–1086.

4. Gazdar AF. Personalized medicine and inhibition of EGFR signaling in lung cancer. *N Engl J Med.* 2009;361:1018–1020.

4a. Gazdar AF. Tyrosine kinase inhibitors and Epidermal Growth Factor Receptor (EGFR) mutations in non-small cell lung cancer: to test or not to test? [*Commentary*] *Medicine (Baltimore).* 2011;90:168–170.

5. Gow CH, Chien CR, Chang YL, Chiu YH, Kuo SH, Shih JY, Chang YC, Yu CJ, Yang CH, Yang PC. Radiotherapy in lung adenocarcinoma with brain metastases: effects of activating epidermal growth factor receptor mutations on clinical response. *Clinical Cancer Res.* 2008;14:162–168.

6. Gu D, Scaringe WA, Li K, Saldivar JS, Hill KA, Chen Z, Gonzalez KD, Sommer SS. Database of somatic mutations in EGFR with analyses revealing indel hotspots but no smoking-associated signature. *Hum Mutat.* 2007;28:760–770.

7. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med.* 1999;341:2061–2067.

8. Inoue A, Suzuki T, Fukuhara T, Maemondo M, Kimura Y, Morikawa N, Watanabe H, Saijo Y, Nukiwa T. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. *J Clin Oncol.* 2006;24:3340–3346.

9. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, Li LY, Watkins CL, Sellers MV, Lowe ES, Sun Y, Liao ML, Osterlind K, Reck M, Armour AA, Shepherd FA, Lippman SM, Douillard JY. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet.* 2008;372: 1809–1818.

10. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res.* 2004;64: 8919–8923.

11. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *N Engl J Med.* 2004;350: 2129–2139.

12. Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, Hatooka S, Shinoda M, Takahashi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol.* 2005;23:2513–2520.

13. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361:947–957.

14. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ.* 1995;311:899–909.

15. Olayioye MA, Neve RM, Lane HA, Hynes NE. The erbB signaling network: receptor heterodimerization in development and cancer. *EMBO J.* 2000;19:3159–3167.

16. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science.* 2004;304:1497–1500.

17. Pallis AG, Voutsina A, Kalikaki A, Souglakos J, Briasoulis E, Murray S, Koutsopoulos A, Tripaki M, Stathopoulos E, Mavroudis D, Georgoulias V. 'Classical' but not 'other' mutations of EGFR kinase domain are associated with clinical outcome in gefitinib-treated patients with non-small cell lung cancer. *Br J Cancer.* 2007; 97:1560–1566.

18. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74–108.

19. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr, Olak J, Stover D, Strawn JR, Turrisi AT, Somerfield MR; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol.* 2004;22:330–353.

20. Pinkas-Kramarski R, Soussan L, Waterman H, Levkowitz G, Alroy I, Klapper L, Lavi S, Seger R, Ratzkin BJ, Sela M, Yarden Y. Diversification of Neu differentiation factor and epidermal growth factor signaling by combinatorial receptor interactions. *EMBO J.* 1996;15:2452–2467.

21. Satouchi M, Negoro S, Funada Y, Urata Y, Shimada T, Yoshimura S, Kotani Y, Sakuma T, Watanabe H, Adachi S, Takada Y, Yatabe Y, Mitsudomi T. Predictive factors associated with prolonged survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib. *Br J Cancer.* 2007;96:1191–1196.

22. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, Solomon B, Stubbs H, Admane S, McDermott U, Settleman J, Kobayashi S, Mark EJ, Rodig SJ, Chirieac LR, Kwak EL, Lynch TJ, Iafrate AJ. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol.* 2009;27:4247–4253.

23. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, Fong KM, Lee H, Toyooka S, Shimizu N, Fujisawa T, Feng Z, Roth JA, Herz J, Minna JD, Gazdar AF. Clinical and biological features associated with epidermal growth factor receptor gene mutation in lung cancers. *J Natl Cancer Inst.* 2005;97:339–346.

24. Shih JY, Gow CH, Yu CJ, Yang CH, Chang YL, Tsai MF, Hsu YC, Chen KY, Su WP, Yang PC. Epidermal growth factor receptor mutations in needle biopsy/aspiration samples predict response to gefitinib therapy and survival of patients with advanced nonsmall cell lung cancer. *Int J Cancer.* 2006;118:963–969.

25. Sriuranpong V, Chantranuwat C, Huapai N, et al. High frequency of mutation of epidermal growth factor receptor in lung adenocarcinoma in Thailand. *Cancer Lett.* 2006;239:292–297.

26. Takano T, Ohe Y, Sakamoto H, Tsuta K, Matsuno Y, Tateishi U, Yamamoto S, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Shibata T, Sakiyama T, Yoshida T, Tamura T. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J Clin Oncol.* 2005;23:6829–6837.

27. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K. 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.

28. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92:205–216.

29. Tokumo M, Toyooka S, Kiura K, Shigematsu H, Tomii K, Aoe M, Ichimura K, Tsuda T, Yano M, Tsukuda K, Tabata M, Ueoka H, Tanimoto M, Date H, Gazdar AF, Shimizu N. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. *Clin Cancer Res.* 2005;11: 1167–1173.

30. Travis W, Brambilla E, Muller-Hermelink HK, Harris CC. *Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart.* Lyon: IARC Press; 2004.
31. Wu CH, Fan WC, Chen YM, Chou KT, Shih JF, Tsai CM, Lee YC, Perng RP. Second-line therapy for elderly patients with non-small cell lung cancer who failed previous chemotherapy is as effective as for younger patients. *J Thorac Oncol.* 2010;5:376–379.
32. Wu JY, Shih JY, Yang CH, Chen KY, Ho CC, Yu CJ, Yang PC. Second-line treatments after first-line gefitinib therapy in advanced nonsmall cell lung cancer. *Int J Cancer.* 2010;126:247–255.
33. Wu JY, Yu CJ, Yang CH, Wu SG, Chiu YH, Gow CH, Chang YC, Hsu YC, Wei PF, Shih JY, Yang PC. First- or second-line therapy with gefitinib produces equal survival in non-small cell lung cancer. *Am J Respir Crit Care Med.* 2008;178:847–853.
34. Wu JY, Wu SG, Yang CH, Gow CH, Chang YL, Yu CJ, Shih JY, Yang PC. Lung cancer with epidermal growth factor receptor exon 20 mutations is associated with poor gefitinib treatment response. *Clin Cancer Res.* 2008;14:4877–4882.
35. Yang CH, Yu CJ, Shih JY, Chang YC, Hu FC, Tsai MC, Chen KY, Lin ZZ, Huang CJ, Shun CT, Huang CL, Bean J, Cheng AL, Pao W, Yang PC. Specific EGFR mutations predict treatment outcome of stage III/IV chemonaive NSCLC patients receiving first-line gefitinib monotherapy. *J Clin Oncol.* 2008;26: 2745–2753.