SUPPLEMENTARY MATERIAL

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Materials and Methods
Fig. S1. Further characterization of PC-9 TKI-resistant cell lines.
Fig. S2. Characterization of *EGFR*-mutant TKI-resistant cells.
Fig. S3. Characterization of H3255 TKI-resistant cells.
Fig. S4. Rate of progression in T790M-harboring *EGFR*-mutant lung cancer.
Fig. S5. Derivation of mathematical parameters.
Fig. S6. Continuation of TKI therapy in cell populations with T790M-harboring clones leads to better tumor cell control.
Fig. S7. Toxicity of "gatekeeper" mutations in other cell models.
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RESEARCH ARTICLE Open Access

Clinical responses to EGFR-tyrosine kinase inhibitor retreatment in non-small cell lung cancer patients who benefited from prior effective gefitinib therapy: a retrospective analysis

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Abstract

Background: Gefitinib was the first epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) approved for the treatment of advanced non-small cell lung cancer (NSCLC). Few treatment options are available for NSCLC patients who have responded to gefitinib treatment and demonstrated tumor progression. The present study was conducted to evaluate the efficacy and toxicity of the 2nd EGFR-TKI administration.

Methods: We retrospectively analyzed 11 patients who had obtained a partial response (PR) or stable disease (SD) with gefitinib treatment and were re-treated with EGFR-TKI after failure of the initial gefitinib treatment.

Results: Three patients (27%) were treated with gefitinib as the 2nd EGFR-TKI, and 8 patients (73%) received erlotinib. Only one patient (9%) showed PR, 7 (64%) achieved SD, and 3 (27%) had progressive disease. The disease control rate was 73% (95% CI, 43% - 91%) and the median progression-free survival was 3.4 months (95% CI, 2 - 5.2). The median overall survival from the beginning of the 2nd EGFR-TKI and from diagnosis were 7.3 months (95% CI, 2.7 - 13) and 36.7 months (95% CI, 23.6 - 43.9), respectively. No statistical differences in PFS or OS were observed between gefitinib and erlotinib as the 2nd EGFR-TKI (PFS, P = 0.23 and OS, P = 0.052). The toxicities associated with the 2nd EGFR-TKI were generally acceptable and comparable to those observed for the initial gefitinib therapy.

Conclusions: Our results indicate that a 2nd EGFR-TKI treatment can be an effective treatment option for gefitinib responders.

Background

Gefitinib was the first epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) to become available for the treatment of non-small cell lung cancer (NSCLC). Several studies have demonstrated that gefitinib is effective for the second-line treatment of NSCLC [1-3]. Although the phase III ISEL trial failed to prove the superiority of gefitinib treatment compared to placebo in previously treated patients, a subgroup analysis demonstrated improved survival in particular populations (Asians and non-smokers) [4]. Further analyses in other studies have also revealed that clinical factors (Asians, females, non-smokers, and adenocarcinoma histology) are associated with the response to gefitinib treatment [5]. EGFR mutations, such as the deletion of exon 19 and the single L858R mutation in exon 21, have also been reported to be correlated with a longer survival and were found more frequently in Asian patients [6-8]. Recently, a superior progression-free survival (PFS) with gefitinib compared with the combination of carboplatin and paclitaxel in untreated NSCLC patients with predictors of gefitinib sensitivity was proven in two large phase III studies [9,10]. Gefitinib is now recommended for advanced

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or metastatic NSCLC patients under such circumstances as a first or a second-line treatment.

Despite the high disease control rate (DCR), gefitinib treatment is not curative and eventually there is disease recurrence, even in patients with predictors of sensitivity. For the many NSCLC patients who previously responded to gefitinib but later showed tumor progression, very few treatment options are available.

Some investigators have conducted studies to evaluate the efficacy of EGFR-TKI re-administration [11-14]. In most of those studies, both gefitinib responders and non-responders were retreated with gefitinib or erlotinib, and gefitinib responders tended to benefit from the 2nd EGFR-TKI.

Here, we retrospectively analyzed the efficacy of the 2nd EGFR-TKI administration after failure of the initial gefitinib treatment in NSCLC patients who had previously achieved disease control with gefitinib. The risks of the 2nd administration of EGFR-TKI, especially the association with adverse events in the initial gefitinib treatment, were also evaluated.

Methods

Patients

We conducted a retrospective search of the medical records at Niigata University Medical and Dental Hospital, from June 2005 through October 2009, and we identified 11 NSCLC patients who had obtained a partial response (PR) or stable disease (SD) with gefitinib treatment and undergone EGFR-TKI retreatment sometime after the failure of the initial gefitinib treatment. All patients were treated initially with oral gefitinib at a dose of 250 mg/day, which was continued until either a radiographic tumor or overt clinical progression was observed. The same dose of gefitinib, or erlotinib at a dose of 150 mg/day, was used for EGFR-TKI retreatment and continued until tumor progression was detected.

Assessment of the response and adverse events

The tumor response was evaluated by radiologic examinations according to the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. Disease control was defined as complete response (CR), PR or SD. PFS and overall survival (OS) were defined as the period from the start of the treatment to the date when disease progression and death, respectively, were observed.

Adverse events were assessed according to Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 3.0) [16].

Statistical analysis

PFS and OS estimates were obtained using the Kaplan-Meier method.

Table 1 Patient Characteristics 1

Characteristics	No. of Patients	%
Total enrolled	11	
Gender		
Female	8	73
Male	3	27
Age (y)		
Median	55	
Range	46-70	
ECOG performance status		
1	6	55
2	0	0
3	3	27
4	2	18
Histology		
Adenocarcinoma	10	91
Squamous	1	9
Smoking history		
Current	3	27
Ex-smoker	1	9
Never	7	64
EGFR mutation		
Exon 19 deletion	2	18
L858R	1	9
Not available	8	73

EGFR, epidermal growth factor receptor.

Results

Patient characteristics

Of the 11 identified patients who benefited from gefitinib and were retreated with EGFR-TKI, 3 patients (27%) received gefitinib and 8 patients (73%) received erlotinib as the 2nd round of EGFR-TKI. As shown in Table 1 the ages of patients ranged from 46 to 70 years (median, 55 years), and there were 8 females (73%), 7 non-smokers (64%), and 10 adenocarcinoma patients (91%). Three patients (27%) exhibited EGFR gene mutations, but the mutation statuses of the other 8 patients (73%) were not determined. All patients had received platinum-based chemotherapy before the initial gefitinib treatment. The patient characteristics, including treatment backgrounds and responses, are summarized in Table 2.

Response to the initial gefitinib treatment

During the 1st EGFR-TKI treatment with gefitinib, 8 patients achieved PR as the best response (73%, Table 3), and 3 patients (27%) were SD. The median PFS was 9.8 months, with a 95% CI of 6.6 to 16.7 months.

Response to the 2nd EGFR-TKI

Three patients (27%) received the 2nd EGFR-TKI immediately after gefitinib failure, and 8 (73%) underwent 1 cytotoxic regimen between the initial gefitinib and the

Table 2 Patient Characteristics 2

Case	Age (y)	Gender	Smoking	Histology	EGFR mutation	PFS to 1st TKI	TKI sequence	Interval from 1st and 2nd	Chemo. after 1st	PS	Response	PFS to 2nd TKI	OS from 2nd TKI
1	50	F	Current	Ad	NA	9.8	G→E	7.9	CBDCA +GEM	1	PD	0.9	13.1
2	46	F	Never	Ad	NA	11.8	G→G	4.5	DOC	1	PR	6.4	24.6
3	58	F	Ex	Ad	19 deletion	38.4	G→G	2.8	DOC	1	SD	7.3	24.1
4	70	F	Never	Sq	NA	10.2	G→E	12.8	GEM	1	SD	1.7	4.3
5	60	F	Never	Ad	NA	13	G→G	5.4	GEM	1	PD	1.6	2.1
6	63	F	Never	Ad	NA	7.4	G→E	2.6	-	3	SD	3.6	7.8
7	52	M	Never	Ad	L858R	5.8	G→E	1	-	4	SD	6.4	6.4
8	51	M	Current	Ad	NA	4.3	G→E	1.6	AMR	3	PD	0.6	0.9
9	61	F	Never	Ad	NA	8.5	G→E	2.3	VNR	3	SD	2.9	4
10	53	F	Never	Ad	NA	12.9	G→E	0	-	4	SD	6.2	7.3
11	54	M	Current	Ad	19 deletion	3.8	G→E	7.3	VNR	1	SD	3.2	5

PFS, progression-free survival; TKI, tyrosine kinase inhibitor; PS, performance status; OS, overall survival; F, female; M, male; Ex, ex-smoker; Ad, adenocarcinoma; Sq, squamous cell carcinoma; G, gefitinib; E, erlotinib; CBDCA, carboplatin; GEM, gemcitabine; DOC, docetaxel; AMR, amrubicin; VNR, vinorelbine; PR, partial response; SD, stable disease; PD, progressive disease.

2nd EGFR-TKI treatments. The median interval from the discontinuation of gefitinib to the 2nd EGFR-TKI was 2.8 months (95% CI, 1.9 - 6.9, Table 3). Only one patient (9%) demonstrated PR, 7 (64%) remained SD, and 3 (27%) had PD. The DCR was 73% (95% CI, 43% - 91%) and the median PFS was 3.4 months (95% CI, 2 - 5.2). The median OS from the beginning of the 2nd EGFR-TKI and from diagnosis were 7.3 months (95% CI, 2.7 - 13.0) and 36.7 months (95% CI, 23.6 - 43.9), respectively. No statistical differences in PFS or OS were observed between gefitinib and erlotinib as the 2nd EGFR-TKI (PFS, P = 0.23 and OS, P = 0.052).

In contrast with previous studies, we further compared the clinical courses of the patients with those of gefitinib responders who were not treated with a 2nd EGFR-TKI following gefitinib failure. We reviewed the medical records at our institute and found 9 patients with backgrounds that were similar to those of the 2nd EGFR-TKI patients (sex, age (< 70 years old or > 70 years old), histology, and response to gefitinib treatment). No statistical differences in PFS to 1st gefitinib treatment were noted between both groups (9.8 months in the 2nd TKI group and 8.7 months (95% CI, 7.6 - 9.8) in the control group, P = 0.87). All of the identified control patients had been treated with platinum-doublet chemotherapy before gefitinib but had not received 2nd EGFR-TKI. The OS from the start of the initial gefitinib treatment tended to be longer in patients who received a 2nd EGFR-TKI (median OS, 21.5 months (95% CI, 14.6 - 28.4)) compared to those in the control group (median OS, 12.3 months (95% CI, 9.4 - 15.2), P = 0.07).

Table 3 Summary of prior therapy

Characteristics	No. of patients	%
No. of chemotherapy regimens before gefitinib		
1	2	18
2	4	36
3	4	36
4	1	9
Best response to gefitinib		
PR	8	73
SD	3	27
PFS to gefitinib		
Median	9.8	
95% CI	6.6 - 16.7	
Interval from discontinuation of gefitinib to 2nd EGFR-TKI		
Median	2.8	
95% CI	1.9 - 6.9	

In the control group, 5 out of 9 patients had been treated with cytotoxic chemotherapy after gefitinib failure. To compare the efficacy of the 2nd EGFR-TKI with chemotherapy after disease progression with gefitinib, data were collected from these 5 patients in the control group who had received chemotherapy after gefitinib failure (Table 4). The DCR for chemotherapy after gefitinib treatment was 20% and comprised one SD and four PD. The median PFS and OS from the start of chemotherapy after gefitinib treatment were only 2 months (95% CI, 1.5 - 2.4) and 2.5 months (95% CI, 2.2 - 2.8), respectively. No significant differences in the PFS or OS from the start of treatment after gefitinib were observed between the patients who received a 2nd EGFR-TKI and those who underwent cytotoxic chemotherapy (PFS, P = 0.1 and OS, P = 0.12); however, a 2nd EGFR-TKI appeared to be a better option for gefitinib responders.

Table 4 Tumor response to 2nd EGFR-TKI vs. chemotherapy

Characteristics	2nd TKI group	Control group	p
OS from 1st gefitinib			
Median	21.5	12.3	0.07
95% CI	14.6 - 28.4	9.4 - 15.2	
Response to 2nd TKI or chemotherapy			
PR	1	0	
SD	7	1	
PD	3	4	
PFS to 2nd TKI or chemotherapy			
Median	3.4	2	0.1
95% CI	2 - 5.2	1.5 - 2.4	
OS from 2nd TKI or chemotherapy			
Median	7.3	2.2	0.12
95% CI	2.7 - 13	2.2 - 2.8	

Table 5 Toxicity profiles for the initial gefitinib and 2nd EGFR-TKI treatments. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 3.0).

Case	Initial gefitinib	2nd EGFR-TKI
1	-	Rash G2
2	Rash G2	-
3	-	-
4	Rash G2, Liver G1, Diarrhea G2	Rash G1, Diarrhea G1
5	Rash G1	Rash G2
6	Diarrhea G2, Taste alteration G2	Rash G1, Diarrhea G1
7	Rash G2, Liver G3	Rash G2, Liver G3
8	Rash G2	Liver G2
9	Rash G1, Nail G1, Nausea G1	Rash G1
10	Liver G1	-
11	-	Rash G1, Diarrhea G1

G, grade; Liver, serum glutamic pyruvic transminase, serum glutamic oxaloacetic transaminase and γ-glutamyltranspeptidase.

Toxicity profiles for the initial gefitinib and 2nd EGFR-TKI treatments

To determine whether the initial gefitinib treatment and EGFR-TKI retreatment caused similar adverse events, we assessed the toxicity profiles of all 11 patients (Table 5). The most common toxicity associated with both treatments was a grade 1/2 skin rash. Although one patient presented a grade 3 elevation of γ-glutamyltranspeptidase during both treatment with gefitinib and with erlotinib (patient no. 7), the other observed toxicities were generally acceptable. In 5 patients, the toxicity profiles for the initial gefitinib and the 2nd EGFR-TKI treatments were similar. None of the patients demonstrated interstitial lung disease in response to EGFR-TKI.

Discussion

To the best of our knowledge, 18 cases of patients who received gefitinib re-administration after failure of the initial gefitinib treatment have been reported to date, including 3 cases reported by our group (Table 6) [17-21]. All 18 patients responded to the initial gefitinib treatment, and most of the cases underwent cytotoxic chemotherapy between the first and second gefitinib therapy. Fourteen patients benefited from the 2nd gefitinib treatment, and the overall DCR was 78%. In our 3 patients, the toxicity of the 2nd gefitinib was similar to that observed for the initial gefitinib treatment and was acceptable. Gefitinib retreatment is likely a good option for patients who have demonstrated a response to a previous gefitinib treatment.

Clinical studies have demonstrated that erlotinib is effective even in patients who are not considered to be good responders to gefitinib, such as those with a negative EGFR mutation, squamous cell carcinoma, or a history of smoking [22]. Because erlotinib is used at its maximum tolerated dose, whereas gefitinib is used at only about one-third of its maximum tolerated dose in daily practice, the biological activity of erlotinib at standard doses may be higher than that of gefitinib [2,4,23-25]. These reports suggest that erlotinib may be active even in patients who demonstrated tumor progression during a prior gefitinib treatment. Thus, erlotinib has been selected as a treatment option for use after gefitinib failure (Table 7) [11-14,26-33]. In most studies, including the present investigation, favorable results have been documented, and the authors have concluded that erlotinib appears to be a useful treatment after gefitinib failure.

Although it is difficult to address the precise mechanism underlying these results, several studies have suggested a possible explanation for the clinical benefit of EGFR-TKI retreatment. Some cytotoxic agents have been reported to restore the sensitivity of NSCLC cells to gefitinib in vitro by increasing EGFR phosphorylation [34,35]. It is also possible that chemotherapy during the EGFR-TKI-free interval could decrease EGFR-TKI resistant tumor cells. However, no significant differences in PFS or OS were observed between our patients who received chemotherapy before the 2nd EGFR-TKI and those who received the 2nd EGFR-TKI immediately after gefitinib failure. In addition, the duration between the initial gefitinib and the 2nd EGFR-TKI treatments was not associated with the response to 2nd EGFR-TKI. Similarly to these findings, other researchers have found no evidence that either chemotherapy among the 1st and 2nd EGFR-TKIs or the duration of the EGFR-TKI-free period affects either PFS or OS in the 2nd EGFR-TKI [31,33].

Secondary EGFR mutations might be associated with the efficacy of erlotinib after gefitinib failure. MET amplification and secondary EGFR mutations, such as

Table 6 Patient characteristics of the previous studies of gefitinib readministration

Author	No. of patients	Response to gefitinib		Response to 2nd gefitinib	
		CR/PR/SD	PD	CR/PR/SD	PD
Yokouchi H et al.	9	9	-	8	1
Yoshimoto A et al.	1	1	-	1	0
Yano S et al.	3	3	-	2	1
Hashimoto N et al.	1	1	-	0	1
Kurata T et al.	1	1	-	1	0

CR, complete response.

T790 M, L747 S, D761Y, and T854A have been identified in NSCLC patients with an acquired resistance to EGFR-TKI [36-42]. T790 M mutation was found in 50%, MET amplification in 20%, and other secondary mutations in less than 5% of the NSCLC patients carrying EGFR mutations with TKI resistance [43,44]. In vitro studies have revealed that tumor cells carrying non-T790 M mutations show a partial resistance to EGFR-TKI, but are much less resistant compared to cells with T790 M. These data suggest that an increased EGFR-TKI dose might circumvent the acquired resistance caused by non-T790 M mutations. Previous studies have indicated that the serum concentration of erlotinib is several-fold higher than that of gefitinib at standard doses [24,25]. This difference in biological activities between the TKIs may contribute to the efficacy of erlotinib after gefitinib failure in patients carrying non-T790 M mutations.

In conclusion, our findings suggest that a 2nd EGFR-TKI can be a treatment option for patients who benefited from a previous gefitinib treatment. However, as shown in Table 7 some studies failed to demonstrate the efficacy of 2nd EGFR-TKI after gefitinib failure. Cho et al. mentioned that the tumor response to 1st gefitinib treatment can be a predictive marker [14]. They described that patients who showed SD during 1st gefitinib treatment had better survival with 2nd EGFR-TKI, however those who had PD to 1st gefitinib rarely responded to 2nd EGFR-TKI. The difference in the percentage of patients with a good predictor might affect the results of these trials about 2nd EGFR-TKI. Intense research has been devoted to clarifying the mechanism responsible for acquired resistance, but it is difficult to obtain clinical samples from all patients to confirm MET amplification or secondary mutations. Jackman et al. recently published a clinical definition of acquired resistance to EGFR-TKI [45]. This consensus definition will facilitate the establishment of standard entry criteria for studies investigating acquired resistance. All of our patients except one met these criteria (no. 8 in Table 2). Despite rapid tumor progression during a previous cytotoxic chemotherapy, this patient obtained SD with an initial gefitinib therapy of 4.3 months, and therefore we considered this patient to have benefited from the gefitinib treatment. Further clinical trials are required to develop a novel treatment for patients with acquired resistance.

Table 7 Patient characteristics of the previous studies of erlotinib after gefitinib failure

Author	No. of patients	Response to gefitinib		Response to erlotinib		
		CR/PR/SD	PD	CR/PR/SD	PD	DCR (%)
Lee DH et al.	23	17	6	2	21	9
Cho BC et al.	21	10	11	6	15	29
Viswanathan A et al.	5	4	1	0	5	0
Costa DB et al.	18	16	2	4	14	22
Sim SH et al.	16	11	5	4	12	25
Chang JW et al.	1	1	0	1	0	100
Garfield DH et al.	1	1	0	1	0	100
Vasile E et al.	8	8	0	5	3	63
Gridelli C et al.	3	3	0	3	0	100
Wong AS et al.	14	9	5	5	9	36
Zhou ZT et al.	21	15	6	10	11	48
Wong MK et al.	21	18	3	12	9	57

Conclusion

In the current study, we analyzed the efficacy and toxicity of a 2nd EGFR-TKI treatment in patients who demonstrated a response to prior gefitinib therapy and tumor progression. A second EGFR-TKI treatment was generally effective in patients who had benefited from the initial gefitinib therapy. The adverse events associated with a 2nd EGFR-TKI were acceptable and comparable with those observed for the initial gefitinib therapy. In Japan, gefitinib has been approved for the treatment of inoperable and recurrent NSCLC since 2002, and many patients have already experienced a need for a new treatment option following gefitinib treatment. Based on the present data, a 2nd EGFR-TKI treatment could represent a potentially new treatment for gefitinib responders. Prospective clinical trials and translational analyses in this area of research are warranted.

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Authors' contributions
SW conducted the study and drafted the manuscript. JT conceived and designed the study and collected the clinical data. TO, RK, HT, HK and TM

participated in the patient care, and collected the data. KI, JK and JB analyzed and interpreted the data. IN and HY provided the administrative support. All the authors have read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

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Clinical Study

The Frequency of Epidermal Growth Factor Receptor Mutation of Nonsmall Cell Lung Cancer according to the Underlying Pulmonary Diseases

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Background. Although epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are effective in patients with nonsmall cell lung cancer with epidermal growth factor receptor (EGFR) mutation, EGFR-TKIs have a risk of inducing fatal interstitial lung disease (ILD). The selection of chemotherapy based on the EGFR mutation status is recommended, however, the frequency of EGFR mutation in patients with ILD and the efficacy and safety of EGFR-TKI in patients with ILD and EGFR mutation are unknown. *Methods.* We retrospectively reviewed the association of the EGFR mutation status of nonsmall cell lung cancer and pulmonary diseases. Based on high-resolution computed tomography (HRCT) performed at diagnosis of lung cancer, patients were categorized into three groups: normal, emphysema, and fibrosis. *Results.* Of 198 patients with nonsmall cell lung cancer, we identified 52 (26.3%) patients with an EGFR mutation. EGFR mutations were identified in 43 (35.2%) of 122 patients with normal lungs, 8 (13.6%) of 59 with emphysema, and 1 (5.9%) of 17 with pulmonary fibrosis. Of the 52 patients with EGFR mutation, 43 patients received gefitinib. One patient with an EGFR mutation and fibrosis developed fatal ILD. There was not a significant difference in median overall survival from gefitinib treatment between never-smokers and smokers (797 days versus not reached; $P = 0.96$). *Conclusions.* Patients with sensitive EGFR mutation and normal lungs may benefit from an EGFR-TKI treatment even if they have smoking history.

1. Introduction

Gefitinib is a reversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) used for the treatment of nonsmall cell lung cancer patients [1]. Although demographic and clinical factors such as East-Asian race, female gender, nonsmoking status, and adenocarcinoma were shown to be predictive of the efficacy of gefitinib, two pivotal studies showed that the presence of somatic mutations in the kinase domain of epidermal growth factor receptor (EGFR) strongly correlates with increased responsiveness to EGFR-TKIs in patients with nonsmall cell lung cancer [2, 3]. It was later found that the subgroups of patients with nonsmall cell lung cancer who had sensitivity to gefitinib had a high incidence of EGFR mutations [4, 5]. Selecting patients on the basis of EGFR mutations, rather than clinical factors, would likely result in a population with a greater sensitivity to gefitinib. First-line gefitinib for patients with advanced nonsmall cell lung cancer who are selected on the basis of EGFR mutations improves progression-free survival, with acceptable toxicity, compared with standard chemotherapy, although it failed to prolong overall survival [6, 7].

However, EGFR-TKI increases the risk of developing life-threatening interstitial lung diseases (ILDs). The estimated incidence of ILD is low in many countries (e.g., 0.3% in the United States) [8] but is relatively high (4 to 6%) in Japan [9, 10]. An older age, poor World Health Organization performance status, reduced normal lung area on computed

tomography scans, preexisting chronic ILD, and concurrent cardiac diseases are known as risk factors for ILD in gefitinib treatment [10]. Although an assessment of pulmonary comorbidities, especially ILDs, is important to decrease the incidence of ILD induced by chemotherapy, the frequency of EGFR mutation in patients with pulmonary fibrosis and the clinical feature of these patients are not clear.

We reviewed 198 patients who were examined for EGFR mutation status and assessed the association of EGFR mutations with the underlying pulmonary diseases on chest high-resolution computed tomography (HRCT).

2. Methods

The medical records of a series of consecutive patients with histologically- or cytologically-proven lung cancer, who were tested for EGFR mutation status in the Division of Diagnostic Pathology, NTT Medical Center Tokyo between April 2008 and November 2010, were retrospectively reviewed. The status of EGFR mutation was examined in a clinical practice, not investigational setting, to decide the indication of EGFR-TKI treatment. Although most patients with severe pulmonary fibrosis or squamous cell carcinoma were excluded from the EGFR mutation test in this period, gender, smoking status, and the existence of emphysema were not considered as the exclusion criteria of the test. Patients with emphysema and fibrosis on chest HRCT at the diagnosis of lung cancer were prospectively identified, and the data before lung cancer treatment was recorded to assess their risk of ILD. Only patients who had a chest HRCT scan, which was performed at diagnosis of lung cancer and was available for review, were included in the study. The study protocol was reviewed and approved by the Ethics Committee of NTT Medical Center Tokyo.

Patients were categorized into three groups; those with normal lungs (except for the tumor), emphysematous lungs, or fibrotic lungs, based on chest CT findings as described previously [11, 12]. Patients who met the following criteria were categorized as having emphysema: the presence of emphysema on CT, defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung, and marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper zone predominance. Patients who met the following criteria were categorized as having fibrosis: the presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on CT, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion, and/or traction bronchiectasis or bronchiolectasis; focal ground-glass opacities and/or areas of alveolar condensation may be associated, but should not be prominent. Patients who met neither criterion emphysema nor fibrosis were categorized as normal. The electronic medical records were reviewed to obtain clinical and demographic data, including gender, age, smoking history, histology results, clinical stage of lung cancer, treatment, treatment-related toxicities, and survival.

2.1. EGFR Mutation Analysis. The presence of EGFR mutations was determined by the peptide nucleic acid-locked nucleic acid PCR clamp method as described previously [13]. The investigated EGFR-TKI sensitive mutations included G719C, G719S, G719A, L858R, L861Q, and exon 19 deletions, as well as a gefitinib-resistant mutation, T790M.

2.2. Statistical Analysis. Differences among the categorized groups were compared using either the two-sided chi-square test or Fisher's exact test. The survival was estimated by the Kaplan-Meier method, and differences in survival between the subgroups were analyzed by the log rank test. Data were analyzed using the StatView version 5.0J software package (Statistical Analysis Systems, Cary, NC, USA).

3. Results

3.1. Subtypes of EGFR Mutations. We examined the EGFR mutation status in 202 patients between April 2008 and November 2010. We excluded 4 patients from this study for the following reasons: one had small cell lung cancer, two had gastric cancer, and one had parotid cancer. Of the 198 patients with nonsmall cell lung cancer, 52 patients (26.3%) had EGFR-TKI-sensitive EGFR mutations, and one patient had an EGFR-TKI-resistant mutation (T790M) with an EGFR-TKI-sensitive mutation (Exon 19 deletion). The patient population in this analysis (Table 1) was a little young, including more female, less never-smoker, and less squamous cell carcinoma of the lung in comparison with the lung cancer cohort that we previously published [12].

3.2. The Variables Associated with the EGFR Mutation Status. We investigated the association of several variables with the EGFR mutations (Table 2). A two-sided chi-square test showed that gender (female), smoking status (never smoker), histology (adenocarcinoma), and chest CT findings (normal) were significantly associated with the presence of an EGFR mutation. Of 122 patients with normal lungs, 69 patients had no history of smoking and 53 patients had a history of smoking. The frequency of EGFR mutations (n, %) in patients with normal lungs did not differ between smokers (17, 32.1%) and never-smokers (26, 37.7%) ($P = 0.5698$).

3.3. Prognosis of Patients with EGFR Mutations Treated with Gefitinib. All patients with an EGFR mutation were treated in the Division of Respirology and Chest Surgery, NTT Medical Center Tokyo. Of the 52 patients with EGFR mutation, 43 patients received gefitinib. The clinical characteristics of the patients with an EGFR mutation treated with gefitinib are shown in Table 3. The median survival after gefitinib treatment was 797 days. We identified ILD in two patients during gefitinib treatment; one had no ILD before gefitinib treatment and one had pulmonary fibrosis. The patient with pulmonary fibrosis developed acute exacerbation of preexisting ILD on day 7 of gefitinib treatment and died on day 14 because of ILD. The survival curves of the 42 patients, excluding the patient with pulmonary fibrosis, according to smoking status and chest CT results, are shown in Figures 1(a) and 1(b), respectively. No differences in survival were observed between smokers ($n = 18$, MST not reached) and never-smokers ($n = 24$, MST 797 days) or between

Table 1: Patient characteristics NSCLC: nonsmall cell lung cancer: LCNEC; large cell neuroendocrine carcinoma.

Total number of patients	198
Age (median, range)	68, 28–92
Gender	
Female	86
Male	112
Smoking-status	
Never	74
Ex/Current	124
Histology	
Adenocarcinoma	169
Squamous cell carcinoma	9
Other NSCLC	15
LCNEC	4
Clinical stage of NSCLC	
IA	29
IB	14
IIA	2
IIB	6
IIIA	12
IIIB	30
IV	105
Chest CT	
Normal	122
Emphysema	59
Fibrosis	17
EGFR mutation	
Wild type	147
Ex18 G718S	1
Ex19 del	34
Ex21 L858R	15
EX19 del + Ex21 L858R	1
Ex 19del + T790M	1

Table 2: Patient characteristics and EGFR mutation status.

	Number	EGFR mutation (n, %)	P-value
Gender			
Male	112	17, 15.2%	$P < 0.0001$
Female	86	35, 40.7%	
Age			
<65	80	23, 28.8%	$P = 0.5156$
65≤	118	29, 24.6%	
Histology			
Adenocarcinoma	169	50, 29.6%	$P = 0.0107$
Nonadenocarcinoma	29	2, 6.9%	
Smoking status			
Never	74	29, 39.2%	$P = 0.0139$
Ex/Current	124	23, 18.5%	
Clinical stage of NSCLC			
I-IIIA	63	21, 33.3%	$P = 0.1649$
IIIB-IV	135	31, 22.9%	
Chest CT			
Normal	122	43, 35.2%	
Emphysema	59	8, 13.6%	$P = 0.0011$
Fibrosis	17	1, 5.8%	

patients with normal lung (n = 36, MST 874 days) and those with emphysematous lungs (n = 6, MST 749 days) on chest CT.

4. Discussion

We herein showed the frequency of EGFR mutation in nonsmall cell lung cancer to be high in patients with the following factors: female gender, no history of smoking, adenocarcinoma, and normal lungs on chest CT. A survival analysis of the patients with EGFR mutations, excluding one patient with pulmonary fibrosis, showed no differences between smokers and never-smokers or between patients with emphysema and those with normal lungs on chest CT.

There is considerable variability in the susceptibility of smokers to developing smoking-related pulmonary diseases [14–16]. The incidence of lung cancer is increased in patients with emphysema and fibrosis, and this effect is independent of the effect of cigarette smoking [17, 18]. We consider that smokers with emphysema or fibrosis are more susceptible to smoking-related inflammation compared to those with normal lungs. Although the frequency of EGFR mutation was low in patients with emphysema and fibrosis, the frequency in those with normal lungs was not different between smokers and never-smokers. Our data suggested that smokers with normal lungs were not susceptible to smoking-related inflammation, and that nonsmall cell lung cancer in smokers with normal lungs showed the same biological features to that in never-smokers. Further investigations are necessary to elucidate whether smoking-related pulmonary diseases and lung cancer might result from overlapping or associated genetic variants implicated in smoking-related inflammation.

Although a history of smoking and the coexistence of emphysema were negatively associated with the frequency of EGFR mutations, these clinical factors did not affect the prognosis of the patients with EGFR mutations treated with gefitinib. Toyooka et al. showed that epidermal growth factor receptor mutation, but not sex or smoking, is independently associated with a favorable prognosis of gefitinib-treated patients with lung adenocarcinoma [5]. EGFR-TKI treatment should be considered in patients with an EGFR mutation, even if they have a history of smoking or emphysema without fibrosis.

The presence of EGFR mutations in patients with pulmonary fibrosis was rare in this study. Only one (5.9%) of 17 patients with pulmonary fibrosis had an EGFR mutation. Preexisting chronic ILD is known as a risk factor for ILD in gefitinib treatment [10]. In this study, one patient with

Table 3: Characteristics of patients with an EGFR mutation treated with gefitinib.

Total number	43
Age (median, range)	67, 28–92
Gender	
Male	13
Female	30
Smoking-status	
Never	24
Ex/Current	19
Pack-years of smokers (median, range)	33, 2.5–225
Histology	
Adenocarcinoma	42
Squamous cell carcinoma	1
Clinical stage of NSCLC	
IB	2
IIIA	1
IIIB	7
IV	22
Recurrence	11
History of chemotherapy before gefitinib treatment	
No	28
Yes	15
EGFR mutation	
Ex18 G719C	1
Ex19 del	30
Ex21 L858R	10
Ex19 del + Ex21L858R	1
Ex19 del + Ex20 T790M	1
Chest CT	
Normal	36
Emphysema	6
Fibrosis	1

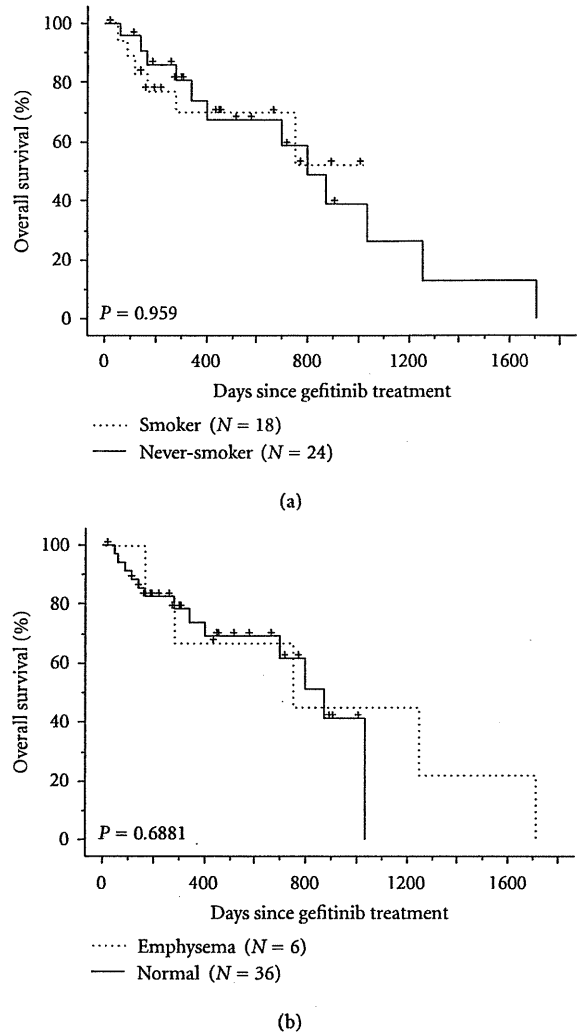

Figure 1: (a) Overall survival of patients with an EGFR mutation treated with gefitinib, according to smoking status (never smokers: solid line; smokers: dotted line). +: censored patient. (b) Overall survival of patients with an EGFR mutation treated with gefitinib, according to underlying pulmonary disease (normal: solid line; emphysema: dotted line). +: censored patient.

pulmonary fibrosis and an EGFR mutation treated with gefitinib developed fatal ILD.

The present study had several limitations, including the fact that it was observational and uncontrolled in design and was performed at a single institution, with retrospective collection of data. The results may have been subject to some selection and treatment bias. The indications for therapy and the selection of treatment were not uniform for all patients, thereby limiting the evaluation of the effects of treatment. The data presented herein should not be interpreted as providing an appropriate evaluation of the efficacy of treatment, which will require randomized prospective studies. A multivariate analysis could not be performed due to the small sample size, and it was therefore not possible to evaluate the potential confounding effects of various other variables related to survival. However, the existence of emphysema and fibrosis on chest CT were prospectively identified at the diagnosis of lung cancer. The EGFR mutation status was identified before the EGFR-TKI treatment. Data on the demographic characteristics and survival of patients were unlikely to be affected by the study design.

In summary, the frequency of EGFR mutations in patients with normal lungs on chest CT was not different between smokers and never-smokers. Of patients with sensitive EGFR mutations and normal lungs on chest CT, smokers had a comparable prognosis with never-smokers. Selecting patients on the basis of chest CT, rather than the smoking status, would likely result in a population with a greater sensitivity to gefitinib.

Conflict of Interests

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

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ABSTRACT

BACKGROUND

Non–small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy.

METHODS

We randomly assigned 230 patients with metastatic, non–small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin–paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects.

RESULTS

In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease.

CONCLUSIONS

First-line gefitinib for patients with advanced non–small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

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Non–small-cell lung cancer is a major cause of death from cancer. The use of cytotoxic chemotherapy is associated with a response rate of 20 to 35% and a median survival time of 10 to 12 months among patients with advanced non–small-cell lung cancer.[1,2] Gefitinib is an orally administered tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). In two phase 2 studies of patients with previously treated non–small-cell lung cancer, the response rate was 9 to 19%.[3,4] In subsequent phase 3 trials, the noninferiority of gefitinib as compared with docetaxel with respect to overall survival was shown in one study (hazard ratio, 1.02)[5] but not another (hazard ratio, 1.12).[6] Meanwhile, demographic and clinical factors such as Asian race, female sex, nonsmoking status, and adenocarcinoma were shown to be predictive of the efficacy of gefitinib, warranting a large comparative trial (First Line Iressa vs. Carboplatin/Paclitaxel in Asia [IPASS]; ClinicalTrials.gov number, NCT00322452) in which patients were selected in accordance with these factors.[7]

In May 2004, two pivotal studies showed that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.[8,9] It was later found that subgroups of patients with non–small-cell lung cancer who had sensitivity to gefitinib had a high incidence of EGFR mutations. In Japan, 30% or more of patients with mutated-EGFR non–small-cell lung cancer are male or have a history of smoking.[10,11] Therefore, we hypothesized that selecting patients on the basis of EGFR mutations rather than clinical factors would result in a population with a greater sensitivity to gefitinib.

Our previous prospective, phase 2 studies of gefitinib therapy in patients with advanced non–small-cell lung cancer and EGFR mutations[12-14] revealed a response rate of more than 70% and progression-free survival of 9 to 10 months. We also developed a rapid, sensitive method for detecting sensitive EGFR mutations: the peptide nucleic acid–locked nucleic acid (PNA-LNA) polymerase-chain-reaction (PCR) clamp method.[15] We then undertook a phase 3 study comparing gefitinib and standard carboplatin–paclitaxel chemotherapy in patients who had advanced non–small-cell lung cancer with sensitive EGFR mutations and who had not previously received chemotherapy.

METHODS

PATIENT POPULATION

This multicenter, randomized, phase 3 trial was approved by the institutional review board of each participating center. Eligibility criteria included the presence of advanced non–small-cell lung cancer harboring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 is substituted by methionine), no history of chemotherapy, and an age of 75 years or younger (because a benefit of a platinum-based regimen in patients >75 years of age is not established). Table 1 in the Supplementary Appendix (available with the full text of this article at NEJM.org) lists the detailed eligibility and exclusion criteria. The authors attest to the fidelity of the article to the full protocol and statistical-analysis plan.

DETECTION OF *EGFR* MUTATIONS

Cytologic or histologic specimens were examined for *EGFR* mutations by means of the PNA-LNA PCR clamp method. Briefly, genomic DNA fragments containing mutation hot spots of the *EGFR* gene were amplified with the use of a PCR assay in the presence of a peptide nucleic acid clamp primer synthesized from a peptide nucleic acid with a wild-type sequence. This method results in preferential amplification of the mutant sequence, which is then detected by a fluorescent primer that incorporates locked nucleic acids to increase the specificity. As a result, a mutant *EGFR* sequence is detected in specimens that contain 100 to 1000 excess copies of wild-type *EGFR* sequence. The sensitivity and specificity of the PNA-LNA PCR clamp method are 97% and 100%, respectively.[15,16]

STUDY DESIGN AND TREATMENT

Before randomization, patients were stratified according to sex, clinical stage of non–small-cell lung cancer (IIIB, IV, or postoperative relapse), and institution. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg per day orally) or standard chemotherapy. The standard chemotherapy consisted of paclitaxel (at a dose of 200 mg per square meter of body-surface area, given intravenously over a 3-hour period) and carboplatin (at a dose equivalent to an area under the concentration–time curve [AUC] of 6, given intravenously over a 1-hour period), both administered on the first day of every 3-week cycle. The

carboplatin dose in milligrams was calculated by means of the Calvert formula (AUC × [the calculated creatinine clearance in milliliters per minute + 25]; www.freekinetics.com/auccalc1.htm). The glomerular filtration rate was estimated according to the Cockcroft–Gault method ([140 − age in years] × [actual weight in kilograms] ÷ [72 × serum creatinine level in milligrams per deciliter {× 0.85 in women}]). Chemotherapy was continued for at least three cycles. Gefitinib was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent.

CLINICAL ASSESSMENTS

Assessments made before enrollment are summarized in Table 2 in the Supplementary Appendix. Assessment of the tumor for a response to treatment was performed by means of computed tomography (CT) every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0).[17] Progression-free survival was evaluated for the period from the date of randomization to the date when disease progression was first observed or death occurred. Treatment response and progression-free survival were determined by external review of the CT films by experts who were not aware of the treatment assignments. Overall survival was evaluated for the period from the date of randomization to the date of death. Toxic effects were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC, version 3.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

The primary end point was progression-free survival, as a measure of the superiority of gefitinib over carboplatin–paclitaxel. From our previous data, we hypothesized that the progression-free survival with gefitinib was 9.7 months; from the results of the Iressa NSCLC Trial Assessing Combination Treatment (INTACT),[18] we hypothesized that the progression-free survival with standard chemotherapy was 6.7 months. We estimated that a total of 230 events would be needed for the study to have a power of 80% to confirm the superiority of gefitinib over standard chemotherapy, with the use of a log-rank test and a two-sided significance level of 5%. Setting the duration of enrollment to 2 years with a minimum follow-up period of 6 months, we initially planned to enroll 320 patients.

Kaplan–Meier survival curves were drawn for progression-free survival and were compared by means of a log-rank test. Hazard ratios (and 95% confidence intervals) were calculated with the use of a Cox proportional-hazards analysis. Prespecified adjustment factors included sex and clinical stage.

Secondary end points included overall survival, response rate, time to the deterioration of performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of ≥3, capability of only limited self-care, or confinement to a bed or chair for >50% of waking hours[19]), and toxic effects. Overall survival and the time to ECOG performance status score of 3 or more were analyzed in the same way as progression-free survival. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test and the Wilcoxon test, respectively. Each analysis was performed with the use of a two-sided, 5% significance level and a 95% confidence interval by means of SAS for Windows software (release 9.1, SAS Institute).

One interim analysis was planned to analyze the primary end point (significance level, $P=0.003$). The Lan–DeMets method was used to adjust for multiple comparisons. The O'Brien–Fleming type alpha-spending function was also used.

RESULTS

PATIENT CHARACTERISTICS

The study was begun in March 2006. The preplanned interim analysis was performed 4 months after the 200th patient was enrolled (May 2009); it showed a significant difference in progression-free survival between the two treatment groups ($P<0.001$), and the independent data and safety monitoring committee recommended termination of the study. Therefore, the study was stopped at the end of May 2009.[20]

In total, 230 patients were enrolled from 43 institutions in Japan (Fig. 1). Half (115 patients) were randomly assigned to receive gefitinib and half to receive carboplatin–paclitaxel. Two patients were excluded because they were found to be ineligible. In the chemotherapy group, 1 patient was not evaluated for safety, owing to lack of receipt of the study drugs, and 3 others were excluded from the analysis of progression-free survival.

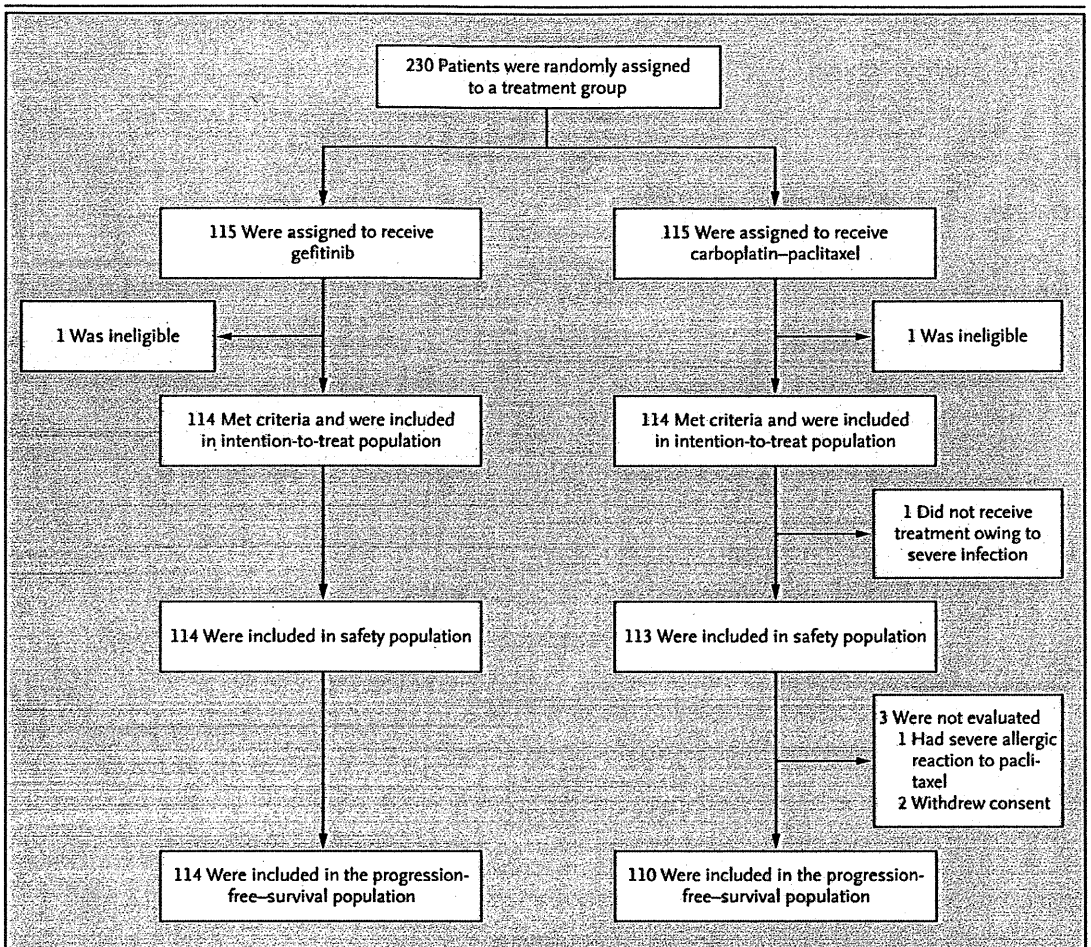


Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

At the data cutoff point (early December 2009), the median follow-up period was 527 days (>17 months; range, 30 to 1261). The median duration of gefitinib treatment was 308 days (range, 14 to 1219); the median number of 3-week cycles of chemotherapy was 4 (range, 1 to 7). Three patients in the gefitinib group and 11 patients in the chemotherapy group received second-line treatment before they had RECIST-defined disease progression. The data on progression-free survival for these patients were censored at the time of the last CT evaluation at which they did not yet have evidence of disease progression. Demographic and disease characteristics at baseline were well balanced between the two groups (Table 1).

EFFICACY

The interim analysis performed in May 2009 showed that progression-free survival was significantly longer in the gefitinib group than in the chemotherapy group (median, 10.4 months vs. 5.5 months; hazard ratio for death or disease progression with gefitinib, 0.36; 95% confidence interval [CI], 0.25 to 0.51; P<0.001) (Fig. 1 in the Supplementary Appendix). A significant difference was again observed in the final analysis, performed in December 2009 (median progression-free survival, 10.8 months with gefitinib vs. 5.4 months with chemotherapy; hazard ratio, 0.30; 95% CI, 0.22 to 0.41; P<0.001) (Fig. 2A). The 1-year and 2-year rates of progression-free survival were 42.1% and 8.4%, respectively, in the gefitinib group and 3.2% and 0%, respectively, in the chemotherapy group. Subgroup analyses showed that women had significantly longer progression-free survival than men (median, 6.5 vs. 6.0 months; hazard ratio for death or disease progression, 0.68; 95% CI, 0.51 to 0.92; P=0.01). The objective response rate was significantly higher in the gefitinib group than the chemotherapy group (73.7% vs. 30.7%,

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

P<0.001) (Table 2). The median progression-free survival and response rate did not differ significantly between patients with the EGFR mutation consisting of an exon 19 deletion (11.5 months and 82.8%) and those with the L858R point mutation (in which leucine at amino acid 858 is replaced by arginine) (10.8 months and 67.3%) (Fig. 2B).

The overall survival did not differ significantly between the two treatment groups. The median survival time and the 2-year survival rate were 30.5 months and 61.4% for the gefitinib group, as compared with 23.6 months and 46.7%, respectively, for the carboplatin–paclitaxel group (P=0.31) (Fig. 2C). Neither sex nor clinical stage had a significant effect on overall survival. The time to an ECOG performance status score of 3 or more did not differ significantly between the two groups.

SAFETY

All patients who had received at least one dose of a study drug were included in the safety analysis. The most common adverse events in the gefitinib group were rash and elevated levels of aspartate aminotransferase or alanine aminotransferase, and in the chemotherapy group, appetite loss, neutropenia, anemia, and sensory neuropathy (Table 3, and Table 3 in the Supplementary Appendix). Interstitial lung disease was reported in six patients (5.3%) in the gefitinib group; three cases were severe, and one of the three was fatal. One grade 4 seizure in the gefitinib group and one grade 4 cerebral infarction and one grade 4 bowel obstruction in the chemotherapy group were observed. The incidence of severe toxic effects (NCI-CTC grade ≥3) was significantly higher in the chemotherapy group than in the gefitinib group (71.7% vs. 41.2%, P<0.001).

TREATMENT AFTER PROTOCOL DISCONTINUATION

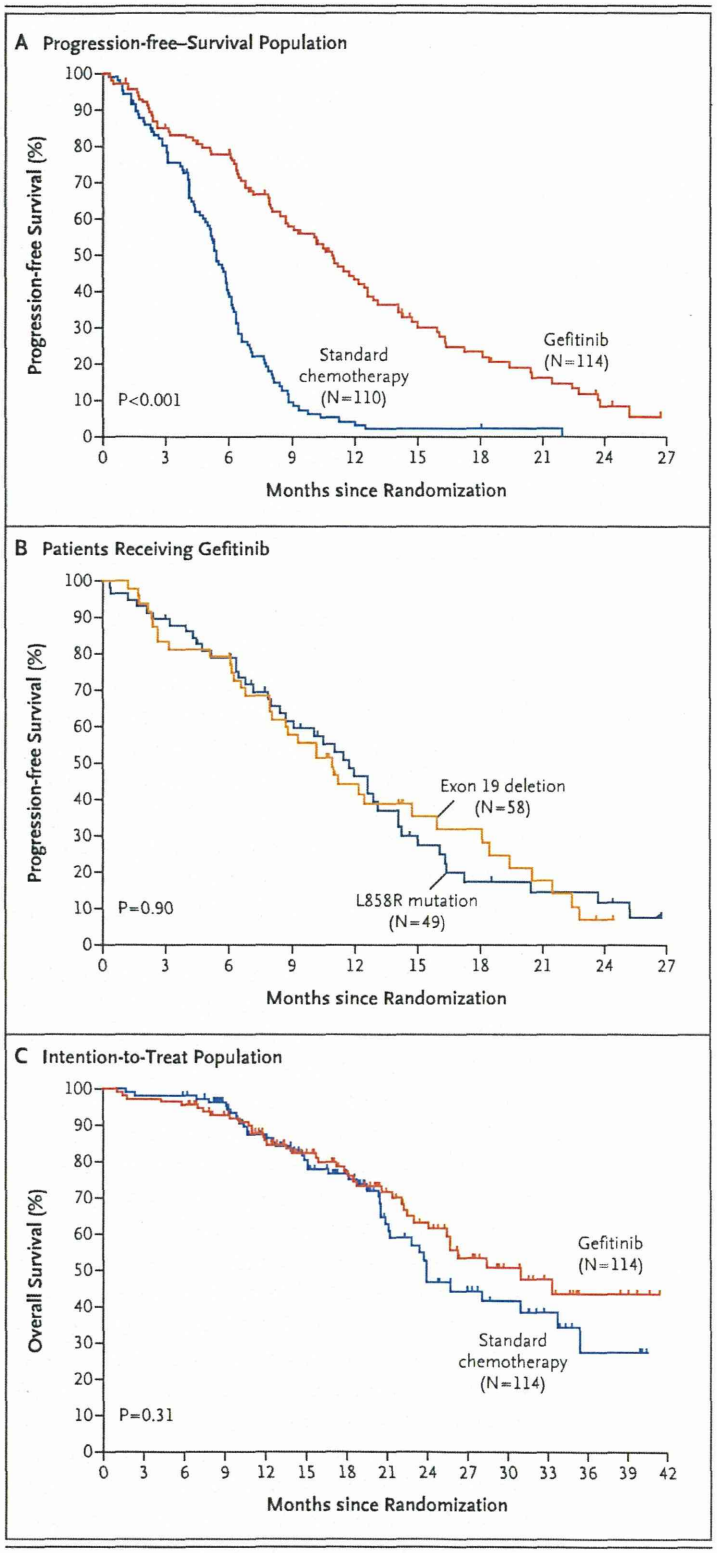
Data on treatment given after the study protocol was discontinued were collected retrospectively. Though any treatment was permitted, the protocol recommended that the crossover regimen be used as second-line treatment. As of the data cutoff point, 37 patients in the gefitinib group had continued their first-line gefitinib therapy. Among the remaining 77 patients in the gefitinb group who had stopped receiving gefitinib, 52 (67.5%) were receiving carboplatin–paclitaxel as second-line treatment, with a response rate of 28.8%. Sixteen other patients in the gefitinib group were receiving other therapies such as carboplatin–gemcitabine. Among the 112 patients who had completed first-line carboplatin–paclitaxel, 106 patients (94.6%) received second-line gefitinib; 58.5% of these patients had a response.

DISCUSSION

Previous phase 2 studies have suggested that EGFR tyrosine kinase inhibitors are highly effective against mutated-EGFR non–small-cell lung cancer. The current phase 3, prospective, randomized study showed that the use of gefitinib results in progression-free survival that is twice as long

Figure 2. Progression-free Survival and Overall Survival among the Study Patients.

Kaplan–Meier curves for progression-free survival are shown for the progression-free–survival population (Panel A) and for the 107 patients in the gefitinib group with either of the two most common types of epidermal growth factor receptor (EGFR) mutation (Panel B). Kaplan–Meier curves for overall survival in the intention-to-treat population are shown in Panel C. In Panels B and C, tick marks indicate patients for whom data were censored at the data cutoff point (early December 2009).



as that obtained with the use of carboplatin–paclitaxel in patients with mutated-EGFR non–small-cell lung cancer, with a tolerable toxicity profile, including less hematologic toxicity and neurotoxicity than is seen with chemotherapy.

The IPASS, which was conducted in Asia, compared gefitinib with carboplatin–paclitaxel as the first-line treatment for advanced non–small-cell lung cancer in patients selected on the basis of clinical characteristics that included a history of no smoking or light smoking as well as histologic evidence of adenocarcinoma.[7] Although IPASS showed the overall superiority of gefitinib (rate of 1-year progression-free survival, 24.9%, vs. 6.7% with chemotherapy; hazard ratio for death or disease progression, 0.74; P<0.001), the most impressive result emerged from subgroup analysis: as compared with chemotherapy, gefitinib was effective in patients with mutant EGFR (hazard ratio for death or disease progression, 0.48) but was ineffective in those with wild-type EGFR (hazard ratio, 2.85). This finding suggested that the presence of EGFR mutations is the best criterion for selection of patients who benefit from gefitinib, an idea that is validated by the present study.[20] Recently, another Japanese phase 3 study (WJTOG3405; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000000539) compared gefitinib to cisplatin–docetaxel as the first-line treatment for advanced non–small-cell lung cancer with EGFR mutations.[21] Although this study also showed the superiority of gefitinib over standard chemotherapy with respect to progression-free survival, the magnitude of the benefit was somewhat smaller than in our study, possibly because of differences in the characteristics of the patients (since 41% of patients in WJTOG3405 had had surgery, vs. only 9% in our study) and the duration of follow-up (median, 81 days in WJTOG3405 vs. 527 days in our study).

The standard end point of phase 3 trials of treatments for advanced non–small-cell lung cancer has been overall survival. However, when our trial was begun in 2006, we had data only on