Low-Dose Gefitinib Treatment for Patients with Advanced Non-small Cell Lung Cancer Harboring Sensitive Epidermal Growth Factor Receptor Mutations

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Introduction: Although standard schedule of gefitinib was the administration of 250 mg tablet every day, many patients need dose reduction because of toxicities. However, the efficacy of such low-dose gefitinib for patients with epidermal growth factor receptor-mutated non-small cell lung cancer has rarely been evaluated.

Methods: A post hoc comparison of the efficacy (response rate and survival) in patients treated with gefitinib with or without any dose reduction in NEJ002 study was performed.

Results: Among 114 patients treated with first-line gefitinib in NEJ002, 61 (54%) continued gefitinib without any dose reduction until their diseases progressed, and 53 (46%) reduced their dose of gefitinib because of some toxicities. There was no significant difference of patient characteristics between the two groups. The progression-free survival of low-dose group tended to be better than that of standard-dose group (median progression-free survival, 11.8 versus 9.9 months; $p = 0.144$), and the overall survival of low-dose group was also better than that of standard-dose group (median survival time, 32.7 versus 25.3 months; $p = 0.049$).

Conclusions: The results suggest that low-dose gefitinib may be clinically not inferior to standard-dose gefitinib for non-small cell lung cancer with sensitive epidermal growth factor receptor mutations. Prospective study of low-dose gefitinib is warranted especially for frail patients who need less toxic treatment.

Key Words: Gefitinib, EGFR mutation, Low-dose, Post hoc analysis.

(*J Thorac Oncol.* 2011;6: 1413–1417)

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Disclosure: Dr. Inoue received lecture fees from AstraZeneca, Eli Lilly, Chugai, KyowaKirin, and Sanofi-Aventis; Dr. Kobayashi received grants from Novartis, Nihon Kayaku, Chugai, Shionogi, KyowaKirin, Yakult, Taiho, and AstraZeneka and lecture fees from Eli Lilly, AstraZeneca, Chugai, Sanofi-Aventis, Janssen Pharmaceutical KK, GlaxoSmithKline, and Bristol-Myers Squibb; Dr. Maemondo received lecture fees from Chugai and Eli Lilly; Dr. Oizumi received lecture fees from AstraZeneca, Chugai, Eli Lilly, Kureha, Novartis, and Taiho; Dr. Isobe received lecture fees from AstraZeneca, Chugai, and Yakult; Dr. Gemma received consulting fees from Taiho, Merckserono, Janssen, Chugai, and Bayer, grants from Glaxo SmithKline, and AstraZeneca, and lecture fees from Chugai, Eli Lilly, and Bristol-Myers Squibb; Dr. Saijo received grants from Chugai, AstraZeneca, Eli Lilly, Sanofi-Aventis, Takeda, Kyowa Kirin, Taiho, Nihon Kayaku, Torii, and Eizai, lecture fees from Chugai, AstraZeneca, Taiho, and Daiichi Sankyo, and payment for making a book from Nihon Kayaku; Dr. Hagiwara received a support for the study from the Tokyo Cooperative Oncology Group (nonprofit organization supporting studies on clinical oncology); and Dr. Nukiwa received grants from AstraZeneca, Eli Lilly, and Daiichi Sankyo and lecture fees from AstraZeneca, Eli Lilly, Chugai, and Daiichi Sankyo.

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ISSN: 1556-0864/11/0608-1413

Cytotoxic chemotherapy such as carboplatin (CBDCA) plus paclitaxel (PTX) had been the standard first-line treatment for advanced non-small cell lung cancer (NSCLC) patients for a long time; however, its efficacy had already reached a plateau in early 2000s, and better treatment strategies have been eagerly anticipated.[1,2] Gefitinib is the first molecular-targeted agent for NSCLC and is classified as a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR-TKI).[3] Although gefitinib was initially approved for the entire NSCLC population, pivotal studies published in 2004 had revealed that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with an increased responsiveness to EGFR-TKI.[4,5] Biomarker analysis performed in Iressa Pan-Asia Study, in which efficacy of gefitinib and CBDCA/PTX was compared as the first-line treatment for NSCLC patients with favorable clinical characteristics including adenocarcinoma and nonsmoking history, showed a significant superiority of gefitinib in progression-free survival (PFS) in the subset analysis for NSCLC with mutated EGFR.[6] Recently, we prospectively demonstrated in NEJ002 phase 3 study that the first-line gefitinib exhibited a significantly longer PFS than CBDCA/PTX in patients with advanced NSCLC with mutated EGFR.[7] According to these results, EGFR-TKI has become one of the

standard treatments for advanced NSCLC with mutated EGFR.

A standard dosage of gefitinib is 250 mg, which is administered every day. Nevertheless, not a few patients need a dose reduction of gefitinib due to toxicities including rash, diarrhea, or liver dysfunction. Because the tablet of gefitinib cannot be divided in half, the dose reduction is usually achieved by changing the interval of taking the tablet from every day to every 2 days. However, clinical evidence of such reduced dose of gefitinib is scanty. According to some preclinical data, lung cancer cell harboring sensitive EGFR mutation are much more sensitive to EGFR-TKI than those with wild-type EGFR.[4] Therefore, we hypothesized that selected patients on the basis of EGFR mutations might sufficiently and safely benefit from such "low-dose" gefitinib. The aim of this post hoc analysis from NEJ002 is to examine the efficacy of low-dose gefitinib compared with that of standard-dose gefitinib in EGFR-mutated NSCLC patients.

METHODS

Patient Population

We retrospectively analyzed the 114 patients treated with gefitinib in NEJ002 study, which is a multicenter, randomized, phase 3 trial that compared gefitinib with CBDCA/TXL as the first-line treatment for advanced NSCLC harboring sensitive EGFR mutations. Eligibility criteria of NEJ002 included the presence of advanced NSCLC harboring sensitive EGFR mutations without the resistant EGFR mutation T790M examined by PNA-LNA polymerase chain reaction clamp method,[8] no history of chemotherapy, an age of 75 years or younger, performance status 0 to 1, appropriate organ functions, and written informed consent.

Treatment with Gefitinib

All the patients initially received 250 mg of gefitinib everyday according to the protocol of NEJ002. In NEJ002, a temporary cessation of the drug administration was recommended by the protocol when an intolerable toxicity such as grade 3 or worse adverse event was observed during the treatment with the standard dose, and a dose reduction of gefitinib by changing the everyday schedule to every 2 days schedule was permitted when grade 2 toxicity was observed.

In this analysis, we categorized patients into two groups according to their treatment status as follows: standard-dose group, in which gefitinib was administered without any dose reductions until disease progression was observed, and low-dose group, in which gefitinib was administered with a reduced dose at least once during the treatment period before disease progression (Figure 1).

Clinical Assessments

According to the protocol of NEJ002, the assessment of antitumor response to gefitinib was performed by computed tomography every 2 months until disease progression was observed. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumor (RECIST, version 1.0).[9] The PFS was defined as the period from the date of randomization to the date when disease progression was first observed or death occurred. The response and PFS were determined by an external review of the computed tomography films by experts who were not aware of the treatment assignment. Overall survival (OS) was defined as the period from the date of randomization to the date of death.

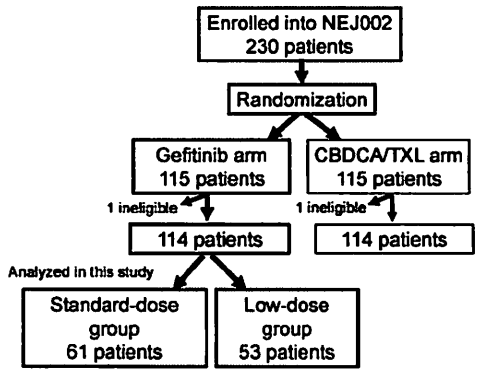

FIGURE 1. Flowchart of the patients analyzed in this study.

Kaplan-Meier survival curves were drawn for PFS and OS, and differences between the groups were compared by log-rank test. The difference in response rate was compared by Fisher's exact test. Each analysis was two-sided, with a 5% significance level and a 95% confidence interval, and was performed using SAS for Windows software (release 9.1, SAS Institute, Cary, NC).

RESULTS

Treatment

The demographics of patients in each group are listed in Table 1. Around half of the patients in NEJ002 were categorized as low-dose group. There was no significant difference in each clinical factor and the type of EGFR mutation between the two groups. Standard-dose group received 250 mg gefitinib for 261 days (median) (Table 2). Nine patients temporarily suspended their treatment (median, 6 days; range, 1–32 days) due to some toxicities but restarted the treatment with standard dose. Low-dose group received 250 mg gefitinib every day for 74 days (median) and then every 2 days for 125 days (median). Before restarting the treatment using a reduced dose, 38 patients needed a break in their treatment (median, 19 days; range, 2–79 days) to recover from adverse events.

At the data cutoff point (early December 2009), 37 patients (61%) in the standard-dose group and 26 patients (49%) in the low-dose group had stopped the first-line gefitinib treatment due to disease progression, while 7 patients (11%) in the standard-dose group and 5 patients (9%) in the low-dose group had terminated the treatment because of treatment-related toxicities such as interstitial lung disease and liver dysfunction.

Efficacy

Low-dose group showed at least not-inferior efficacy (response and survival) compared with standard-dose group.

TABLE 1. Patient Characteristics

	Standard Dose	Low Dose	*p*
No. of patients	61	53	
Sex			
Male	27	15	0.084
Female	34	38	
Mean age (range)	64 (43–75)	64 (47–75)	0.742
Mean body weight (range)	56.2 (41.1–81.6)	54.2 (34.7–93.0)	0.443
Smoking status			
Never smoker	37	38	0.876
Smoker	24	15	
Performance status			
0/1/2	28/33/0	26/26/1	0.824
Histology			
Adenocarcinoma	53	50	0.483
Others	8	3	
Clinical stage			
IIIB	8	7	0.805
IV	46	42	
Postoperative	7	4	
Type of EGFR mutation			
Exon 19 deletion	27	31	
L858R	27	22	
Others	7	0	

TABLE 2. Treatment Pattern with Gefitinib in Each Group

	Standard Dose	Low Dose
Given continuously	*n* = 61	*n* = 53
Mean (SD)	287 d (211)	160 d (197)
Median (range)	261 d (14–790)	74 d (19–1153)
Given intermittently		*n* = 53
Mean (SD)		205 d (200)
Median (range)		125 d (7–897)
Treatment break period	*n* = 9	*n* = 38
Mean (SD)	13 d (11)	23 d (18)
Median (range)	6 d (1–32)	19 d (2–79)

The response rate and disease control rate were 83% and 98% in the low-dose group and 66% and 82% in standard-dose group, respectively.

PFS for low-dose group tended to be superior to that of standard group, although a statistical significance was not detected. Median PFS and 1-year PFS rate were 11.8 months and 50% in low-dose group and 9.9 months and 36% in standard-dose group, respectively (Figure 2*A*). As some patients in low-dose group had switched to the low dose after a long-term treatment with standard-dose gefitinib, we additionally investigated the efficacy of more "refined" low-dose group (n = 25) who had been treated with gefitinib at standard dose during less than 60 days. The response rate, median PFS, and 1-year PFS rate of the group were 83%, 7.1 months, and 27%, respectively, which was not statistically different from those results of standard-dose group (Figure 2*B*). The OS was significantly longer in low-dose group than standard-dose group (median: 32.7 versus 25.3 months: $p = 0.049$) (Figure 2*C*, Table 3).

DISCUSSION

Recent phase 3 studies including NEJ002 have suggested that EGFR-TKIs are more effective than cytotoxic chemotherapy in the first-line treatment against advanced NSCLC with mutated EGFR.[6,7,10] However, many patients could not continuously receive standard dose of gefitinib because of some adverse effects. In fact, about half of the patients treated with gefitinib in NEJ002 required a dose reduction. Therefore, treatment strategy with less toxicity is required especially for patients with a poor condition or for elderly patients. In this report, we demonstrated that low-dose gefitinib may not be inferior to standard-dose gefitinib for NSCLC patients with EGFR mutations.

Previous reports of EGFR mutations had suggested that NSCLC cell with mutated EGFR was highly sensitive to EGFR-TKI than those without mutations.[5] Recently, Yeo et al.[11] also showed that both erlotinib and gefitinib suppressed the proliferation of EGFR-mutated NSCLC cell lines even at a very low concentration. Moreover, they reported a retrospective observation that patients treated with 25 mg of erlotinib which was equivalent to 250 mg of gefitinib where 5 out of examined 7 patients respond to the "low-dose" erlotinib and median PFS of those patients was 17 months. The current study employed a larger number of patients and supported their results that NSCLC patients with mutated EGFR received a similar level of efficacy from low-dose gefitinib as standard-dose gefitinib. Although low-dose gefitinib in this study are considered to be much less than 25 mg of erlotinib, twice longer half life in plasma and much higher tumor/plasma concentration ratio of gefitinib compared with erlotinib may favor gefitinib.[12–14]

There are some limitations in the current study. Because the study was a retrospective analysis, biases in patient characteristics or undetectable factors may exist and affected the results. From a pharmacokinetics point of view, as mean body weight tended to be lighter in the low-dose group, relatively higher drug concentration might be obtained in those patients even from the low-dose gefitinib. Considering that the OS for low-dose group was significantly longer than that for standard-dose group, the low-dose group might include more patients with slow-growing tumor than standard-dose group incidentally. More importantly, even for the patients in low-dose gefitinib group, the treatment was not initiated with low dose but with standard dose, thus the period with standard-dose gefitinib might affect the efficacy. Although the refined low-dose group still showed a similar efficacy to standard-dose group, its small sample size cannot draw a definite conclusion. To examine the efficacy and safety, and appropriate treatment schedule of low-dose gefitinib (e.g., initial standard dose followed by low dose versus thoroughly low dose), prospective comparative trials should be conducted.

In conclusion, our retrospective analysis suggests that low-dose gefitinib may be clinically equivalent to standard treatment with gefitinib for NSCLC with sensitive

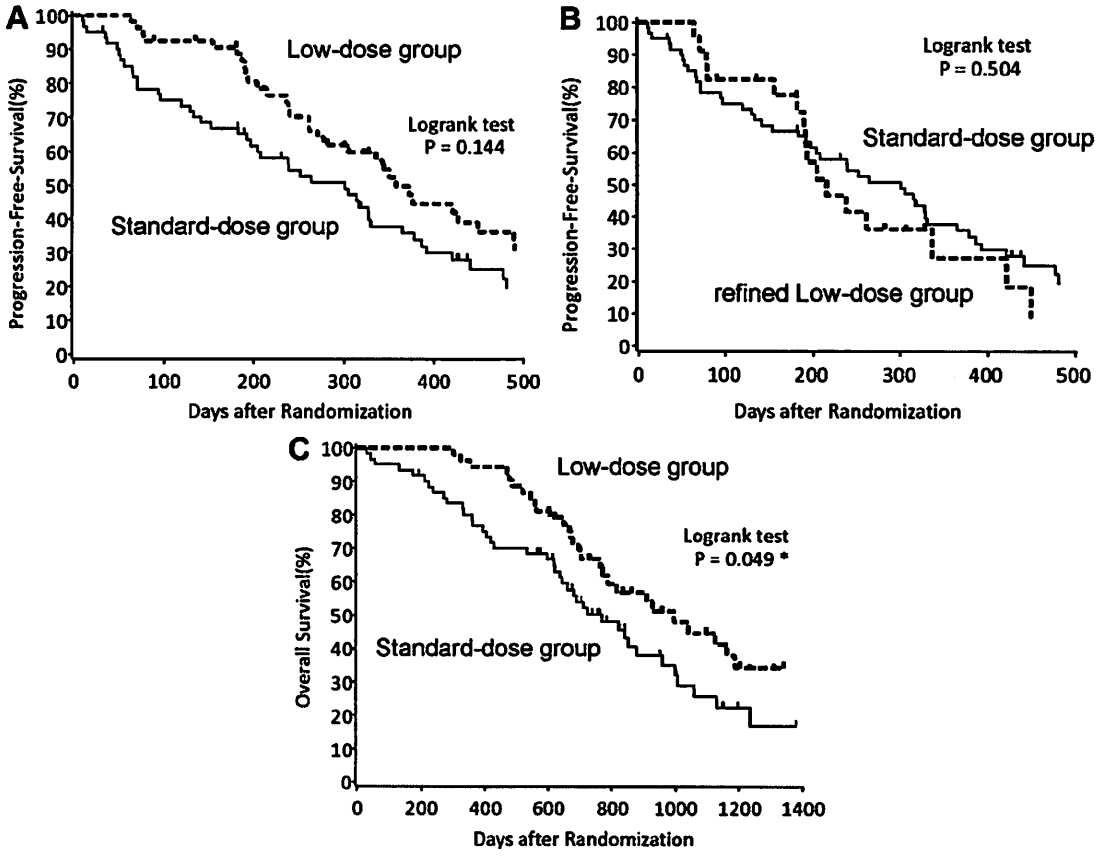

FIGURE 2. Progression-free survival curve of standard-dose group (solid line) and low-dose group (dotted line) with entire population (*A*) and another comparison of progression-free survival between standard-dose group and refined low-dose group (*B*). Overall survival curve of each group (*C*).

TABLE 3. Response and Survival

	Standard Dose	Low Dose	*p*
Overall response rate	66%	83%	0.005
95% CI	52 77	70 92	
Progression-free survival			
Median	9.9 mo	11.8 mo	0.144
1-yr PFS rate	36%	50%	
Overall survival			
Median	25.3 mo	32.7 mo	0.049
2-yr survival rate	50%	67%	

CI, confidence interval; PFS, progression-free survival.

EGFR mutations. Considering the merit of low-dose gefitinib in terms of risk-benefit balance, prospective studies using low-dose gefitinib is warranted targeting NSCLC patients with mutated EGFR, especially elderly or those with poor PS.

ACKNOWLEDGMENTS

Supported in part by grants-in-aid from the Japan Society for Promotion of Science and the Japanese Foundation for the Multidisciplinary Treatment of Cancer and a grant from the Tokyo Cooperative Oncology Group.

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