Treatment after the Failure of Gefitinib in Patients with Advanced or Recurrent Non-small Cell Lung Cancer

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Abstract. *Background: The optimal treatment for patients with progressive non-small cell lung cancer who initially show a good response to gefitinib is unclear. Patients and Methods: This study retrospectively analyzed 60 consecutive patients who experienced treatment failure after achieving disease control with gefitinib and thereafter underwent post initial gefitinib treatment either with or without continuing gefitinib. Results: Continuing gefitinib was independently associated with a good survival based on multivariate analyses (hazard ratio (HR)=0.51; 95% confidence interval (CI)=0.26-0.98; p=0.0426), and performance status at the failure of gefitinib (0.05; 0.02-0.17; p<0.0001). The adjusted HR of continuing gefitinib based on Cox regression analysis and a propensity score of 0.61 (95% CI, 0.41-0.92) indicated an association between a prolonged survival and the continuation of gefitinib. Conclusion: In addition to post gefitinib treatment, continuing the administration of gefitinib should be considered in patients who previously achieved disease control with gefitinib, even after a failure of gefitinib.*

Gefitinib (Iressa™; AstraZeneca, London, UK) is an orally active and selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that blocks signal transduction pathways. International phase II studies (IDEAL-1 and -2) have been conducted on the efficacy of gefitinib as a second- or third-line treatment in patients with advanced non-small cell lung cancer (NSCLC). These studies demonstrated the response rate to be 18% and 12%, respectively (1, 2). The Iressa Survival Evaluation in Lung Cancer (ISEL) trial was a randomized, placebo-controlled phase III trial conducted to investigate the effect of gefitinib on survival as a second-line or third-line treatment for patients with locally advanced or metastatic NSCLC (3). Treatment with gefitinib was not associated with a significant improvement in survival in comparison to a placebo in this study. However, a subgroup analysis showed there was a greater treatment effect among never-smokers (median time to treatment failure 5.6 months for gefitinib and 2.8 months for placebo; hazard ratio (HR) 0.55; 95% confidence interval (CI) 0.42-0.72; $p<0.0001$) than among former and current smokers (HR 0.89; 95% CI 0.78-1.01; $p=0.0707$), and among patients of Asian origin (median time to treatment failure 4.4 months for gefitinib and 2.2 months for placebo; HR 0.69; 95% CI 0.52-0.91; $p=0.0084$) than among those of non-Asian origin (HR 0.86; 95% CI 0.76-0.98; $p=0.0197$) (3). Recently, our group (4) and Kim *et al*. (5) reported the definitive data of two trials comparing gefitinib with docetaxel in second-line treatment of metastatic NSCLC. In the former trial (V-15-32), gefitinib did not reach non-inferiority in comparison with docetaxel (4). Conversely, in the latter trial (INTEREST), non-inferiority was reached using a more powered clinical and statistical design (5).

Unfortunately, most patients who are initially sensitive to gefitinib ultimately relapse. In addition, patients often experience a rapid progression of the disease once gefitinib administration is terminated following a relapse. The molecular mechanism of acquired resistance to gefitinib has been reported (6, 7). However, there have so far been few studies addressing treatment after the failure of gefitinib. The present study retrospectively evaluated the clinical value of continuing gefitinib administration after the failure of initial gefitinib treatment.

Patients and Methods

Patients. This institute had 62 consecutive pretreated patients with cytologically or histologically diagnosed advanced NSCLC or postoperative recurrence, who initially achieved disease control with gefitinib, but thereafter developed resistance to the treatment and underwent post initial gefitinib therapy from October 2002 to November 2007. Two patients who received gefitinib as a first-line treatment were excluded from the present study. Gefitinib was orally administered, at a daily dose of 250 mg. The clinical or pathological stage of the disease was based on the TNM classification of the Union Internationale Contre Cancer (UICC) (8). The histological analysis of the tumors was based on the WHO classification for cell types (9). The clinicopathological characteristics of the patients are

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Key Words: Non-small cell lung cancer, gefitinib, treatment failure, post initial gefitinib therapy.

Table I. *Clinicopathological characteristics of the patients.*

Parameter	n=60
Median age, years (range)	64 (34-77)
Gender, female/male	34/26
Histological type, ad/other	56/4
Smoking status, never/current or former smoker	38/22
Performance status at failure (ECOG), 0-1/≥2	51/9
No. of prior chemotherapy regimens, 1/2/>3	37/14/9
Response to prior chemotherapy, PR/SD	27/24
Response to gefitinib, CR/PR/SD	2/34/24
Median duration of disease control with gefitinib (months) (range)	12 (1-27)
Reason for PD with gefitinib, progression of the pre-existing target lesions/appearance of new lesions	17/43
Post initial gefitinib treatment, chemotherapy alone/radiotherapy alone/combination	22/16/22

ad, Adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

shown in Table I. Of these, 36 patients continued to receive gefitinib while the remaining 24 patients received other types of therapy due to their physician's decision.

Prior treatment and therapy after the failure of initial gefitinib. All patients received at least one prior chemotherapy regimens (platinum-doublet consisting of a so-called new cytotoxic agent) before the administration of gefitinib as shown in Table I. Approximately half of all patients had a partial response (PR) as the best response to prior chemotherapy. The majority of the patients had received gefitinib as a second-line therapy. After the failure of the initial gefitinib treatment, the patients received various therapies. Radiation therapy included palliative therapy for bone metastases and whole brain irradiation or gamma-knife surgery for brain metastases. Most of the chemotherapy regimens after the failure of the initial gefitinib therapy were single agent or a combination of new non-platinum agents, such as docetaxel, gemcitabine or vinorelbine and so on. Platinum-based combination regimens were selected for patients who had a good performance status (PS).

Tumor assessment during and after treatment. The change in disease was assessed by computed tomography (CT) findings of the chest every two months. The measurability of target lesions at baseline and the response criteria were based on the Response Evaluation Criteria in Solid Tumors (RECIST) (10).

Statistical analysis. The overall survival time in the current study was defined as the time from the date of failure of the initial gefitinib treatment to the date of death due to any cause. Patients who were alive on the date of the last follow-up were censored on that date. The duration of disease control with the initial gefitinib therapy was defined as the time from the initial date of gefitinib administration to the date of progression of the disease, the discontinuation of treatment, or death due to any cause and was censored at the date of the last follow-up visit for patients who did not discontinue, who were still alive and who did not have disease progression. Because the distribution of the duration time was rightly-skewed, this variable was dichotomized at the median value of 10 months. The distribution of the baseline clinical factors was compared using Fisher's exact test for categorical parameters and by pooled *t*-test for continuous parameters. Survival curves were estimated using the nonparametric Kaplan-Meier method (11, 12). A univariate Cox proportional hazards regression (13) was used to evaluate the possible association between the baseline covariates and patient prognosis.

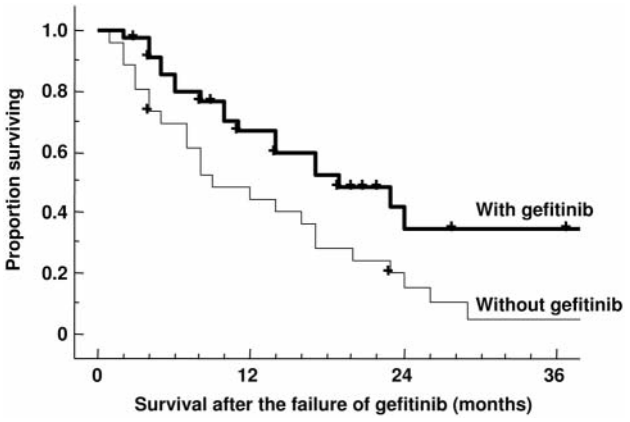

Figure 1. *The overall survival curves after the failure of gefitinib in the patients who underwent post initial gefitinib treatment with continued administration of gefitinib or other therapies alone.*

The primary scope of this study was to evaluate the value of continuing gefitinib therapy in patients with progressive NSCLC that initially responded to gefitinib. To reduce any possible selection bias due to an imbalance of clinical factors, whether continuing gefitinib or not, a covariate adjustment was performed using the propensity score (14). In this method, the propensity score (on the probability scale) and a variable denoting the continuation of gefitinib administration were entered in the Cox proportional hazards regression. The prognostic effect of continuing the drug was thus determined according to the regression coefficient. The propensity scores were estimated using a logistic regression model. All *p*-values reported as two-tailed and statistical significance was defined as $p<0.05$. The analyses were conducted using StatView statistical software program (Abacus Concepts, Inc., Berkeley, CA, USA) and SAS (SAS Institute Inc., Cary, NC, USA).

Table II. *Univariate Cox analysis for overall survival after the failure of gefitinib treatment.*

Variable	Referent	HR	95% CI	*p*-Value
Age (years)	<65 *vs.* ≥65	0.67	0.36-1.27	0.222
Gender	Female *vs.* Male	0.81	0.43-1.52	0.506
Smoking history	No *vs.* Yes	1.00	0.53-1.90	0.998
ECOG PS at the failure of gefitinib	0-1 *vs.* ≥2	0.05	0.02-0.15	<0.0001
No. of prior chemotherapy regimens	1 *vs.* ≥2	0.74	0.39-1.41	0.359
Response to prior chemotherapy	Yes *vs.* No	0.70	0.37-1.33	0.277
Response to gefitinib	CR/PR *vs.* SD	0.74	0.39-1.40	0.351
Duration of disease control with gefitinib (months)	≥10 *vs.* <10	0.41	0.21-0.80	0.009
Gefitinib continued	Yes *vs.* No	0.49	0.26-0.91	0.025

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Table III. *Multivariate Cox analysis with covariates selected by univariate analysis.*

Variable	Referent	HR	95% CI	*p*-Value
ECOG PS at the failure of gefitinib	0-1 *vs.* ≥2	0.05	0.02-0.17	<0.0001
Duration of disease control with gefitinib (months)	≥10 *vs.* <10	0.57	0.28-1.15	0.1145
Gefitinib continued	Yes *vs.* No	0.51	0.26-0.98	0.0426

Results

Treatment and response after the relapse of gefitinib. The response rate (RR) and disease control rate (DCR; PR plus stable disease, SD) for post-treatment after the failure of gefitinib was 13.3% (8/60) and 33.3% (20/60), respectively. The RR was 11.1% (4/36) and 16.7% (4/24) of patients with gefitinib and without gefitinib, respectively and the DCR was 27.8% (10/36) and 41.7% (10/24), respectively. There was no significant difference between the two groups (p=0.40).

Survival after the failure of gefitinib. The median follow-up duration from the failure of initial gefitinib treatment was 12 months (range: 1-41 months). The survival curves with or without continuing gefitinib are shown in Figure 1. There was a statistically significant difference between the patients who underwent therapy after the failure of initial gefitinib therapy with and without gefitinib (HR=0.48; 95% CI, 0.26-0.88). A univariate Cox analysis was used to determine the prognostic effect of covariates including age, gender, smoking status, PS at failure, the number of prior chemotherapy regimens, the response to prior chemotherapy, the response to gefitinib, the duration of disease control with initial gefitinib and the continuation of gefitinib administration. Of these, in addition to continuing gefitinib, PS at failure (HR=0.05; 95% CI, 0.02-0.15) and duration of disease control with initial gefitinib (HR=0.61; 95% CI, 0.42-0.89) indicated a possible independent association with the overall survival (Table II). Continuing gefitinib (HR=0.51; 95% CI, 0.26-0.98) and PS at the failure of gefitinib (HR=0.05; 95% CI, 0.02-0.17) indicated an independent association with the overall survival using a multivariate Cox analysis (Table III).

Table IV. *Adjusted hazard ratio of continuing gefitinib administration by using propensity score analysis.*

Parameter	HR	95% CI	*p*-Value
Gefitinib continued			
No	1.00		
Yes	0.61	0.41-0.92	0.0196
Propensity score	0.73	0.57-0.94	0.0148

The prognostic effect of continuing gefitinib was adjusted for known, measurable confounders using propensity score methods. The propensity score with regard to continuing gefitinib treatment was assigned to each patient by a logistic regression model with seven covariates (age, gender, smoking status, PS at failure, the number of prior chemotherapy regimens, the response to prior chemotherapy, the response to gefitinib, and the duration of disease control with initial gefitinib). Since the prognostic factors were not distributed evenly in the two groups with/without continuing gefitinib, the propensity scores were therefore different between them. The median propensity score (on the

probability scale) was 0.74 (range, 0.14-0.96) for the group without continuing gefitinib in comparison to 0.87 (0.39-0.99) for the group with continuing gefitinib. The adjusted HR of continuing gefitinib which was obtained by the Cox regression and the propensity score was 0.61 (95% CI, 0.41-0.92) indicating a prolonged survival associated with the continuation of gefitinib (Table IV).

Discussion

Two subsequent phase III trials randomized previously untreated patients with advanced NSCLC into standard platinum-based chemotherapy alone or that with the addition of two different doses of gefitinib (15, 16). These trials demonstrated no difference in the response rate, time to progression, or either 1-year or overall survival with the addition of gefitinib to standard chemotherapy. Therefore, no discernible improvement was observed in the outcome following the addition of gefitinib to standard cytotoxic chemotherapy. However, the effects of gefitinib in combination with cytotoxic chemotherapy in the refractory patients who have disease control with gefitinib remains unknown. Shoji *et al*. reported the characteristics and failure pattern of gefitinib responders with postoperative recurrence of pulmonary adenocarcinoma. Most responders failed due to the appearance of new lesions without progression of the pre-existing target lesions (17). Some gefitinib-resistant tumors develop new lesions while some gefitinib-sensitive tumors remain. It is possible that gefitinib may suppress the initial target lesions even after the appearance of new lesions. Therefore, the careful consideration of both gefitinib treatment for the gefitinib-sensitive lesions and additional treatment for gefitinib-resistant lesions is therefore recommended.

Riely *et al*. reported prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in NSCLC patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus, an inhibitor of mammalian target of rapamycin. Thirteen patients had 18-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography/CT and CT scans at baseline, 3 weeks after stopping erlotinib or gefitinib, and 3 weeks after restarting erlotinib or gefitinib. Three weeks after restarting erlotinib or gefitinib, everolimus was added to their treatment (18). Although the addition of everolimus failed to shrink tumors further in their clinical setting, this prospective study of 10 patients who previously responded to erlotinib or gefitinib suggested that these patients continued to benefit from treatment with erlotinib or gefitinib despite documented progression of disease by RECIST. When patients with acquired resistance to erlotinib or gefitinib discontinued EGFR-TKI treatment, the majority of patients had worsening in lung cancer symptoms, an increase in tumor size, and an increase in tumor FDG uptake. Just 3 weeks after resuming the EGFR-TKI, the majority of patients had stabilization or improvement in symptoms, a decrease in tumor size and a reduction in tumor FDG uptake. Disease progression generally implies resistance to therapy and leads to a change in the therapy regimen. However, this theory might not apply to EGFR-TKIs. Gefitinib administration should not be terminated following a relapse so as not to experience a rapid progression of the disease or worsening symptoms caused by lung cancer.

Grothey *et al*. reported same results as our study concerning the survival benefit of exposure to molecular targeting agents beyond progression in BRiTE, the first-line Bevacizumab Regimens: Investigation of Treatment Effects and Safety, a large observational study in patients with metastatic colorectal cancer. In this study, all patients received bevacizumab, a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF), as part of first-line therapy. Patients who had first progression were grouped into 3 subgroups: i) no treatment, ii) post-progression treatment without bevacizumab, and iii) post-progression treatment with bevacizumab by physician decision not randomization. In multivariate analysis, exposure to bevacizumab beyond first progression and exposure to any second-line chemotherapy were independently associated with increased overall survaival (both $p<0.001$) (19).

Cho *et al*. reported a phase II study of erlotinib in advanced NSCLC after the failure of gefitinib. The erlotinib produced a greater clinical benefit in patients who had shown SD with prior gefitinib therapy in their study (20). The standard doses of 250 mg gefitinib and 150 mg erlotinib are not equivalent. Erlotinib was administered at its maximum-tolerated dose, whereas gefitinib was administered at approximately one third of its maximum-tolerated dose. Instead of gefitinib, the administration of another EGFR-TKI such as erlotinib may lead to a clinical benefit in patients who initially achieved disease control while receiving gefitinib.

A secondary mutation that substitutes methionine for threonine at position 790 (T790M) in the EGFR kinase domain (6, 7) and *MET* amplification with or without T790M mutation (21, 22) are associated with the acquisition of resistance to EGFR-TKI. A novel mutation, which leads to the substitution of tyrosine for aspartic acid at position 761 (D761Y) was found in a brain metastasis (23). Further mutation analyses are ongoing.

In conclusion, post initial gefitinib treatments with the continued administration of gefitinib should therefore be considered in those patients who achieved disease control by gefitinib, even after the failure of gefitinib therapy. A prospective randomized clinical trial is necessary to evaluate the benefits of the continued use of gefitinib after relapse in patients who initially achieved disease control by gefitinib.

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