Early Radiographic Response to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor in Non-small Cell Lung Cancer Patients with Epidermal Growth Factor Receptor Mutations: A Prospective Study

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Background: The time schedules for response evaluation of epidermal growth factor receptor-tyrosine kinase Inhibitor (EGFR-TKI) in non-small cell lung cancer (NSCLC) patients are still ill-defined.

Methods: Stage IIIB/IV patients with histologically proven NSCLC were enrolled in this study if the tumor cells bore *EGFR* mutations other than T790M. Eligible patients were treated with either 250 mg of gefitinib or 150 mg of erlotinib once daily. The early response rate [computed tomography (CT) scan on Day 14], definitive response rate determined on Day 56, progression-free survival (PFS), overall survival (OS), and toxicity profile were assessed prospectively.

Results: Thirty-nine patients were enrolled in this study. A total of 29 patients (29/39, 74.4%) achieved partial response (PR). Twenty-one patients (21/39, 53.8%) had early radiological response on Day 14. The early radiological response rate in patients with PR was 72.4% (21/29). Only eight patients without a PR on early CT still ended with PR. Among the 29 patients with PR, the PFS (8.1 months) and OS (18.3 months) of the 21 patients with early CT response were shorter than those of the 8 patients without early CT response (11.9 and 24.0 months for PFS and OS, respectively). But the survival differences were statistically non-significant.

Conclusions: A very high percentage (72.4%, 21/29) of NSCLC patients with *EGFR* mutations with PR demonstrates early radiological response to EGFR-TKIs, which would advocate early radiological examination for EGFR-TKI therapy in NSCLC patients.

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Key words: computed tomography scan, epidermal growth factor receptor, non-small cell lung cancer, treatment response, tyrosine kinase inhibitor

At a Glance Commentary

Scientific background of the subject

The time schedules for response evaluation of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in non-small cell lung cancer (NSCLC) patients are still ill-defined. In this prospective study, we attempted to determine the TKI response, including the early radiological response rate (on Day 14), overall response rate (ORR), PFS, and overall survival (OS) to EGFR-TKI treatment in NSCLC patients bearing *EGFR* mutations.

What this study adds to the field

A very high percentage (72.4%, 21/29) of NSCLC patients with *EGFR* mutations with PR demonstrated early radiological response to EGFR-TKIs, which would advocate early radiological examination for EGFR-TKI therapy in NSCLC patients.

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Lung cancer, especially non-small cell lung cancer (NSCLC), has become the leading cause of cancer deaths in most parts of the world due to its high mortality rate.[1,2] Thus, it has also become the leading target for the development of new anti-cancer agents. Among the targeted therapies that inhibit activated protein kinases with small-molecule drugs, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been active in the treatment of advanced NSCLC. Two drugs, erlotinib (Tarceva) and gefitinib (Iressa; AstraZeneca Inc., Menchester, UK), have been shown to have survival benefit in Caucasians and Asians, respectively, when compared to placebo in controlled, double-blinded, randomized phase III trials.[3,4] These two EGFR-TKIs disrupt *EGFR* signaling by competing with adenosine triphosphate (ATP) for the binding sites at tyrosine kinase domain, and result in inhibition of phosphorylation and the downstream signaling network. These EGFR-TKIs are only effective to a subgroup of NSCLC patients and act faster than conventional chemotherapy, but have relatively mild side effects.[5,6] In 2004, Lynch *et al.* and Paez *et al.* identified mutations in the tyrosine kinase domain of *EGFR* gene, which were correlated with the clinical responsiveness to gefitinib.[7,8] We reported a very high *EGFR* mutation rate in the NSCLC patients in Taiwan, mainly with adenocarcinoma, and its association with the clinical responsiveness (the first report from Asian countries) in 2004,[9] soon after the above two reports from Harvard Medical School. Various reports from other Asian countries have shown similar results.[10-12] Three prospective studies from Japan demonstrated that the overall response rate (ORR) in patients who have mutated NSCLC and received TKI treatment was 75%, and the median progression-free survival (PFS) was 8.9-11.5 months.[13-15] Yang *et al.* also reported a longer time of progression to TTF (time to treatment failure) in NSCLC patients bearing exon 19 deletion or L858R mutation of *EGFR* than the wild type in advanced NSCLC patients receiving first-line gefitinib monotherapy.[16] In contrast, among unselected NSCLC patients, the objective response rate was only about 10%.[5,6] Thus, *EGFR* mutations have become an important molecular biomarker for physicians to choose an appropriate first-line treatment for NSCLC patients.[17,18]

Conventionally, the response to anticancer treatment, including targeted therapy, is evaluated after the patient completes the second course of treatment.[17] Although the response to EGFR-TKI could be dramatic in a few days, the actual timing to reach a radiographic response has not been well studied. The time schedules for response evaluation are also still ill-defined. In order to predict the early responsiveness to gefitinib, Sunaga *et al*. evaluated the changes in ^{18}F-fluorodeoxyglucose (FDG) uptake by positron emission tomography (PET) on Day 2 and Day 28 after the initiation of gefitinib therapy in five patients with NSCLC.[19] In patients who eventually achieved radiographic partial response (PR) and stable disease (SD), the uptake of FDG decreased up to 61% and 59%, respectively, on Day 2 and 26% and 43%, respectively, on Day 28. In contrast, FDG uptake was increased up to 153% on Day 2 and 232% on Day 28 in one patient with progressive disease (PD). Also, in a xenograft model, Ullrich *et al*. demonstrated that erlotinib-sensitive tumors exhibited a striking and reproducible decrease in 3′-deoxy-3′-[^{18}F]-fluoro-l-thymidine (^{18}F-FLT) uptake after only 2 days of treatment.[20] The above preliminary results suggested that PET may be useful in predicting EGFR-TKI response in very early days. However, a recent study has demonstrated that it is the radiographic response, rather than the PET scan response, that predicted survival after neoadjuvant chemotherapy for resectable NSCLC.[21] The role of PET in evaluating the treatment outcome is yet to be determined. Consequently, defining the early response of patients with NSCLC by computed tomography (CT) scan examination remains a very important issue.

In this prospective study that was started in 2005, we attempted to determine the TKI response, including the early radiological response rate (on Day 14), ORR, PFS, and overall survival (OS) to EGFR-TKI treatment in NSCLC patients bearing *EGFR* mutations. Radiological response to EGFR-TKIs was found on Day 14 in 21 of 39 patients (53.8%) and on Day 56 in 21 of 29 patients (72.4%) with confirmed PR. This may be the first report regarding the correlation between the early radiological image change and the overall response to EGFR-TKI in NSCLC patients with *EGFR* mutations.

PATIENTS AND METHODS

Phase II clinical trial design

This single-center, phase II study was approved by the Institutional Review Board (IRB) of the Chang Gung Memorial Hospital (CGMH) in 2005 (protocol No. CMRPG: 350031, IRB No. 94-0615B and No. 96-0086C), and written informed consent was obtained from all enrolled patients. The primary objective of this study was to determine the treatment response to EGFR-TKIs on Day 56 and the early radiological response (by CT scan on Day 14) in NSCLC patients with *EGFR* mutations and stage IIIB/stage IV disease. Secondary objectives were to correlate the TKI response with different *EGFR* mutations and to evaluate the safety and efficacy (PFS and OS) of TKI treatment.

The inclusion criteria were: Patients of age 18 years or older, having confirmed non-squamous NSCLC histology, positive for *EGFR* mutation other than T790M (the mutation analyses need to done on fresh tumor tissue samples only), not amenable to curative surgery or radiotherapy, chemotherapy-naïve or failure of prior treatment with one chemotherapy regimen (platinum-based regimen), Eastern

Cooperative Oncology Group performance status of 0-3 and an estimated life expectancy of more than 12 weeks, fully recovered from toxic effects of previous antitumor therapy, not having taken chemotherapy within 1 month, and with adequately functioning liver [total bilirubin <1.25 times the upper normal limit (UNL) of the institutional normal value, transaminases <5 × UNL, alkaline phosphatase <6 × UNL], kidneys (serum creatinine < 1.5 × UNL), and bone marrow (hemoglobin ≧ 10 g/dl, neutrophils ≧ 2000/μl, platelets ≧ 100,000/μl). The postoperative recurrent NSCLC could also be included. Brain metastasis could be included only if no symptoms were present.

The exclusion criteria were: Central nervous system (CNS) metastasis unless the patients were clinically stable 6 weeks after radiotherapy, secondary malignancies, and major systemic diseases. The eligible patients received erlotinib 150 mg/day or gefitinib 250 mg/day after signing the informed consent and completing the screening procedures. CT scan of all of the measurable tumor sites was performed on Day 14, Day 56, and then every 8 weeks, and the lesions were evaluated using Response Evaluation Criteria in Solid Tumor (RECIST).[22] The time point for determination of treatment response was on Day 56. Treatment was continued until disease progression as documented by imaging studies or until development of unacceptable toxicity. Adverse events were recorded every 2 weeks according to the National Cancer Institute Common Toxicity Criteria version 3. If the patients had documented treatment failure to EGFR-TKIs, they were withdrawn from this study and were advised to receive chemotherapy after the discontinuation of EGFR-TKIs.

Tissue acquisition and *EGFR* gene mutation analysis

Most of the tumor tissues for mutation analyses (34/39, 87.2%) were fresh-frozen tissues acquired from CT-guided core needle biopsy or from wedge resection of lung or craniotomy for brain metastasis at the time of diagnosis. Two samples were collected from pleural effusion and three samples were formalin-fixed paraffin-embedded tissues. For the mutational analysis of the kinase domain of *EGFR*, coding sequences from exons 18 to 21 were amplified by polymerase chain reaction (PCR) and subjected to direct sequencing as previously described.[9,23] Sequencing reactions was electrophoresed on an ABI 3700 genetic analyzer. Chromatography was reviewed by two investigators with manual and BLAST software with the *EGFR* reference sequence (NM_005228.3, NCBI). All sequence variations were re-examined by a second independent PCR amplification and repeated sequencing reactions.

Statistical analyses

The PFS and OS were estimated by the Kaplan–Meier method. The log-rank test was used to assess between-group differences. A two-sided $p < 0.05$ was considered statistically significant. The response and toxicity data were analyzed using simple descriptive statistics.

RESULTS

Patient characteristics and *EGFR* gene mutations

From October 2005 to December 2008, 112 NSCLC patients of non-squamous histology had the tumor samples available for *EGFR* mutation analyses. Sixty patients (54%) were *EGFR* mutation positive. Patients with T790M mutations were not included. Among the 60 patients, 39 were enrolled in this study; the remaining 21 patients were either not eligible or underwent chemotherapy [Figure 1]. All patients were Taiwanese and the median age was 62 years (range 41-79). The clinicopathologic characteristics are listed in Table 1. The pathological diagnoses for all samples were adenocarcinoma. The *EGFR* mutations identified were mainly exon 19 deletions (15 patients) and L858R point mutations (21 patients).

TKI therapeutic response evaluated by CT scan

Thirty-four patients received gefitinib 250 mg daily and five patients received erlotinib 150 mg daily. In two of these five patients, erlotinib was the second targeted therapy after they developed drug resistance to gefitinib. One of these two patients has been reported previously.[24] All 39 patients were fully assessable for efficacy and toxicity. The response patterns and survival data are shown in Table 2. The median follow-up time was 24.0 months (range 9.5-47.5 months). Twenty-nine (74.4%) of the 39 patients achieved PR, 6 (15.4%) had SD, and 4 (10.2%) had PD. The median PFS was 6.8 months [95% confidence interval (CI): 4.3-9.5 months]. The median OS was 15.9 months (95% CI: 6.6-25.2 months). A total of 21 (53.8%) of the 39 patients demonstrated early radiographic response by CT scan performed on Day 14 [Figure 2]. The early radiological response rate in patients with PR was 72.4% (21/29). Only eight patients without a PR on the early CT still ended with PR.

TKI therapeutic response and survival

For patients with PR confirmed by the CT scan on Day 56, but not shown on Day 14, the median PFS was 11.9 months (95% CI: 9.6-14.2 months). For patients with PR detected on Day 14, the median PFS was 8.1 months (95% CI: 6.0-11.9 months). The PFS showed no significant differences between patients with and without early response ($p = 0.4059$). The median PFS for patients with SD and PD were 4.9 months and 2.1 months, respectively. The overall log-rank test for PFS, when comparing the four

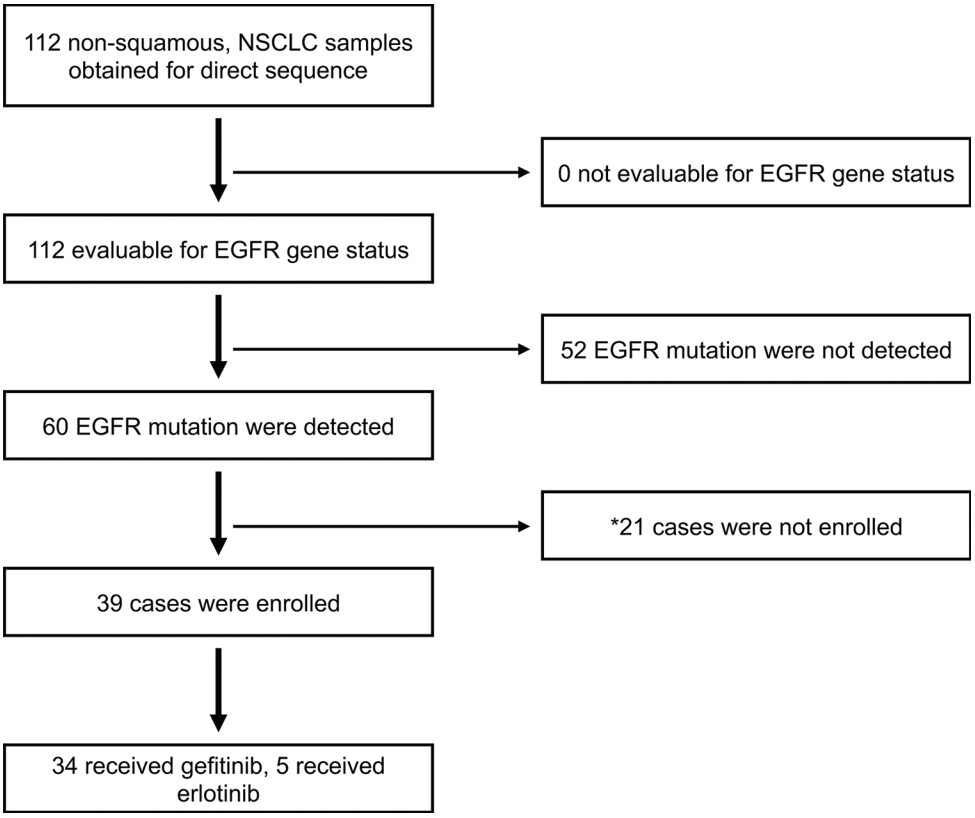

Figure 1: The schema of patient selection is presented in a consort diagram. Initially, we analyzed 112 consecutive non-squamous NSCLC samples for the DNA sequence, and all the samples were evaluable for *EGFR* mutation. Sixty samples were EGFR mutation positive other than T790M. A total of 39 patients were enrolled in the study. Thirty-four patients received gefitinib and five patients received erlotinib. *Twenty-one patients were either not eligible or received chemotherapy.

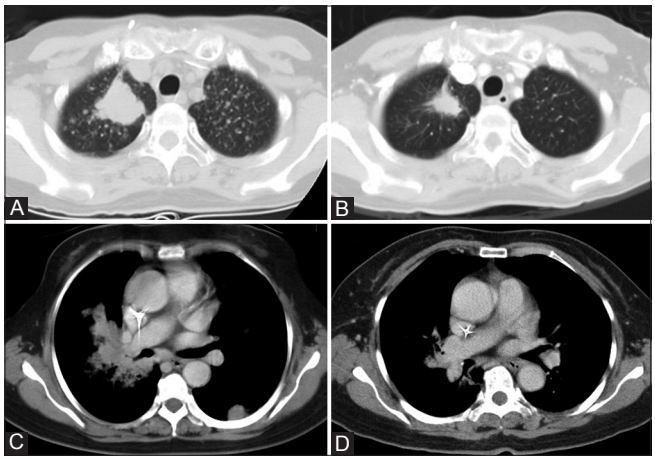

Figure 2: Early responses to EGFR-TKI were determined by CT scan performed on Day 14. (A and C) The CT scan images before EGFR-TKI treatment for Patient 1 and Patient 16, respectively. (B and D) Marked tumor shrinkage was found after EGFR-TKI treatment for 2 weeks in Patient 1 and Patient 16, respectively.

groups of patients (PR, early PR, SD, and PD), showed a significant difference ($p < 0.0001$) [Figure 3A]. For patients with PR confirmed by CT scan on Day 56, but not shown on Day 14, the median OS was 24.0 months (95% CI: 22.0 months). For patients with PR detected on Day 14, the median OS was 18.3 months (95% CI: 9.9-28.1 months). Also, there was no significant difference in the OS between patients with and without early response ($p = 0.3999$). The median OS for patients with SD was 9.8 months (95% CI: 6.8-12.8 months). The median OS for patients with PD had not reached yet due to the small number of cases (two died and two still alive). The overall log-rank test for OS, when comparing the four groups of patients (PR, early PR, SD, and PD), also showed significant difference ($p = 0.0186$) [Figure 3B]. There was no significant difference in the OS between patients with PR determined on Day 56, and PD was mainly due to the small number of cases in the PD group.

Among the 39 patients, 27 receiving gefitinib as the first-line treatment had similar efficacy. The median PFS was 8.1 months (95% CI: 5.9-10.2 months) and the median OS was 15.9 months (95% CI: 9.9-21.9 months). Twenty-one (77.8%) patients achieved PR on Day 56 and 14 (72.4%) of the 21 patients with PR achieved early response on Day 14.

EGFR mutation subtypes and survival

We also analyzed the relationship between the efficacy and subtypes of *EGFR* mutation. The early

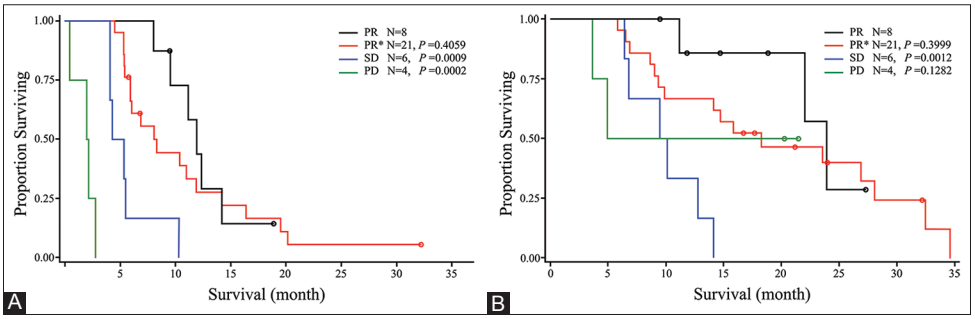

Figure 3: The 39 lung adenocarcinoma patients were divided into four groups according to their response patterns: PR, patients with partial response confirmed by the CT scan on Day 56, but not shown on Day 14; PR*, patients with early partial response confirmed by CT scan on Day 14; SD, patients with stable disease; and PD, patients with progressive disease. (A) Kaplan–Meier curves for progression-free survival (PFS) of the PR group versus the other three groups (PR*, SD, and PD, respectively). The median PFS of the four groups were: PR = 11.9 months, PR* =8.1 months, SD = 4.9 months, and PD = 2.1 months. Of the patients with PR, there were no significant differences between patients with and without early response ($p = 0.4059$). (B) Kaplan–Meier curves for overall survival (OS) of the PR group versus the other three groups (PR*, SD, and PD, respectively). The median survival of the four groups was: PR = 24.0 months, PR* =18.3 months, SD = 9.8 months, and PD = not reached yet (two died and two were alive).

Table 1: The clinicopathologic characteristics of 39 NSCLC patients

Variables	Number	%
Patients enrolled	39	100
Gender		
Male	16	41
Female	23	59
Age (years)		
Median (range)	62 (41-79)	
Stage		
IIIB	3	8
IV	36	92
Pathology diagnosis		
Adenocarcinoma	39	100
Site of distant metastasis		
Lung	15	39
Liver	8	21
Bone	17	44
Brain	13	33
ECOG PS		
0	2	5
1	21	54
2	16	41
Number of prior chemotherapies		
>2	2	5
1-2	10	26
0	27	69
Previous targeted therapy		
Yes	2	5
No	37	95

Abbreviations: NSCLC: Non-small cell lung cancer; ECOG PS: Eastern cooperative oncology group performance status

response rates were 60% (9/15) in patients with exon 19 deletion and 52.4% (11/21) in patients bearing L858R. The ORRs were 80% (12/15) in patients with exon 19 deletion and 71.4% (15/21) in patients bearing L858R. The PFS and OS of patients with exon 19 deletion were 5.9 months (95% CI: 3.8-8 months) and 18.3 months (95% CI: 9.6-27 months), respectively. In the group of patients bearing L858R, the PFS and OS were 8.1 months (95% CI: 5-11 months) and 12.8 months (95% CI: 7-18.5 months), respectively. There were no significant differences in these two groups in terms of PFS ($p = 0.82$) and OS ($p = 0.858$).

Safety

Treatment-related adverse effects (AEs) are summarized in Table 3. The most frequent AEs seen in this study were skin rash (46.2%), dry skin (38.5%), diarrhea (30.7%), and anemia (41%). Grade 3 or 4 paronychia, skin rash, and diarrhea were seen in 5.1%, 7.7%, and 2.6% of the patients, respectively. Three patients required dose reduction to 250 mg of gefitinib every other day because of toxicity (one with liver toxicity, one with skin toxicity, and one with paronychia). No life-threatening AEs, such as interstitial lung disease (ILD), were observed in this study. The complication rate of CT-guided core needle biopsy was 12.8% for pneumothorax and 6.4% for hemoptysis. There was no procedure-related mortality.

DISCUSSION

It was well demonstrated in Iressa Pan-Asia Study (IPASS) trial and a recent report from Japan that gefitinib was active mainly in *EGFR*-mutated NSCLC.[25,26] Therefore, it is very important to pinpoint the *EGFR* status by applying sensitive techniques to adequate tumor samples. In all the prospective studies published previously, the efficacy of EGFR-TKI in *EGFR*-mutated NSCLC patents was quite good. The response rate varied from 75% to 91%, and the PFS from 7.7 to 12.9 months.[13,14,19,27] In the current study, we also found that the NSCLC patients with *EGFR* muta-

Table 2: Clinical features of 39 adenocarcinoma patients of lung treated with EGFR-TKI

Gender	Age (years)	Smoking	Prior regimen[1]	TKI	Response	PFS (months)	OS (months)	Survival status[2]	Mutation 1	Mutation 2
M	41	Y	3	Erlotinib[3]	E-PR	19.5	26.87	D	delE746-A750	
M	61	Y	0	Gefitinib	E-PR	5.37	8.6	D	delE746-A750	
F	50	N	0	Gefitinib	E-PR	6.87	15.87	D	delE746-A750	
M	55	Y	1	Erlotinib	E-PR	5.4	9.87	D	delE746-A750	
F	79	N	1	Gefitinib	E-PR	20.17	28.1	D	delL747-P753	
F	51	N	4	Erlotinib[3]	E-PR	5.8	5.8	D	delK745-A750	
M	54	N	1	Gefitinib	E-PR	5.93	17.73	A	delL747-P753insS	
F	71	N	0	Gefitinib	E-PR	5.37	18.3	D	delE746-A750	
M	69	Y	0	Gefitinib	E-PR	5.43	14.13	D	delL747-E749	A750P
F	70	N	0	Gefitinib	PR	14.23	14.7	A	delL747-P753insS	
M	54	N	0	Gefitinib	PR	18.9	18.9	A	delE746-S752insV	
M	40	Y	0	Gefitinib	PR	11.17	23.97	D	delE746-A750	
F	71	Y	0	Gefitinib	SD	4.1	6.8	D	delE746-A750	
M	71	N	1	Gefitinib	SD	10.33	14.1	D	delE746-A750	
F	57	N	0	Gefitinib	PD	0.47	20.33	A	delE746-A750	
M	52	N	1	Erlotinib	E-PR	16.37	34.63	D	L858R	
M	73	N	0	Gefitinib	E-PR	8.1	14.7	D	L858R	
M	62	N	0	Gefitinib	E-PR	11	23.57	D	L858R	
F	51	Y	0	Gefitinib	E-PR	32.23	32.23	A	L858R	
F	74	N	0	Gefitinib	E-PR	8.3	9.33	D	L858R	
F	74	N	0	Gefitinib	E-PR	6.83	6.83	D	L858R	
F	73	N	0	Gefitinib	E-PR	14.27	21.17	A	L858R	
F	47	N	0	Gefitinib	E-PR	4.5	6.5	D	L858R	
F	89	N	0	Gefitinib	E-PR	11.9	16.73	A	L858R	
M	43	N	0	Gefitinib	E-PR	5.97	9.03	D	L858R	
F	57	Y	0	Gefitinib	E-PR	10.4	24.03	A	L858R	S768I
M	78	Y	0	Gefitinib	PR	9.57	11.17	D	L858R	
F	68	N	0	Gefitinib	PR	12.37	27.33	A	L858R	
F	44	N	0	Gefitinib	PR	8.07	11.87	A	L858R	
M	68	N	0	Gefitinib	PR	9.5	9.5	A	L858R	
F	52	N	0	Gefitinib	SD	5.37	12.77	D	L858R	
M	48	N	0	Gefitinib	SD	4.13	6.37	D	L858R	
F	66	N	1	Gefitinib	SD	5.53	9.47	D	L858R	
F	55	N	2	Gefitinib	SD	4.33	10.1	D	L858R	
F	38	N	0	Gefitinib	PD	2.13	21.47	A	L858R	
M	81	N	0	Gefitinib	PD	1.97	4.9	D	L858R	
F	64	N	1	Erlotinib	E-PR	6.07	32.5	D	E709K	G719A
F	57	N	2	Gefitinib	PR	11.93	22.03	D	G719C	S768I
F	66	N	2	Gefitinib	PD	2.8	3.6	D	P772_V774dup	

[1]Number of prior chemotherapy regimens; [2]survival status by the time of last follow-up; [3]erlotinib was their second targeted therapy. Abbreviations: M: Male; F: Female; TKI: Tyrosine kinase inhibitor; PFS: Progression-free survival; OS: Overall survival; PR: Partial response; E-PR: Partial response detected on Day 14; SD: Stable disease; PD: Progressive disease; D: Died; A: Alive

tions had a high response rate (29/39, 74.4%) to EGFR-TKI treatment. The efficacy is similar to that in the study series published previously. Among the 39 patients, 27 received gefitinib as the first-line therapy. The response rate, PFS, and OS showed no significant difference to the overall study.

On the other hand, although the response rate to EGFR-TKI treatment was high, some of the NSCLC patients with *EGFR* mutations were still non-responsive to TKIs in all reported series. Thus, detection of *EGFR* mutation alone is not sufficient for physicians to determine the best therapy. Earlier determination of EGFR-TKI treatment response will still be very helpful for physicians to make appropriate decision for further treatment. Although the changes in FDG uptake by PET has been reported useful in predicting early treatment response results,[19,20] the number of cases was quite small and whether it could correlate with the prognosis was still undetermined. In this study, we have demonstrated that a very high percentage (21/29, 72.4%) of patients with PR could have radiological response detected as early as 14 days after TKI treatment. Since TKI therapy fails in about 25% of patients with *EGFR* mutations, our study suggests that early CT imaging may be of value in selecting appropriate patients

Table 3: Drug toxicities by common toxicity criteria grade

Adverse events	CTC grade 1-2 (%)	CTC grade 3-4 (%)
Nonhematological		
Paronychia	8 (20.5)	2 (5.1)
Diarrhea	12 (30.7)	1 (2.6)
Skin rash	18 (46.2)	3 (7.7)
Dry skin	15 (38.5)	1 (2.6)
Acne	14 (35.9)	1 (2.6)
Nausea	10 (25.6)	1 (2.6)
Vomiting	4 (10.3)	1 (2.6)
Edema	5 (12.8)	1 (2.6)
Keratitis	7 (17.9)	0
Fatigue	8 (20.5)	0
Neuropathy	3 (7.7)	0
Mucositis	9 (25.0)	0
Constipation	3 (7.7)	0
Alopecia	1 (2.6)	0
Folliculitis	2 (5.1)	0
Hematological		
Leukocytopenia	4 (10.3)	3 (7.7)
Anemia	16 (41.0)	2 (5.1)
Thrombocytopenia	4 (10.3)	2 (5.1)
Neutropenia	0	4 (10.3)
Nephrotoxicity	6 (15.4)	1 (2.6)
Hepatotoxicity	11 (28.2)	2 (5.1)

Abbreviation: CTC: Common toxicity criteria

with TKI therapy. On the other hand, there were still eight patients actually ending up with a PR (8/18, 44%). Thus, the standard CT scan study on Day 56 still could not be replaced for determination of treatment response.

Interestingly, the median PFS and OS of the patients without early CT response were both longer than of patients with early CT response (11.9 months vs. 8.1 months for PFS and 24 months vs. 18.3 months for OS), but the differences were statistically non-significant. Since the patient number in this trial was small, future prospective studies with a larger patient number are necessary to clarify whether there are significant differences in the survival between patients with and without early radiological response.

In conclusion, this prospective study demonstrated a high correlation (72.4%) in the radiological response between early (Day 14) and regular evaluation time (Day 56), and a very high percentage (21/29, 72.4%) of early radiological response to EGFR-TKIs in NSCLC patients with *EGFR* mutations and PR, which would advocate early radiological examination for EGFR-TKI therapy in NSCLC patients. It can be very helpful for physicians to make appropriate decision for further treatment, even though it still cannot replace the standard CT scan study on Day 56.

Acknowledgments

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