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Phase II study of erlotinib for previously treated patients with EGFR wild-type non-small-cell lung cancer, following EGFR mutation status reevaluation with the Scorpion Amplified Refractory Mutation System

MASAHIRO MORISE[1], HIROYUKI TANIGUCHI[2], HIDEO SAKA[3], JOE SHINDOH[4], RYUJIRO SUZUKI[5], EIJI KOJIMA[6], TETSUNARI HASE[1], MASAHIKO ANDO[7], MASASHI KONDO[1], HIROSHI SAITO[8] and YOSHINORI HASEGAWA[1]

[1]Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Aichi 466-8550; [2]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Aichi 489-8642; [3]Department of Respiratory Medicine, National Hospital Organization, Nagoya Medical Center, Nagoya, Aichi 460-0001; [4]Department of Respiratory Medicine, Ogaki Municipal Hospital, Ogaki, Gifu 503-8502; [5]Department of Respiratory Medicine, Toyohashi Municipal Hospital, Toyohashi, Aichi 441-8085; [6]Department of Respiratory Medicine, Komaki Municipal Hospital, Komaki, Aichi 485-8520; [7]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Aichi 466-8550; [8]Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Okazaki, Aichi 444-0011, Japan

Received January 30, 2014; Accepted June 4, 2014

DOI: 10.3892/mco.2014.354

Abstract. While assessing the efficacy of erlotinib in patients with epidermal growth factor receptor (EGFR) wild-type (WT) non-small-cell lung cancer (NSCLC), the sensitivity of the method used for the EGFR mutation analysis may affect the evaluation of the efficacy. We conducted a phase II study of erlotinib for previously treated patients with EGFR WT NSCLC screened by the peptide nucleic acid-locked nucleic acid (PNA-LNA) polymerase chain reaction (PCR) clamp method, which is known to be highly sensitive. The primary endpoint was the objective response rate (ORR). Preplanned reevaluation of the EGFR genotype as an exploratory endpoint was performed using the Scorpion Amplification Refractory Mutation System (S-ARMS) assay. Erlotinib was administered daily until disease progression or development of unacceptable toxicity. A total of 53 evaluable patients were enrolled. The histological subtypes were adenocarcinoma in 40 patients, squamous cell carcinoma in 9 patients and not otherwise specified NSCLC in 4 patients. Partial response (PR) was achieved in 6 patients (4 with adenocarcinoma and 2 with squamous cell carcinoma). The ORR was 11.3% [95% confidence interval (CI): 4.3-23.0]. The median progression-free survival (PFS) was 1.8 months (95% CI: 1.2-2.3). Samples from 26 of the 53 patients (49.0%) were available for EGFR mutation reanalysis with the S-ARMS assay. Of these 26 samples, only 1 sample of adenocarcinoma was found to be EGFR mutation-positive (exon 19 deletion) and the patient achieved a PR. The EGFR WT genotype was reconfirmed by the S-ARMS assay in the remaining 25 patients and 2 of these patients exhibited a PR. This study did not meet the primary endpoint, although erlotinib was found to be moderately effective in pretreated patients with EGFR WT NSCLC, even when the EGFR mutational status was confirmed by the highly sensitive PNA-LNA clamp PCR method.

Correspondence to: Dr Masahiro Morise, Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Nagoya, Aichi 466-8550, Japan
E-mail: morisem@med.nagoya-u.ac.jp

Key words: erlotinib, non-small-cell lung cancer, epidermal growth factor receptor wild-type

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide. Non-small-cell lung cancer (NSCLC) is the predominant histological type of lung cancer and ~70.0% of all NSCLC patients have advanced-stage IIIB or IV disease at diagnosis. Platinum-based chemotherapy is currently the standard treatment for advanced NSCLC; however, almost all the patients treated by initial chemotherapy alone eventually develop a relapse.

Erlotinib, a selective epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), is currently recommended as second- or third-line standard treatment in patients with NSCLC (1). The presence of activating somatic

mutations in the EGFR gene has been shown to be a predictor of the response to treatment with EGFR-TKIs (2) and first-line EGFR-TKI therapy for patients with EGFR mutation-positive NSCLC was shown to improve the progression-free survival (PFS) compared to standard platinum-based chemotherapy (3-6). However, the results of subgroup analyses in the BR21 and SATURN trials suggest that erlotinib may also be beneficial to patients with EGFR wild-type (WT) NSCLC (1,7).

While assessing the efficacy of erlotinib in patients with EGFR WT NSCLC, the sensitivity of the method(s) used for the EGFR mutation analysis may affect the results of the evaluation. Although direct DNA sequencing has been widely used for EGFR mutation analysis, several new techniques, such as the peptide nucleic acid-locked nucleic acid (PNA-LNA) polymerase chain reaction (PCR) clamp method and the Scorpion Amplification Refractory Mutation System (S-ARMS) assay are currently available (8,9). Kim *et al* (10) reported a higher sensitivity of the PNA-LNA clamp method as compared to direct DNA sequencing for the detection of EGFR mutations in patients with NSCLC. In their study, the EGFR mutation positivity rate in 240 NSCLC patients was 34.6% when assessed by the PNA-LNA clamp method, but only 26.3% when assessed by direct DNA sequencing. Therefore, it is possible that erlotinib is found to be considerably less effective in patients with EGFR WT NSCLC, when the EGFR genotype is confirmed by highly sensitive methods, such as the PNA-LNA clamp method.

In addition, the predictive value of KRAS mutations for the efficacy of erlotinib in patients with EGFR WT NSCLC has not been fully elucidated. It was previously suggested that the presence of KRAS mutations may predict a poor response to EGFR-TKI therapy in patients with NSCLC (11). However, the EGFR mutation status may be a confounding factor in the analysis of the predictive value of KRAS mutations, since KRAS and EGFR mutations exhibit a strong negative correlation and EGFR mutation is a predictor of the response to EGFR-TKI therapy. Therefore, further evaluation of the predictive value of KRAS mutations in patients with EGFR WT NSCLC is required.

Based on these findings, we conducted a multicenter phase II trial of erlotinib for previously treated patients with EGFR WT NSCLC. The primary endpoint of this study was to assess the efficacy and safety of erlotinib in patients with EGFR WT NSCLC, as confirmed by the PNA-LNA clamp method, which is a highly sensitive method for EGFR mutation analysis. Preplanned reevaluation of the EGFR and KRAS mutation status as exploratory endpoints was performed using the S-ARMS assay in this study.

Patients and methods

Study design. This study was a multicenter, open-label, single-arm, phase II trial conducted in Japan. The study protocol was approved by the Central Japan Lung Study Group (CJLSG) Protocol Review Committee and the Institutional Review Board of each center as the CJLSG 0903 trial. The study was performed in accordance with the principles laid out in the Declaration of Helsinki and is registered with the University Hospital Medical Information Network in Japan (no. 000002692). The primary endpoint was the objective response rate (ORR) and the secondary endpoints were disease control rate (DCR), PFS, overall survival (OS) and safety. Moreover, if residual samples were available, we performed a preplanned reevaluation of the EGFR mutation status and KRAS mutation analysis with the S-ARMS assay as a secondary endpoint.

Eligibility criteria. Pretreated stage IIIB/IV NSCLC patients were assessed regarding their eligibility for enrollment in this study. The main inclusion criteria were as follows: Pathologically proven NSCLC; EGFR WT genotype confirmed by the PNA-LNA PCR clamp method; history of one or two prior chemotherapies, including at least one platinum-based chemotherapy; age ≥20 years; Eastern Cooperative Oncology Group performance status (PS) of 0-2; adequate bone marrow, hepatic and renal function; at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (12); life expectancy of ≥3 months; and patient willingness to provide written informed consent. The main exclusion criteria were as follows: Pulmonary disorders, such as interstitial lung disease, pneumoconioses, or active radiation pneumonitis; severe eye disorders; and massive pleural or pericardial effusion.

EGFR genotype testing for eligibility. The PNA-LNA PCR clamp method was used for confirmation of the EGFR mutation status in the NSCLC patients prior to enrollment. This method is a highly sensitive and simple procedure for the detection of 13 known EGFR mutations (8). For this study, we enrolled patients with the WT allele of EGFR in all 13 mutation sites. A total of 5 tissue slides (5-μm) or pleural effusion cytology samples containing tumor cells were used for the analysis. Tissue slides were prepared from tumor cell-rich sections of formalin-fixed paraffin-embedded tumor samples. In Japan, the PNA-LNA PCR clamp method is commercially available and performed by the Mitsubishi Chemical Medience Corporation (Tokyo, Japan).

Screening of tumors for the KRAS genotype and reanalysis of the EGFR mutation status using the S-ARMS assay. Following completion of patient enrollment, the tumor samples available for KRAS mutation analysis and EGFR mutation reanalysis were collected. DNA was extracted at the laboratory of the Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, using the QIAamp DNA Mini kit (Qiagen, Tokyo, Japan), followed by quantitation of the DNA. According to a previous report, the PNA-LNA PCR clamp method and the S-ARMS assay exhibit an equally high sensitivity for the detection of the EGFR mutation status (13). Therefore, we prioritized KRAS mutation screening if the amount of DNA available was not sufficient for evaluation of both the KRAS and EGFR mutation status by the S-ARMS assay. S-ARMS analysis for the detection of EGFR mutation was performed using the EGFR Mutation RGQ PCR kit (Qiagen, Manchester, UK) and S-ARMS analysis for evaluation of the KRAS mutation status was performed using the KRAS PCR kit (Qiagen, Manchester), which is able to detect 7 mutations in codons 12 and 13 of the KRAS gene.

Treatment. Oral erlotinib was administered at a dose of 150 mg daily until disease progression or development of unacceptable toxicity. The erlotinib dose was reduced (first reduction to 100 mg daily and second reduction to 50 mg daily) or treatment was interrupted in the event of any grade 3 non-hematological toxicity. Dose escalation was not permitted. In the event of development of interstitial lung disease (ILD) of any grade or any grade 4 toxicity, the protocol was discontinued.

Efficacy and safety evaluation. Tumor response was assessed in accordance with RECIST, version 1.1 (12). The baseline assessment included chest and upper abdominal computed tomography (CT), head CT or magnetic resonance imaging and bone scintigraphy or ^{18}F-fluorodeoxyglucose-positron emission tomography. Assessment of the tumor response was performed every 4 weeks during the first 8 weeks, every 8 weeks during the subsequent 40 weeks and every 12 weeks thereafter. In this study, the definition of stable disease (SD) required a duration of ≥8 weeks. PFS was defined as the time from the date of study enrollment until the date of objectively determined progressive disease (PD) or death due to any cause or the date of the last follow-up. OS was defined as the time from the date of study enrollment until death due to any cause or the date of last follow-up. Toxicity was evaluated using the Common Toxicity Criteria for Adverse Events (version 3.0).

Statistical analysis. The primary endpoint was the ORR and the sample size for the trial was calculated using Simon's two-stage design. Assuming that a response rate of 18.0% indicates potential usefulness, while a rate of 6.8% is the lower limit of interest, with α=0.05 and β=0.20, the estimated accrual number was 49 patients. In this study, the rate of the lower limit of interest was adopted based on the ORRs of docetaxel reported in previous phase III studies (14,15). Among these, ≥7 responders were required for this therapy to be considered worthy of further evaluation. We selected a target sample number of 54, to allow for 5 dropouts. The differences in ORR according to histology were analyzed using the Mantel extension test adjusted for PS and M factor (M0, M1a and M1b). A stratified log-rank test adjusted for these factors was used to evaluate the difference in PFS according to histology. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Between February, 2010 and April, 2012, a total of 55 patients were enrolled. A review of the data indicated that 2 of the patients enrolled in this study did not fulfill the eligibility criteria listed in the study protocol and the remaining 53 patients were included in the analysis as evaluable. The characteristics of the 53 patients are summarized in Table I. The median age of the patients was 67 years (range, 47-77 years). The histological subtypes were non-squamous cell carcinoma (non-SCC) in 44 patients [adenocarcinoma, 40 patients; and not otherwise specified (NOS), 4 patients] and SCC in 9 patients. The number of prior chemotherapies was 1 in 26 patients (49.0%) and 2 in the remaining 27 patients (51.0%).

Table I. Patient characteristics.

Characteristics	Patient no. (%) (n=53)
Age, years	
Median	67
Range	47-77
Gender	
Male	43 (81.0)
Female	10 (19.0)
Smoking status	
Never	7 (13.0)
Former/current	46 (87.0)
Histology	
Adenocarcinoma	40 (75.0)
Squamous cell carcinoma	9 (17.0)
NOS	4 (8.0)
No. of prior chemotherapies	
1	26 (49.0)
2	27 (51.0)
Stage	
IIIB	2 (4.0)
IV	
M1a	16 (30.0)
M1b	35 (66.0)
ECOG PS	
0	23 (43.4)
1	24 (45.3)
2	6 (11.3)

NOS, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy. The median treatment duration was 51 days (range, 5-404 days). Of the 53 eligible patients, partial response (PR) was obtained in 6 patients (4 with adenocarcinoma and 2 with SCC), yielding an ORR of 11.3% (95% confidence interval (CI): 4.3-23.0). SD was observed in 9 patients and the DCR was 28.3% (95% CI: 16.8-42.3). The ORR according to the histology was 9.1% (95% CI: 2.5-21.7) in patients with non-SCC and 22.2% (95% CI: 2.8-60.0) in patients with SCC. The difference in the ORR between these two groups was not statistically significant (P=0.29, Mantel extension test). A summary of the tumor responses is provided in Table II. At the time of the analysis, 48 patients (91.0%) had developed disease progression and 34 (64.0%) had succumbed to the disease. The median PFS of the entire patient cohort was 1.8 months (95% CI: 1.2-2.3). The median PFS in the patients with non-SCC and SCC was 1.7 months (95% CI: 1.2-2.1), and 2.2 months (95% CI: 1.0-11.3), respectively, without a statistically significant difference (P=0.54, stratified log-rank test). The Kaplan-Meier survival curve for PFS is shown in Fig. 1. The median OS was 6.4 months (95% CI: 4.5-10.4) and the

Table II. Tumor response.

Type of response	Total (n=53)	Non-SCC (n=44)	SCC (n=9)
CR	0	0	0
PR	6	4	2
SD	9	7	2
PD	37	32	5
NE	1	1	0
ORR, % (95% CI)	11.3 (4.3-23.0)	9.1 (2.5-21.7)	22.2 (2.8-60.0)
DCR, % (95% CI)	28.3 (16.8-42.3)	25.0 (13.2-40.3)	44.4 (13.7-78.8)

SCC, squamous cell carcinoma; non-SCC, adenocarcinoma and not otherwise specified non-small-cell lung cancer; CR, complete response; PR, partial response; SD, stable disease (a duration of ≥8 weeks was required for the definition of SD in this study); PD, progressive disease; NE, not evaluable; ORR, objective response rate; CI, confidence interval; DCR, disease control rate.

Table III. Adverse events in the patients (n=53).

Adverse events	Grade (patient no.) 1	2	3	4	% of patients with grade 3-4 toxicity
Skin rash	11	26	6	0	11.3
Diarrhea	16	1	1	0	1.9
Anorexia	14	6	5	0	9.4
Nausea	4	2	0	0	0.0
Vomiting	1	1	1	0	1.9
Fatigue	8	7	3	0	5.7
Stomatitis	10	2	1	0	1.9
Ocular disorders	2	0	1	0	1.9
ALT increased	7	4	1	2	5.7
AST increased	10	4	1	2	5.7
Amy increased	0	1	0	1	1.9
Leukopenia	1	1	0	0	0.0
Thrombocytopenia	6	0	0	0	0.0
ILD	2	0	1	0	5.6[a] (G3-5)

[a]Grade 5 ILD was observed in 2 patients. ALT, alanine transaminase; AST, aspartate transaminase; amy, amylase; ILD, interstitial lung disease.

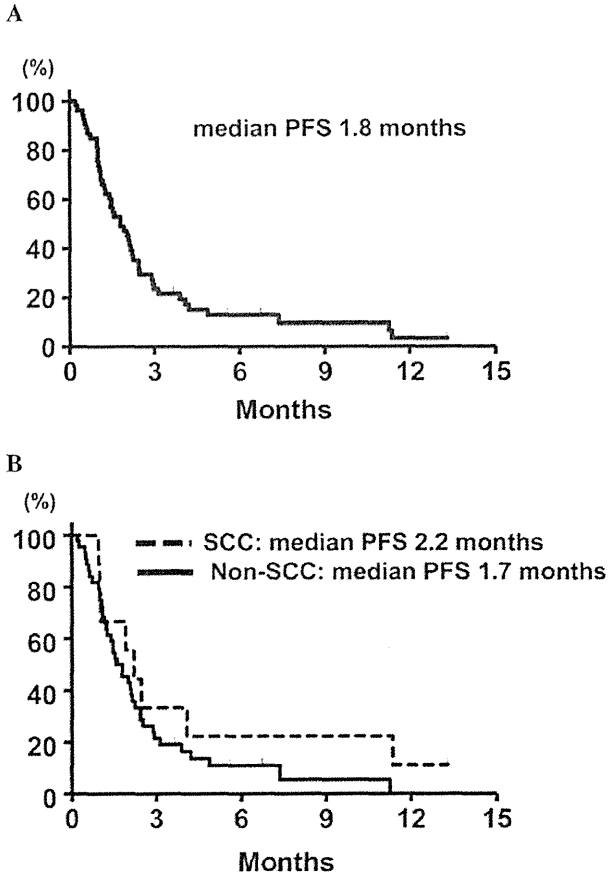

Figure 1. Kaplan-Meier survival curves for (A) progression-free survival (PFS) in the overall study population (n=53) and (B) progression-free survival in subgroups classified according to histology [squamous cell carcinoma (SCC) (n=9) vs. non-SCC (n=44)].

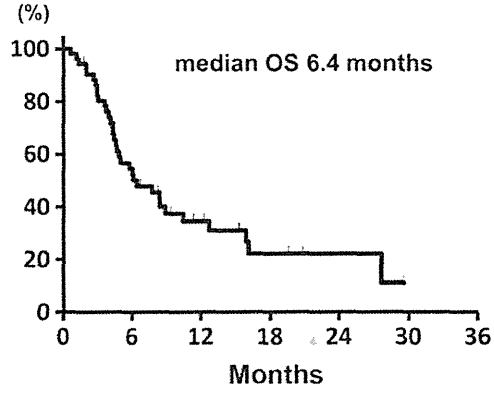

Figure 2. Kaplan-Meier survival curves for overall survival (OS) of the overall study population (n=53).

Kaplan-Meier survival curve for OS is shown in Fig. 2. The median OS in the patients with 1 and 2 prior chemotherapies was 8.5 and 5.5 months, respectively.

Safety. The adverse events are summarized in Table III. The major adverse events were rash in 81.1% of the patients (11.3% ≥grade 3) and anorexia in 47.1% (9.4% ≥grade 3). No grade 3 or 4 hematological adverse events were observed. Grade 3-5 ILD was reported in 3 patients (5.6%) and grade 5 ILD possibly related to erlotinib in 2 patients (3.8%). In the 2 patients with grade 5 ILD, the baseline chest CT revealed carcinomatous lymphangitis and lung cancer progression was concurrently detected by chest CT at the time of development of the ILD.

EGFR mutation reanalysis with the S-ARMS assay and KRAS mutation screening. Samples from 26 patients (49% of the

Table IV. KRAS mutation-positive patients.

Case	Gender	Smoking status	Smoking index	Amino acid change	Best overall response
1	Male	Former	1020	Gly12Ala (GGT>GCT)	PD
2	Male	Current	1020	Gly12Cys (GGT>TGT)	PD
3	Male	Current	1000	Gly12Ala (GGT>GCT)	PD
4	Male	Former	1520	Gly12Cys (GGT>TGT)	PD

Gly, glycine; Ala, alanine; Cys, cysteine; PD, progressive disease.

eligible patients) were available for EGFR mutation reanalysis. Of these, only 1 patient with adenocarcinoma was found to be EGFR mutation-positive (exon 19 deletion) NSCLC with the S-ARMS assay and this patient exhibited a PR. In the remaining 25 patients, EGFR WT was reconfirmed by the S-ARMS assay and two of these patients exhibited a PR. The ORR was 8.0% in the NSCLC patients with EGFR WT as confirmed by both the PNA-LNA PCR clamp method and the S-ARMS assay.

The KRAS mutation status was screened by the S-ARMS assay in samples obtained from 44 patients, of which DNA amplification was unsuccessful in 2. KRAS mutation screening was successfully performed in the samples from the remaining 42 patients (79.0% of eligible patients). Of these 42 patients, 4 (9.1%) were found to be KRAS mutation-positive. The characteristics of these 4 patients and the sites of the KRAS mutations are listed in Table IV. As regards treatment response, PD was observed in all 4 patients. By contrast, the ORR and median PFS in the patients with KRAS WT NSCLC were 6.9% and 1.9 months, respectively.

Discussion

In this study, we evaluated the efficacy and safety of erlotinib in pretreated patients with NSCLC harboring EGFR WT as confirmed by the PNA-LNA clamp method, which is reported as being highly sensitive. This study did not meet the primary endpoint based on the reported ORRs of docetaxel in previous studies, although erlotinib treatment was associated with an ORR of 11.3%.

Two recent phase III studies reported the inferiority of erlotinib compared to docetaxel regarding ORR and PFS in EGFR WT NSCLC patients (16,17). Based on these results, including the findings of our study, it appears that docetaxel should be preferred as second-line therapy, if not used as a part of first-line platinum based combination therapy.

However, there remains the clinical question of whether erlotinib should not be used for EGFR WT NSCLC in any-line setting. In our opinion, erlotinib monotherapy may be an viable option in pretreated patients with EGFR WT NSCLC following failure of docetaxel treatment for the following reasons: First, EGFR WT was reconfirmed by the S-ARMS assay in 25 of the 26 patient samples examined in this study, of which 2 (8.0%) achieved a PR. Our results suggested that erlotinib may still be effective against EGFR WT NSCLC, even when the EGFR mutation status is confirmed by two different highly sensitive methods.

Second, a discordance in the EGFR mutation status between the PNA-LNA clamp method and S-ARMS assay was observed in 1 patient in this study. Although large, tumor cell-rich samples are required for accurate EGFR mutation analysis, we cannot, in general, obtain surgically resected specimens from advanced NSCLC patients in clinical practice. Fukui *et al* (18) verified the accuracy of the EGFR mutation analysis in small samples by high-resolution melting analysis, which has also been reported to be a highly sensitive method. In that study, the results of DNA sequencing combined with laser capture microdissection in paired surgically resected specimens revealed a few false-negative results in small samples. Those data suggested that it may be difficult to determine the EGFR mutation status with complete accuracy in small tissue samples, irrespective of the sensitivity of the method used. Therefore, if we do not use erlotinib for EGFR WT NSCLC in any-line setting, we may miss the opportunity to attempt elrotinib treatment for patients with a false-negative EGFR mutation result. This may also lead to loss of the significant survival benefit obtained from EGFR-TKI therapy for EGFR mutation-positive NSCLCs.

We succeeded in obtaining 42 samples (79% of the eligible patients) for KRAS mutation screening. KRAS mutations were detected in 4 of the 42 patients screened (9.5%) and all the KRAS mutation-positive patients exhibited PD. In a phase III study conducted to compare erlotinib and pemetrexed, none of the patients with KRAS mutation-positive NSCLC responded to erlotinib treatment, which was similar to the findings of our study (19). These results should be interpreted with caution, as we could not exclude the KRAS mutation status as a potential prognostic factor. However, the presence of KRAS mutation may be useful as a negative predictive factor, at least regarding response to erlotinib therapy, in patients with EGFR WT NSCLC.

We performed a subgroup analysis according to histological subtype. In patients with EGFR mutated NSCLC, the efficacy of EGFR-TKIs for SCC appeared to be lower compared to that for non-SCC (20). However, SCC histology may not be associated with poor efficacy of erlotinib in patients with EGFR WT NSCLC based on our results. Molecular biomarkers, such as KRAS, may be required to select suitable candidates for erlotinib treatment among patients with EGFR WT NSCLC.

The toxicity profile of erlotinib in this study, in terms of the incidence/grade of skin rash, diarrhea and hematological toxicities, was consistent with previous reports. However, grade 3-5 ILD was reported in 3 patients (5.8%). In a large-scale surveillance study conducted in Japan, the incidence of ILD

was also higher compared to that reported by the BR21 and SATURN trials (1,7,21). Further studies are required to determine whether there are ethnic differences in the incidence of ILD, as suggested by a previous study (22).

In conclusion, this study did not meet the primary endpoint, although erlotinib was found to be moderately effective in pre-treated patients with EGFR WT NSCLC, even when the EGFR mutational status was confirmed by the highly sensitive PNA-LNA clamp PCR method.

Acknowledgements

This study was supported by the Central Japan Lung Study Group (CJLSG), a non-profit organization supported by unrestricted donations from the following pharmaceutical companies: Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan); Shionogi & Co., Ltd. (Osaka, Japan); Daiichi Sankyo Co., Ltd. (Tokyo, Japan); Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan); Janssen Pharmaceutical K.K. (Tokyo, Japan); Eli Lilly Japan K.K. (Kobe, Japan); Taisho Toyama Pharmaceutical Co., Ltd.; Meiji Seika Pharma Co., Ltd.; MSD K.K.; Bayer Holding Ltd.; Astellas Pharma Inc. and Nippon Boehringer Ingelheim Co., Ltd. (all from Tokyo, Japan). Dr Morise reported receiving honoraria for lecturing from Chugai Pharmaceutical Co.; Dr Taniguchi has served as a member of the advisory boards at Chugai Pharmaceutical Co., Boehringer Ingelheim and Shionogi & Co., Ltd.; Dr Saka reported receiving two grants from Chugai Pharmaceutical Co., which were paid to Nagoya Medical Center (Nagoya, Japan); Dr Hase reported receiving honoraria for lecturing from Chugai Pharmaceutical Co., Pfizer Inc. (New York City, NY, USA) and Astra Zeneca Co. (London, UK); Dr Ando reported having a board membership at Chugai Pharmaceutical Co.; Dr Kondo reported receiving honoraria for lecturing from Chugai Pharmaceutical Co.; Dr Saito received research funding from Chugai Pharmaceutical Co.; Dr. Hasegawa reported receiving honoraria for lecturing from Chugai Pharmaceutical Co. and receiving a grant from Chugai-Pharmaceutical Co. that was paid to Nagoya University

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Cancer Chemother Pharmacol (2014) 74:721–727
DOI 10.1007/s00280-014-2548-z

ORIGINAL ARTICLE

First-line gefitinib therapy for elderly patients with non-small cell lung cancer harboring EGFR mutation: Central Japan Lung Study Group 0901

Kosuke Takahashi · Hiroshi Saito · Yoshinori Hasegawa · Masahiko Ando · Masashi Yamamoto · Eiji Kojima · Yasuteru Sugino · Tomoki Kimura · Fumio Nomura · Tomohiko Ogasawara · Joe Shindoh · Norio Yoshida · Ryujiro Suzuki

Received: 10 January 2014 / Accepted: 25 July 2014 / Published online: 3 August 2014

Abstract
Background The population of elderly patients with lung cancer is increasing worldwide. Although first-line gefitinib is one of the standard treatments for advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation, few data have been reported regarding gefitinib and elderly patients.
Patients and methods Chemotherapy-naïve patients aged 70 years or older with stage IIIB or IV NSCLC harboring EGFR-activating mutation were enrolled and treated with 250 mg of gefitinib daily until disease progression. The primary end point was response rate, and secondary end points were survival, safety, and quality of life.
Results Twenty patients were enrolled, and the median age was 79.5 years (range 72–90). Overall response rate was 70 % (95 % CI 45.7–88.1 %), and the disease control rate was 90 % (95 % CI 68.3–98.7 %). The median progression-free survival and overall survival time were 10.0 and 26.4 months, respectively. The Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) scores improved significantly 4 weeks after the initiation of gefitinib ($P = 0.037$) and maintained favorably over a 12-week assessment period. Among the seven items of FACT-LCS, shortness of breath and cough improved

This trial is registered at UMIN-CTR, Number UMIN000001863.

K. Takahashi (✉) · H. Saito
Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, 18 Kuriyado Kake-machi, Okazaki, Aichi 444-0011, Japan
e-mail: ktakahashi@acc-aichi.com

Y. Hasegawa
Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

M. Ando
Center for Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan

M. Yamamoto
Department of Respiratory Medicine, Nagoya Ekisaikai Hospital, Nagoya, Japan

E. Kojima
Department of Respiratory Medicine, Komaki Municipal Hospital, Komaki, Japan

Y. Sugino
Department of Respiratory Medicine, Toyota Memorial Hospital, Toyota, Japan

T. Kimura
Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Japan

F. Nomura
Department of Respiratory Medicine, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan

T. Ogasawara
Department of Respiratory Medicine, Japanese Red Cross Nagoya Daini Hospital, Nagoya, Japan

J. Shindoh
Department of Respiratory Medicine, Ogaki Municipal Hospital, Ogaki, Japan

N. Yoshida
Department of Respiratory Medicine, Kariya Toyota General Hospital, Kariya, Japan

R. Suzuki
Department of Respiratory Medicine, Toyohashi Municipal Hospital, Toyohashi, Japan

significantly after 4 weeks of treatment ($P = 0.046$ and $P = 0.008$, respectively). The most common adverse events were rash and liver dysfunction. Although Grade 1 pneumonitis developed in one patient, no treatment-related death was observed.

Conclusion First-line gefitinib therapy is effective and feasible for elderly patients harboring EGFR mutation, and improves disease-related symptoms, especially pulmonary symptoms like shortness of breath and cough.

Keywords Non-small cell lung cancer · EGFR mutation · Elderly · Gefitinib · Quality of life · First-line treatment

Introduction

Lung cancer is the leading cause of cancer mortality. Non-small cell lung cancer (NSCLC) accounts for 85 % of lung cancer cases, with at least 40 % of the patients at an advanced stage. The population of elderly patients with lung cancer is increasing worldwide. Two-thirds of the lung cancer cases are diagnosed in patients over the age of 65, and the median age at diagnosis is 70 years [1, 2].

Aging is associated with physiologic changes in organ function and altered drug pharmacokinetics. Furthermore, the presence of comorbidities and polypharmacy is frequent in elderly populations. Elderly patients are more likely to experience severe hematologic and non-hematologic toxicity from conventional chemotherapy than their younger counterparts [3]. Before the discovery of driver mutations including epidermal growth factor receptor (EGFR) mutation, single-agent chemotherapy was considered to be a standard of care for elderly patients with advanced NSCLC [4–6]. Although carboplatin and weekly paclitaxel doublet chemotherapy improved overall survival compared with vinorelbine or gemcitabine monotherapy in the IFCT-0501 trial, accompanying toxicity such as Grade 3 or Grade 4 neutropenia, febrile neutropenia, and asthenia was more frequent in the doublet chemotherapy arm [7]. Therefore, investigations of effective treatments with less toxicity are needed for this population.

Gefitinib is an orally administered EGFR tyrosine kinase inhibitor (TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells. Since EGFR somatic mutation was reported to be strongly related to the response of EGFR-TKI therapy, several studies have demonstrated the efficacy of gefitinib for NSCLC harboring EGFR-activating mutation [8–11]. Two phase III studies comparing gefitinib with platinum doublet chemotherapy as a first-line treatment for NSCLC patients with EGFR mutation showed that the gefitinib group had a higher response and longer progression-free survival than a standard chemotherapy group [12, 13]. However, these studies targeted patients aged 75 years or younger, and few data were available on the efficacy and feasibility of first-line gefitinib therapy for elderly NSCLC patients with EGFR mutation. Therefore, we started our current study of this population. The present study included the assessment of quality of life (QOL) besides the efficacy and feasibility of treatment.

Patients and methods

Patient eligibility

Patients aged 70 years or older with a histologically or cytologically proven diagnosis of non-small cell lung cancer were eligible for this study. Other eligibility criteria included the following: EGFR-activating mutation (either exon 19 deletion or L858R in exon 21); measurable disease; stage IIIB/IV or postoperative recurrence; no prior therapy including chemotherapy or radiotherapy of the primary tumor; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; an adequate organ function defined as leukocyte count $\geq$3,000/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dl, aspartate aminotransferase and alanine aminotransferase $\leq$100 IU/l, total bilirubin $\leq$1.5 mg/dl, serum creatinine $\leq$1.5 mg/dl, and PaO_2 at rest $\geq$60 mmHg. Patients with any of the following criteria were ineligible: superior vena caval syndrome; history of serious drug allergy; massive pleural or pericardial effusion or ascites that required drainage; interstitial lung disease or pulmonary fibrosis detected by conventional computed tomography of the chest; symptomatic brain metastasis; other concurrent active malignancy; pregnancy, lactation, or other concomitant serious medical conditions. All patients gave written informed consent before enrollment. The study protocol was approved by each institutional review board and was carried out in accordance with the Declaration of Helsinki 1964 (as revised 2000).

Study design and treatment

This was a single-arm, prospective, multicenter, phase II trial. Patients were treated with 250 mg of oral gefitinib daily. Therapy was continued unless there was evidence of disease progression, unacceptable toxicity, or withdrawal of consent. If Grade 3 toxicity other than pneumonitis was observed, gefitinib was discontinued for a maximum of 4 weeks. After the toxicity recovered to the level of Grade 2, gefitinib was given every other day. If toxicity further improved, gefitinib was given daily. If Grade $\geq$1 pneumonitis or Grade 4 toxicity other than pneumonitis was observed, the patient was removed from the study.

Evaluation of response and toxicity

The pretreatment baseline evaluation included a complete medical history and physical examination, complete blood cell count, blood chemistry studies, computed tomography scan of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, bone scintigraphy or positron emission tomography, arterial blood gas analysis, pulmonary function tests, and electrocardiography. Tumor response was assessed every 2 months during the first year after enrollment and every 3 months between 12 and 18 months. Thereafter, the interval was at the physician's discretion.

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for response assessment [14]. Disease control rate (DCR) was defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). An extramural review was conducted to validate staging and response. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria (version 3.0).

Quality of life (QOL) was assessed with the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) questionnaire version 4. The maximum attainable score on the FACT-LCS was 28, with which the patient was considered to be asymptomatic. Patients were asked to complete the FACT-LCS questionnaire at the time of enrollment and at 4, 8, and 12 weeks after the initiation of treatment.

Mutational analysis of EGFR

Epidermal growth factor receptor (EGFR) genetic testing methods included either direct sequencing, PCR invader, peptide nucleic acid-locked nucleic acid PCR clamp, or the combination of fragment analysis and the Cycleave method.

Statistical analyses

The primary end point of this study was the response rate. We calculated the sample size based on Simon's two-stage design of the phase II study [15]. Assuming that a response rate of 60 % from eligible patients would indicate potential usefulness, and that a rate of 30 % would be the lower limit of interest (with a power of 0.8 at a one-sided significance level of 0.05), accrual of 17 eligible patients was required. Therefore, we planned to accrue a total of 19 patients, assuming there would be a 10 % dropout rate. The duration of survival was measured from the day of enrollment, and the overall survival curve and progression-free survival curve were calculated according to the method of Kaplan and Meier [16]. Repeated-measures analysis of variance was used to assess the differences in the FACT-LCS between baseline and each point during the treatment. Comparisons of the FACT-LCS scores with the baseline scores were adjusted for multiple comparisons using the Dunnett–Hsu test. The software SAS/Proc Mixed version 9.2 (SAS Institute Inc., Cary, NC) was used for statistical analysis. All comparisons were two-sided, and the statistical significance level was set at $P < 0.05$.

Results

Patient characteristics

Between April 2009 and March 2011, 20 patients were enrolled in this study. Sixteen patients (80 %) were aged 75 years or older, and the median age was 79.5 years (range 72–90 years old) (Table 1). All of the 20 patients had adenocarcinoma, 13 (65 %) were female, two (10 %) had an ECOG performance status of 2, and 12 (60 %) had exon 19 deletion mutations.

Tumor responses and survival

Overall response rate was 70 % (95 % CI 45.7–88.1 %), and the disease control rate was 90 % (95 % CI 68.3–98.7 %) (Table 2). Although the response of one patient who developed pneumonitis was not evaluable, progressive disease was observed in only one patient. The median progression-free survival and overall survival time were 10.0 and 26.4 months, respectively (Figs. 1, 2).

Table 1 Patient characteristics

Characteristics	$N = 20$	(%)
Age, years		
Median (range)	79.5 (72–90)	
Sex		
Male	7	35
Female	13	65
Smoking status		
Never smoker	14	70
Former/current smoker	6	30
ECOG performance status		
0	13	65
1	5	25
2	2	10
Stage		
IIIB	4	20
IV	15	75
Postoperative recurrence	1	5
Type of EGFR mutation		
Exon 19 deletion	12	60
L858R	8	40

ECOG Eastern Cooperative Oncology Group

Table 2 Response rate

Response	$N = 20$	% (95% CI)
Partial response	14	70
Stable disease	4	20
Progressive disease	1	5
Inevaluable	1	5
Overall response rate	14	70 % (45.7–88.1)
Disease control rate	18	90 % (68.3–98.7)

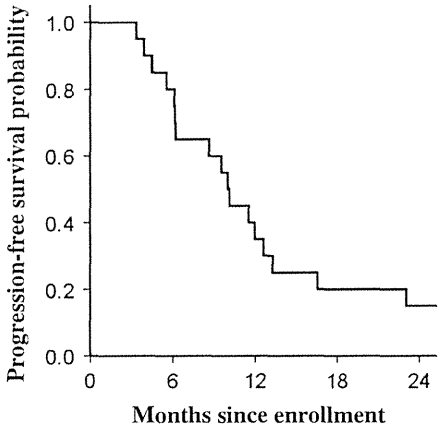

Fig. 1 Kaplan–Meier progression-free survival curve with gefitinib

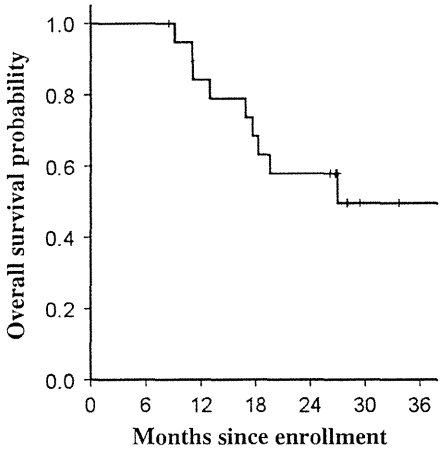

Fig. 2 Kaplan–Meier survival curve with gefitinib

Quality-of-life assessment

All 20 patients completed the FACT-LCS questionnaire at registration and after 4, 8, and 12 weeks of treatment. The adjusted mean FACT-LCS score was 22.8 ± 1.0 at baseline and 25.1 ± 0.7 at 4 weeks. The score improved

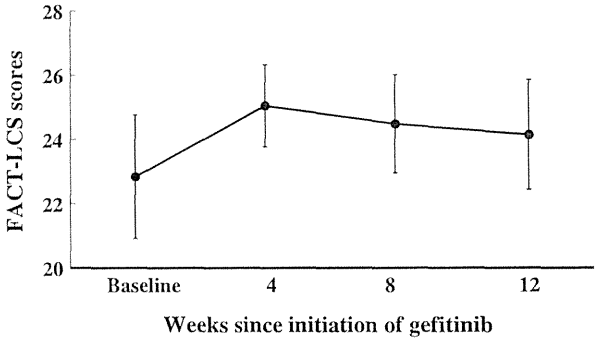

Fig. 3 FACT-LCS scores before treatment and at 4, 8, and 12 weeks after initiation of gefitinib. *Abbreviation FACT-LCS* Functional Assessment of Cancer Therapy-Lung Cancer Subscale

significantly at 4 weeks ($P = 0.037$) and maintained favorably during the 12-week assessment period (Fig. 3). FACT-LCS consisted of seven items: shortness of breath, cough, chest tightness, ease of breathing, changes in appetite, body weight loss, and disruptions to clear thinking. Among those seven items, shortness of breath and cough improved significantly after 4 weeks of treatment ($P = 0.046$ and $P = 0.008$, respectively).

Toxicity

Toxicity data for all 20 patients are listed in Table 3. Nonhematologic toxicity was the principal toxicity from gefitinib treatment and mainly consisted of liver dysfunction, skin rash, anorexia, diarrhea, and fatigue. Grade 3 or Grade 4 liver dysfunction occurred in 3 patients (15 %) but no other Grade 3 or Grade 4 toxicity was occurred. One case of Grade 1 pneumonitis developed in an 87-year-old woman. She had no specific symptoms; however, routine chest X-ray on day 14 showed an increase in density in the bilateral lower lung fields. Since subsequent chest computed tomography revealed bilateral diffuse interstitial opacities and the bronchoalveolar lavage findings were consistent

Table 3 Adverse events ($N = 20$)

	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3–4
AST/ALT	8	4	2	1	3
Rash	8	10	0	0	0
Anorexia	8	2	0	0	0
Diarrhea	6	2	0	0	0
Fatigue	6	2	0	0	0
Mucositis	1	3	0	0	0
Nausea	3	0	0	0	0
Pneumonitis	1	0	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

with pneumonitis, gefitinib was discontinued and the treatment with oral prednisolone (0.5 mg/kg/day) was started. Although the pneumonitis was stable, pulmonary and brain metastases gradually progressed and she died of progression of lung cancer 6 months after the occurrence of this adverse event. No treatment-related death was observed.

Discussion

The present study evaluated the efficacy and feasibility of first-line gefitinib treatment for elderly patients harboring EGFR mutation, achieving the response rate of 70 % and disease control rate of 90 %. After we started this phase II study, three groups reported comparable results of response rates from 45.5 to 74 %, and progression-free survival of 9.7–12.9 months for similar populations [17–19]. Efficacy of the present study is also comparable to the results obtained from non-elderly phase III studies. Two prospective studies (WJTOG3405 and NEJ002) and subset analysis of EGFR-mutated patients in the IPASS showed response rates of 62.1–73.7 % and progression-free survival of 9.2–10.8 months [11–13, 20]. From these data, gefitinib treatment for elderly EGFR-mutated patients appears to be as effective as that for the younger population. A randomized trial of EGFR-TKI focusing on efficacy is needed to further improve survival of elderly patients.

We also revealed that disease-related symptoms improved significantly with gefitinib therapy. FACT-LCS score improved more than two points, which is considered a clinically meaningful change [21]. Although superior QOL results were reported with gefitinib versus chemotherapy in the IPASS and NEJ002 studies, the QOL benefit for the elderly population has not been reported [22, 23]. Among the seven items of FACT-LCS, shortness of breath and cough improved significantly. This finding is in accordance with two previous QOL analyses during gefitinib treatment. Cella et al. [24] found that more patients showed an improvement in the pulmonary items of FACT-LCS, such as shortness of breath, cough, or chest tightness than in the non-pulmonary items in the IDEAL2 study, which evaluated two doses of gefitinib for the mutation-unselected population. Oizumi et al. [23] reported that more patients showed an improvement in pain and shortness of breath in the gefitinib arm in the NEJ002 study. With regard to the speed of symptom improvement, our data demonstrated significant improvement at the first follow-up, namely at 4 weeks of treatment. A former analysis reported that the median time to symptom improvement was as immediate as 10 days with gefitinib [24]. In light of its rapid effect, gefitinib could be a good treatment option for patients suffering from pulmonary symptoms like cough or dyspnea.

Toxicity in the present study was generally mild and well tolerated. Grade 3 or Grade 4 adverse events were only in three cases of liver dysfunction. No unpredicted toxicity or treatment-related death was observed. On the other hand, a subgroup analysis of a phase III study of erlotinib treatment indicated that elderly patients experienced significantly more toxicity and tended to discontinue treatment more than their younger counterparts [25]. This difference may be partly explained by the difference in EGFR-TKIs. Gefitinib 250 mg is about one-third of the maximum tolerated dose, and erlotinib 150 mg is just the maximum tolerated dose [26, 27]. Accordingly, gefitinib may have some safety margin, especially for the frail population. In the present study, the oldest patient, aged 90 years, was able to continue gefitinib therapy for about 7 months with side effects no more severe than Grade 2 mucositis and Grade 2 rash.

Pneumonitis is one of the most serious adverse events related to EGFR-TKI therapy. In our previous study evaluating gefitinib in mutation-unselected elderly NSCLC patients, three out of 30 patients (10 %) had pneumonitis, two of them with a Grade $\geq$3 [28]. In the present study, Grade 1 pneumonitis developed in one patient (5 %). Since risk factors of pneumonitis include smoking, preexisting interstitial lung disease, and older age, careful monitoring is desirable for elderly patients [29, 30].

In conclusion, the present study revealed that first-line therapy with gefitinib is effective and feasible for elderly patients harboring EGFR mutation, and improves disease-related symptoms.

Conflict of interest Kosuke Takahashi, Hiroshi Saito, Yoshinori Hasegawa, Yasuteru Sugino, and Joe Shindoh received honoraria from AstraZeneca. Yoshinori Hasegawa received research funding for his institute from AstraZeneca.

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RESPIRATORY INVESTIGATION 53 (2015) 68–72

Contents lists available at ScienceDirect

Respiratory Investigation

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Original article

Disease flare after gefitinib discontinuation

Hiroaki Akamatsu[a,b,*], *Akira Ono*[a], *Takehito Shukuya*[a,c], *Asuka Tsuya*[a,d], *Yukiko Nakamura*[a,e], *Hirotsugu Kenmotsu*[a], *Tateaki Naito*[a], *Haruyasu Murakami*[a], *Masahiro Endo*[f], *Takashi Nakajima*[g], *Nobuyuki Yamamoto*[a,b], *Toshiaki Takahashi*[a]

ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form
17 September 2014
Accepted 25 October 2014
Available online 13 November 2014

Keywords:
Disease flare
Gefitinib
Epidermal growth factor receptor (EGFR) mutation
EGFR-tyrosine kinase inhibitor (EGFR-TKI)

ABSTRACT

Introduction: A recent retrospective analysis found that 23% of non-small cell lung cancer patients who acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) demonstrated "disease flare" after discontinuation of EGFR-TKIs. However, limitations of this study present the need for further investigation to elucidate this phenomenon in more detail.

Methods: We reviewed the clinical records of EGFR mutated patients with advanced lung adenocarcinoma who were treated with gefitinib monotherapy in our hospital between January 2007 and December 2010. Disease flare was defined as unexpected interventions (e.g. radiation therapy or pleural drainage), hospitalization, or death attributable to disease progression after gefitinib discontinuation.

Results: Among 52 eligible patients, only two experienced disease flare (4%; 95% confidence interval: 1–13%). In both cases, interval time from gefitinib discontinuation to disease flare was 11 days, and the brain was the site of flare. Survival time after gefitinib was significantly shorter in the flare patients (78 and 97 days, respectively) compared with the no-flare patients (median 388 days).

Conclusions: Our analysis demonstrated a lower incidence rate of disease flare after gefitinib discontinuation compared with the previous report, but the prognosis was similarly poor.

[a]*Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan*
[b]*Third Department of Internal Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8509, Japan*
[c]*Department of Respiratory Medicine, Juntendo University, School of Medicine, 2-1-1 Hongou, Bunkyou-ku, Tokyo 113-8421, Japan*

*Corresponding author at: Third Department of Internal Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-8509, Japan. Tel.: +81 73 411 0619; fax: +81 73 464 2877.
E-mail addresses: h-akamat@wakayama-med.ac.jp (H. Akamatsu), a.ono@scchr.jp (A. Ono), tshukuya@juntendo.ac.jp (T. Shukuya), a-tsuya@hospital.city.osaka.jp (A. Tsuya), yu43-nakamura@city.yokohama.jp (Y. Nakamura), h.kenmotsu@scchr.jp (H. Kenmotsu), t.naito@scchr.jp (T. Naito), ha.murakami@scchr.jp (H. Murakami), m.endo@scchr.jp (M. Endo), t.nakajima@scchr.jp (T. Nakajima), nb.yamamo@wakayama-med.ac.jp (N. Yamamoto), t.takahashi@scchr.jp (T. Takahashi).

http://dx.doi.org/10.1016/j.resinv.2014.10.005
2212-5345/

[d]Department of Clinical Oncology, Osaka City General Hospital, 2-13-22 Miyakojimahondohri, Miyakojima-ku, Osaka 534-0021, Japan
[e]Department of Respiratory Medicine, Yokohama Munincipal Citizen's Hospital, 56 Okazawa-cho, Hodogaya-ku, Yokohama, Kanagawa 240-8555, Japan
[f]Division of Diagnostic Radiology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan
[g]Division of Radiation Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan

1. Introduction

Discovery of driver mutations and development of targeted inhibitors have provided a drastic paradigm shift in the treatment of various types of malignancies. In non-small cell lung cancer (NSCLC), *epidermal growth factor receptor* (EGFR) mutation was the first discovered oncogene [1,2]. EGFR-tyrosine kinase inhibitors (EGFR-TKIs) have demonstrated higher overall response rates (ORR) and longer progression-free survival (PFS) than platinum containing chemotherapy in advanced NSCLC patients with EGFR mutation in phase III trials [3–7].

Unfortunately, almost all patients treated with EGFR-TKIs ultimately show disease progression. Although switching to cytotoxic chemotherapy is the standard treatment, we sometimes experience rapid progression after discontinuation of EGFR-TKIs [8]. In 2011, Chaft et al. reported "disease flare" after discontinuation of EGFR-TKIs [9]. They defined disease flare as "hospitalization or death attributable to disease progression after the TKI discontinuation and before initiation of study therapy", and reported that about 23% of patients experienced disease flare. However, their study had several limitations, and their incidence rate seemed to be higher in our clinical practice. Thus, we did this retrospective study to elucidate the phenomenon in more detail.

2. Methods

2.1. Patient selection

We reviewed the clinical records of EGFR mutated patients with advanced lung adenocarcinoma who were treated with gefitinib monotherapy in Shizuoka Cancer Center between January 2007 and December 2010. At the data cut off time, patients who did not demonstrate disease progression were ineligible. Exclusion criteria were as follows: (1) inappropriate washout period (<1 week) before subsequent chemotherapy, (2) durable cessation interval (>1 month) due to adverse events, (3) refractory cases (progressed within 3 months), and (4) harboring de novo EGFR T790M mutation.

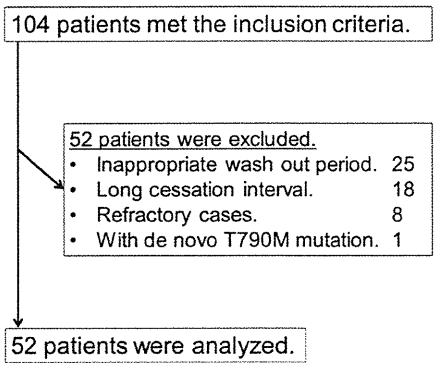

Fig. 1 – Flow chart of the patients analyzed in this study.

2.2. Assessment of outcomes and statistical analysis

The primary outcome of this study was to evaluate the incidence rate of disease flare after discontinuation of gefitinib. Definition of disease flare was almost the same as Chaft's, but we added "unexpected interventions (e.g. radiation therapy, or pleural drainage)". If these events occurred more than three weeks after discontinuation of gefitinib, we regarded them as no-flare. Tumor response was classified in accordance with the Response Evaluation Criteria for Solid Tumors (RECIST), ver. 1.1. PFS was assessed from the first day of treatment with gefitinib

Table 1 – Baseline characteristics of the study patients (*n*=52).

Characteristic	*n*
Age (years)	
Median	67.5
Range	42–87
Sex	
Male	20
Female	32
Smoking status	
Non- or light smoker	36
Current or former smoker	16
ECOG performance status	
0,1	46
≥2	6
Site of EGFR mutation[a]	
Exon 19	33
Exon 21	19
Other	1
Treatment line of gefitinib	
First line	26
Second line	17
Third line	9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
[a] One patient had both exon 19 deletion and exon 21 L858R mutation.

to the earliest signs of disease progression as determined by CT or MRI imaging, or death from any cause.

A p value of <0.05 indicated statistical significance. The Kaplan–Meier method was used to estimate PFS, and overall survival as a function of time. All the analyses were performed using JMP ver.7 (SAS Institute Inc, USA). This retrospective analysis was approved by the institutional review board of Shizuoka Cancer Center (Approved #: 26-J70-26-1-3).

3. Results

A total of 104 consecutive patients were enrolled in this retrospective study, and 52 were eligible (Fig. 1). Baseline characteristics of the patients are summarized in Table 1. Median age was 67.5 years, 62% of patients were female, 69% were non or light smokers, and 88% had an ECOG performance status of 0–1. Almost all sites of EGFR mutation consisted of exon 19 deletion (63%) or exon 21 L858R (36%). Half of the patients were treated with gefitinib as their first line of therapy. Gefitinib demonstrated favorable efficacy results (overall response rate of 73% and median PFS of 343 days). Median time of gefitinib administration was 342 days (123–814 days). Median interval time from gefitinib discontinuation to subsequent chemotherapy was 20.5 days (7–280 days).

There were only two patients who experienced disease flare (4%; 95% confidence interval: 1–13%). In both cases, interval time from gefitinib discontinuation to disease flare was 11 days, and the brain was the site of flare. Flare patients demonstrated slightly shorter PFS with gefitinib (209 and 299 days, respectively) than no-flare patients (median 354 days), but not significant ($p=0.16$). Survival time after gefitinib was significantly shorter among flare patients (78 and 97 days, respectively) compared with no-flare patients (median 388 days). No-flare patients tended to receive more subsequent chemotherapy than flare patients (71% versus 50%, respectively).

The clinical courses of flare patients are described below. The first case was a 69-year-old, female with both exon 19 deletion and exon 21 L858R. First line treatment with gefitinib provided partial response for 10 months. Although subsequent cytotoxic chemotherapy was planned, her brain metastases rapidly progressed. We started whole brain radiotherapy and erlotinib, but she did not respond (Fig. 2). She died 97 days after gefitinib discontinuation. Another patient was a 71-year-old male with exon 19 deletion. Gefitinib was his third line of treatment, and seven months of PFS were obtained. For multiple brain metastases, we started whole brain radiotherapy. However he demonstrated carcinomatous meningitis during radiotherapy. He died 78 days after gefitinib discontinuation.

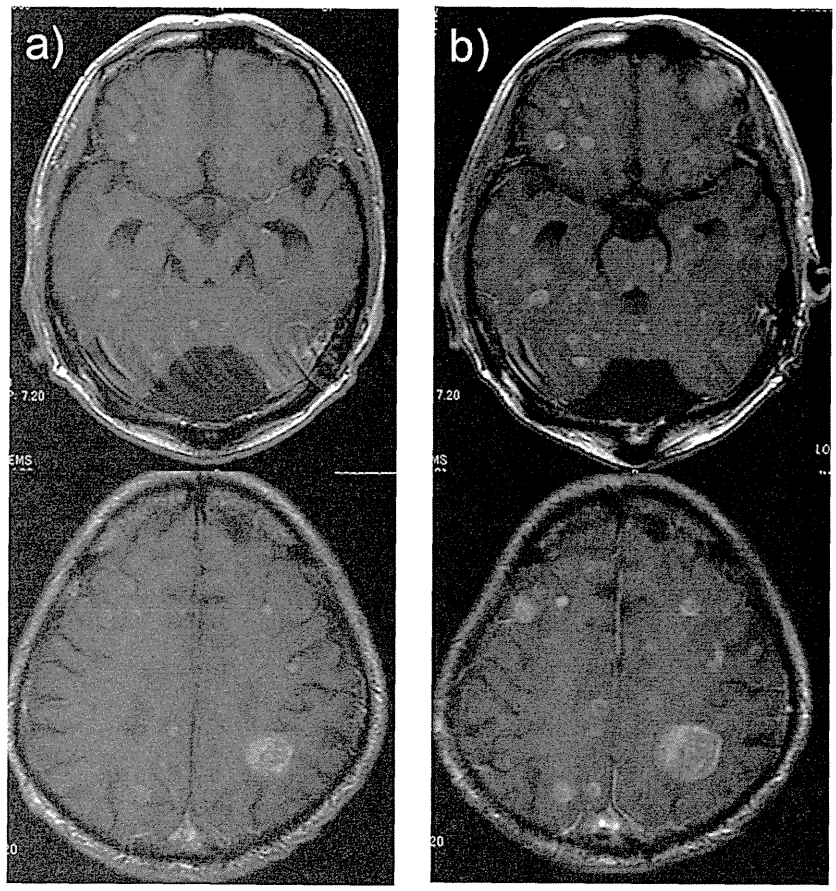

Fig. 2 – Brain MRI at the time of progression (a), and disease flare (b: after completion of whole brain radiotherapy).

Table 2 – Summary of the retrospective studies on disease flare.

Author	Total number of patients	Characteristics of disease flare patients			
		Incidence (%)	mPFS after TKI treatment (months)	Time to flare after TKI treatment (days, range)	MST after flare (months)
Chaft	61	23	15	8 (3–21)	–
Chen	227	9	10.1	7 (3–18)	4.1
Present study	52	4	8.2	11	2.8

Abbreviations: mPFS, median progression-free survival; TKI, tyrosine-kinase inhibitor; MST, median survival time.

4. Discussion

There were two retrospective studies about disease flare (Table 2). The first report by Chaft et al. mentioned that about 23% of patients experienced disease flare. In contrast, Chen's report on a study of Chinese NSCLC patients showed that only 9% demonstrated disease flare [10]. The incidence rate was the lowest in our analysis.

The characteristics of the flare patients were slightly different among the studies. In Chaft's study, their administration period of EGFR-TKIs was about 19 months, while median PFS of EGFR-TKIs were much shorter (9 months among flare patients, 15 months among no-flare patients, respectively). Although there were some studies addressing the benefit of beyond PD treatment with EGFR-TKIs [11,12], we should realize the risk that extended administration sometimes hamper the chance of subsequent chemotherapy. Secondly, the washout period of EGFR-TKIs was an important issue. From the pharmacokinetic studies of EGFR-TKIs [13,14], five to seven days should be set. Thus, some of the flare patients in the prior studies might not be suitable. In our study, most of the patients did not receive beyond PD treatment and they were given an appropriate washout period. We believe our results did not underestimate the disease flare.

The mechanism of disease flare is not yet understood. Mochizuki et al. suggested that continuous inhibition of the EGFR pathway brought clinical benefit to patients even when radiological progression was present [15]. However, subsequent erlotinib therapy was not effective in our first case. Recently, there have been reports demonstrating the utility of liquid biopsy in monitoring molecular profiles during treatment [16,17]. These techniques will bring advances for EGFR mutated NSCLC patients in the near future.

The present study has several limitations. First, the timing of radiological evaluation depended on investigators because this was a retrospective study. Second, the varied backgrounds of patients might have affected the results. However, our efficacy results were not different from pivotal trials [3,4]. Third, this analysis did not contain patients treated with erlotinib. Some reports demonstrated that erlotinib had some clinical advantages for CNS relapse compared with gefitinib [18,19]. This might affect the site of flare in our study.

5. Conclusion

Our analysis demonstrated a lower incidence rate of disease flare after gefitinib discontinuation compared with previous reports, but the prognosis was similarly poor.

Conflict of interest

HM, NY, and TT have received honoraria, and research funding from Astra Zeneca KK. NY has received honoraria from Chugai pharmaceutical Co. LTD, and Boehringer Ingelheim. TT has received research funding from Chugai pharmaceutical Co. LTD. All other authors declare no conflicts of interest.

Acknowledgments

We thank Charles McKay who provided medical assistance.

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