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Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer

Kyoichi Kaira[a], Tateaki Naito[a], Toshiaki Takahashi[a], Eriko Ayabe[a], Rai Shimoyama[a], Rieko Kaira[a], Akira Ono[a], Satoshi Igawa[a], Takehito Shukuya[a], Haruyasu Murakami[a], Asuka Tsuya[a], Yukiko Nakamura[a], Masahiro Endo[b], Nobuyuki Yamamoto[a,*]

[a] Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
[b] Division of Diagnostic Radiology, Shizuoka Cancer Center, 1007 Shimonagakubo Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

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ABSTRACT

Purpose: The use of erlotinib after gefitinib failure in patients with non-small cell lung cancer (NSCLC) is not clearly clarified in clinical practice. We sought to compile the available clinical reports to better understand the effectiveness of erlotinib after failure of gefitinib.
Methods: We searched published reports including erlotinib and gefitinib. Eleven reports were identified (published between November 2004 and December 2008). Advanced NSCLC who documented progressive disease (PD) for gefitinib 250 mg/day, received erlotinib 150 mg once daily.
Results: A total of 106 patients were pooled from these studies. Asian was observed in 70.8%, women in 72.6%, adenocarcinoma in 85.1%, never smoker in 75.3%. In erlotinib therapy, there was observed in 9.9% in partial response (PR), 18.9% in stable disease (SD) and 70.8% in PD. Disease control (DC) rate for gefitinib and erlotinib was 71.7% and 29.2%, respectively. No significant difference of disease control rate (37.5% vs 21.7%, $p = 0.1503$) and response rate (6.3% vs 8.7%, $p = 1.000$) was observed between patients with *EGFR* mutations and those with wild type *EGFR*. The significantly different response on erlotinib therapy was observed in patients who had shown SD for gefitinib therapy ($p = 0.0095$) and those who had a PFS of more than 6 months during gefitinib treatment ($p = 0.0261$). The common toxicities were skin rash and diarrhea.
Conclusion: Erlotinib may produce clinical benefits in patients who had shown long SD on prior gefitinib therapy. Moreover, *EGFR* mutations were not positive predictors for erlotinib response after gefitinib failure.

1. Introduction

Epidermal growth factor receptor (*EGFR*) inhibition has widely been used to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC). Molecular targeted therapies, such as *EGFR* tyrosine kinase inhibitors (TKIs), provide a different mechanism of action from chemotherapy and can be much specific in their approach to cancer treatment. Recently, erlotinib and gefitinib, both reversible, oral inhibitors of the *EGFR* were approved for second- or third-line treatment of metastatic or advanced NSCLC. In BR-21, a placebo-controlled, phase III study of erlotinib in patients with NSCLC previously treated with one or two prior cytotoxic chemotherapy regimens, patients treated with erlotinib achieved an 8.9% response rate and 43% improvement in median survival from 4.7 to 6.7 months [1]. This incremental benefit in survival is at least comparable with second-line cytotoxic chemotherapy.

The maximum-tolerated doses of gefitinib and erlotinib are 1000 and 150 mg, respectively, therefore the usual dose of erlotinib 150 mg may be a higher biological dose than that of gefitinib 250 mg [2,3]. Some reports suggest that the response of erlotinib after gefitinib failure is associated with the maximum-tolerated dose of TKIs and *EGFR* mutation status [4,5]. Recently, several researchers have reported a trial to evaluate erlotinib in NSCLC patients with progressive disease after gefitinib treatment [4,6–15]. Few small studies have shown that erlotinib after gefitinib failure yielded disease control rate from 28 to 35% [4,9], although other studies have shown contradictory results [7,12]. Cho et al. described that most patients who benefited from erlotinib had disease control on prior gefitinib treatment [4]. However, these published reports consisted of the clinical trials with small sample sizes and case reports, and we cannot conclude the effectiveness of erlotinib after gefitinib failure from these results.

* Corresponding author. Tel.: +81 55 989 5222; fax: +81 55 989 5634.
E-mail address: n.yamamoto@scchr.jp (N. Yamamoto).

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Table 1
Characteristics of the published reports of erlotinib after gefitinib failure in non-small cell lung cancer.

Author (reference)	No. of patients	Country of origin	Study design	Gender (female/male)	ECOG PS (0 or 1/2 or 3)	Histology (AC/SQC/other)	Smoking history (yes/no)	*EGFR* mutation (positive/negative/unknown)
Cho et al. [4]	21	Korea	Prospective	11/10	6/15	16/3/2	10/11	5/12/4
Vasile et al. [6]	8	Italy	Prospective	4/4	5/3	6/0/2	1/7	NR
Lee et al. [7]	23	Korea	Prospective	19/4	12/11	22/0/1	NR	5/5/13
Sim et al. [8]	16	Korea	Retrospective	16/0	2/14	16/0/0	0/15	5/5/6
Wong et al. [9]	14	Singapore	Retrospective	10/4	NR	10/1/3	1/13	8/6/0
Costa et al. [10]	13	USA	Retrospective	9/4	NR	11/0/2	5/8	13/0/0
Gridelli et al. [11]	3	Italy	Case report	3/0	NR	3/0/0	0/3	NR
Viswanathan et al. [12]	5	USA	Case report	4/1	NR	NR	NR	NR
Chang et al. [13]	1	Taiwan	Case report	0/1	NR	1/0/0	1/0	1/0/0
Walther et al. [14]	1	UK	Case report	1/0	NR	1/0/0	0/1	NR
Garfield [15]	1	USA	Case report	0/1	0/1	0/0/1	1/0	NR
Total	106			77/29	25/44	86/4/11	19/58	37/33/23

Note: ECOG PS, Eastern Cooperative Oncology Group performance status; AC, adenocarcinoma; SQC, squamous cell carcinoma; *EGFR*, epidermal growth factor receptor; NR, not reported; USA, United States of America; UK, United Kingdom.

Based on their backgrounds, the purpose of this study is to compile the published reports dealing with the effectiveness of erlotinib after failure of gefitinib treatment in pretreated NSCLC.

2. Materials and methods

2.1. Literature search

We performed a systematic search of the MEDLINE and PUBMED databases to identify all clinical trials and case reports that contained advanced or metastatic NSCLC patients who were treated with erlotinib after gefitinib failure. The search strategy included articles from November 2004 to December 2008 indexed under the subject headings *erlotinib*, *gefitinib*, *failure* and *lung cancer*. The search did not restrict the type of publication or periodical. We did not include preliminary sets published as abstracts or meeting's proceedings. We selected all published reports that clearly described that erlotinib was administered with advanced or metastatic NSCLC patients who had documented progressive disease on gefitinib. The search was also restricted to published manuscripts in the English language.

2.2. Patient selection and EGFR mutation analysis

Patients included in these published reports had cytologically or histologically proven advanced NSCLC who were treated with erlotinib following disease progression on gefitinib. The reports identified included only adult patients and contained a mixed population of patients who had received prior chemotherapy or were receiving gefitinib as first line therapy. Patients excluded were those who were treated with erlotinib for reasons other than disease progression on gefitinib, such as toxicity or financial reasons or those who were treated erlotinib before gefitinib.

Mutations in the tyrosine kinase domain (exons, 18–21) of *EGFR* were identified using the protocols as described previously [4,16–23]. We included any of the reports based on the method of DNA isolation from fresh tissue or paraffin-embedded tissue, and the technique used to enhance tumor-derived DNA, which included either microdissection or use of more sensitive polymerase chain reaction (PCR) amplification techniques.

2.3. Treatment schedule, response, survival assessment and statistical analysis

All of the identified reports had same treatment schedule for gefitinib and erlotinib. Advanced NSCLC who documented progressive disease on gefitinib 250 mg/day received erlotinib 150 mg once daily. Therapy was continued until disease progression, intolerable toxicity, or withdraw of consent. Treatment response was determined by Response Evaluation Criteria in Solid Tumors (RECIST) [24]. Response based on target (and nontarget lesions) was defined as follows: complete response (CR), disappearance of all target (nontarget) lesions, partial response (PR), ≥30% reduction in size (or disappearance of one or more nontarget lesions); stable disease (SD), less than 30% decrease and less than 20% increase in size (or the persistence of one or more nontarget lesions); progressive disease (PD), more than 20% increase in size (or the appearance of new nontarget lesions and/or progression of existing nontarget lesions). The overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence, confirmed by repeated assessments performed not less than 4 weeks after the criteria for response were first met. Response rates (RR) were defined as CR + PR. Disease control (DC) was defined as the best tumor response of CR, PR, or SD that was confirmed and sustained for 60 days or longer.

Progression-free survival (PFS) was defined as the period from the start of treatment to the date when disease progression or death was observed. Median PFS was calculated using the Kaplan–Meier method [25]. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 or 3.0. Fisher's exact test was used to compare response rates in the two-tailed probability reported. In order to estimate the Odds ratios, logistic regression models were applied for categorical variables. We used direct data as extracted from the author's publications for response rate and PFS. Statistical analysis was performed using JMP 8 (SAS Institute Inc., Cary, NC, USA) for windows.

3. Results

3.1. Characteristics of the published reports of erlotinib after gefitinib failure

Based on our research criteria, we identified 3 prospective studies, 3 retrospective studies and 7 case reports that evaluated advanced NSCLC who received erlotinib following disease progression on gefitinib [4,6–15,26,27]. Since 2 of the 7 case reports were described in the one prospective and one retrospective study, we excluded the two case reports from further analysis. Table 1 summarizes the 11 identified clinical reports. Overall 106 patients received erlotinib after failure of gefitinib therapy. Of these 106 patients, 75 (70.8%) were Asian and 31 (29.2%) were Caucasian. Seventy-seven patients (72.6%) were women and 29 (27.4%) were men. Performance status (PS), histology of the patients and smoking history were as follows: PS 0 or 1 (25/69, 36.2%), PS 2 or 3 (44/69, 63.8%); adenocarcinoma (86/101, 85.1%), squamous cell car-

Table 2
Response to erlotinib after failure of gefitinib.

Author (reference)	No. of patients	Response to prior gefitinib			Response to erlotinib		
		PR (%)	SD (%)	PD (%)	PR (%)	SD (%)	PD (%)
Cho et al. [4]	21	6 (28.6%)	4 (19.0%)	11 (52.4%)	2 (9.5%)	4 (19.0%)	15 (71.5%)
Vasile et al. [6]	8	4 (50.0%)	4 (50.0%)	–	2 (25.0%)	3 (37.5%)	3 (37.5%)
Lee et al. [7]	23	15 (65.2%)	2 (8.7%)	6 (26.1%)	1 (4.3%)	1 (4.3%)	21 (91.4%)
Sim et al. [8]	16	9 (56.3%)	2 (12.5%)	5 (31.2%)	1 (6.3%)	3 (18.7%)	12 (75.0%)
Wong et al. [9]	14	–	9[a] (64.3%)	5 (35.7%)	–	5[a] (35.7%)	9 (64.3%)
Costa et al. [10]	13	11 (84.6%)	2 (11.1%)	0 (0.0%)	1 (5.5%)	2 (15.4%)	10 (76.9%)
Gridelli et al. [11]	3	–	3 (100%)	–	1 (33.3%)	2 (66.7%)	–
Viswanathan et al. [12]	5	–	4[a] (80.0%)	1 (20.0%)	–	–	5 (100%)
Chang et al. [13]	1	1 (100%)	–	–	1 (100%)	–	–
Walther et al. [14]	1	–	–	1 (100%)	1 (100%)	–	–
Garfield [15]	1	–	–	1 (100%)	1 (100%)	–	–
Total	106	46 (43.4%)	30 (27.0%)	30 (28.3%)	11 (9.9%)	20 (18.9%)	75 (70.8%)
Disease control rate			71.7%			29.2%	

Note: PR, partial response; SD, stable disease; PD, progressive disease.
[a] Reported only the disease control rate (as the sum of PR and SD).

cinoma (4/101, 3.9%), other (11/101, 11.0%); smoker (19/77, 24.7%), non-smoker (58/77, 75.3%). *EGFR* mutations were investigated in 70 (66.0%) of 106 patients, and *EGFR* mutations were detected in 37 (52.9%) of 70 patients. In all of these 37 patients, the analysis of *EGFR* mutations was examined in the tumor sampling before initiation of gefitinib therapy.

3.2. Response rate to erlotinib after gefitinib failure in all patients

In erlotinib therapy after gefitinib failure, there was observed in 9.9% in PR, 18.9% in SD and 70.8% in PD (Table 2).

Table 3 shows the response to erlotinib after gefitinib failure with or without *EGFR* mutation. Thirty-seven patients had *EGFR* mutations. Response to erlotinib after gefitinib failure was observed in 6.3% in PR, 31.3% in SD and 62.5% in PD. Disease control rate was 37.5% for erlotinib treatment. On the other hand, in 23 patients who had a wild type *EGFR*, response to erlotinib after gefitinib failure was observed in 8.7% in PR, 13.1% in SD and 78.2% in PD. Disease control rate was 21.7% for erlotinib treatment. No significant difference of disease control rate (37.5% vs 21.7%, $p = 0.1503$) and response rate (6.3% vs 8.7%, $p = 1.000$) was observed between patients with *EGFR* mutations and patients with wild type *EGFR*.

3.3. Progression-free survival of erlotinib and gefitinib

Median PFS was investigated in the identified 59 patients, and it ranged from 6.3 to 17.0 months for gefitinib therapy and from 1.7 to 5.9 months for erlotinib therapy (Table 4). Cho et al. [4] reported that median PFS for erlotinib was significantly longer in patients who had shown PR or SD for gefitinib than in those who had shown PD. Vasile et al. [6] also reported that the median PFS for gefitinib seemed to be longer in patients who have shown PR or SD on erlotinib as compared with those who has shown PD.

3.4. Characteristics according to the response on erlotinib after gefitinib failure

Table 5 summarizes the characteristics of the 47 patients (44.3%, 47/106) who we could find the detailed information about individual patients. Twenty-five patients had a response rate of PR or SD for erlotinib, whereas 22 patients had a response rate of PD. There was no significant difference between patients with PR or SD and those with PD in the gender, smoking history, histology and *EGFR* mutation status. However, the significantly different response on erlotinib therapy was observed in patients who had shown SD for gefitinib therapy ($p = 0.0095$) and those who had a PFS of more than 6 months during gefitinib treatment ($p = 0.0261$).

3.5. Erlotinib-related adverse events

Erlotinib-related adverse events were described in 57 (53.8%) of 106 patients [4,6,7,11,13,15]. The common toxicities were those related to the skin. Twenty-six (45.6%) of 57 patients developed grade 1 or 2 skin rash, however four patients (7.0%) were described as having grade 3 or 4 skin toxicities. The second most common adverse event was diarrhea. Grade 1 or 2 diarrhea was observed in 12 (21.1%) of 57 patients, and no grade 3 or 4 diarrhea was observed. Other less common effects reported, including hyperbilirubinemia and vomiting [4,7,13]. The most serious adverse event related to *EGFR* TKI exposure, interstitial lung disease (ILD), was not observed in all of these 57 patients.

Table 3
Response to erlotinib after failure of gefitinib in non-small cell lung cancer with or without *EGFR* mutation.

Author (reference)	*EGFR* mutation (+)				*EGFR* mutation (−)			
	No. of patients	PR (%)	SD (%)	PD (%)	No. of patients	PR (%)	SD (%)	PD (%)
Cho et al. [4]	5	–	1 (20.0%)	4 (80.0%)	12	2 (16.7%)	2 (16.7%)	8 (66.6%)
Sim et al. [8]	5	–	2 (40.0%)	3 (60.0%)	5	–	1 (20.0%)	4 (80.0%)
Wong et al. [9]	8	–	5[a] (62.5%)	3 (37.5%)	6	–	–	6 (100%)
Costa et al. [10]	13	1 (7.7%)	2 (15.4%)	10 (76.9%)				
Chang et al. [13]	1	1 (100%)	–	–				
Total	32	2/32 (6.3%)	10/32 (31.3%)	20/32 (62.5%)	23	2/23 (8.7%)	3/23 (13.1%)	18/23 (78.2%)
Disease control rate			37.5%				21.7%	

Note: *EGFR*, epidermal growth factor receptor; PR, partial response; SD, stable disease; PD, progressive disease; NR, not reported.
[a] Reported only the disease control rate (as the sum of PR and SD).

Table 4
Progression-free survival (PFS) of erlotinib and gefitinib.

Author (reference)	No. of patients	Median PFS of gefitinib (months)			Median PFS of erlotinib (months)				
		Total	PR/SD on erlotinib	PD on erlotinib	Total	PR/SD on gefitinib	PD on gefitinib	PR/SD on erlotinib	PD on erlotinib
Cho et al. [4]	21	–	9.0[a]	3.6[a]	4.0	4.5[b]	1.2[b]	4.8[c]	1.1[c]
Vasile et al. [6]	8	17.0	18.0	8.5	5.9	–	–	8.0	–
Sim et al. [8]	16	6.3	–	–	1.7	–	–	–	–
Wong et al. [9]	14	–	7.3	–	–	–	–	3.1	–

Note: PFS, progression-free survival; PR, partial response; SD, stable disease; PD, progressive disease.
[a] Significant difference between PR/SD on erlotinib and PD on erlotinib ($p = 0.019$).
[b] Significant difference between PR/SD on gefitinib and PD on gefitinib ($p = 0.005$).
[c] Significant difference between PR/SD on erlotinib and PD on erlotinib ($p = 0.004$).

4. Discussion

This current study pooled from 3 prospective studies, 3 retrospective studies and 5 case reports, of advanced NSCLC who received erlotinib after failure of gefitinib therapy. We believed that our pooled analysis is able to strengthen the individual observations of each of these small prospective and retrospective studies alone. The primary endpoint of these studies was objective tumor response rate. Approximately 30% of the 106 patients displayed PR or SD as best response to erlotinib after gefitinib failure, and the identified PR rate was 9.9%, which is comparable with a response rate of 8.9% in BR-21 study which erlotinib as single agent has been evaluated in comparison with best supportive care after failure of one or two standard chemotherapy regimens [1]. In our study, response rate to erlotinib in patients with *EGFR* mutations seemed to be similar to that in those with a wild type *EGFR*. Moreover, disease control rate also had no significant difference between patients with *EGFR* mutations (37.5%) and those with wild type *EGFR* (21.7%), and median PFS ranged from 1.7 to 5.9 months. In BR-21 trial, disease control rate and PFS were 45.0% and 2.2 months, respectively [1]. Tsao et al. [28] described that mutational status had no significant association with responsiveness: 7% of those with wild type *EGFR* had a response, as compared with 16% of those with *EGFR* mutations. Comparing the current study with BR-21 trial, the efficacy of erlotinib after *EGFR* TKI failure may be similar to that of erlotinib after failure of one or two standard chemotherapy regimens. Moreover, the common toxicities in BR-21 trials were skin rash and diarrhea. Grade 3–5 skin rash was observed in 9%, and grade 3–5 diarrhea was observed in 4%. The adverse events in our study seemed to be similar to those in BR-21 trials. Even if erlotinib was administered after prior gefitinib therapy, the erlotinib-related toxicities seemed not to be worse as compared with previous reports.

Table 5
Characteristics according to the response on erlotinib after failure of gefitinib ($n = 47$).

	Disease control rate (%) on erlotinib (PR + SD/total)	Odds ratio (95% CI)[a]	*p*-Value
Number of Patients	47		
Gender			
Male	63.6% (7/11)	Reference	
Female	52.8% (19/36)	0.57 (0.13–2.23)	0.4248
Smoking history			
Yes	53.5% (5/9)	Reference	
No	52.6% (20/38)	0.88 (0.19–3.86)	0.8743
Histology			
Adenocarcinoma	53.5% (23/43)	Reference	
Non-Adenocarcinoma	50.0% (2/4)	1.15 (0.12–10.30)	0.8937
Gefitinib therapy			
Response rate			
CR + PR	44.0% (11/25)	Reference	
SD	80.0% (12/15)	5.84 (1.50–29.54)	0.0095
PD	42.9% (3/7)	0.61 (0.11–3.13)	0.5528
Progression-free survival			
Under 6 months	27.3% (3/11)	Reference	
More than 6 months	60.6% (20/33)	4.37 (1.18–18.90)	0.0261
EGFR mutation			
Mutant	45.8% (11/24)	Reference	
Wild type	50.0% (5/10)	0.85 (0.20–3.53)	0.8198
Unknown	61.5% (8/13)	1.59 (0.44–6.24)	0.4765

Note: *EGFR*, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval. The data above was collected from Refs. [4,7–10,11,13,15].
[a] Odds ratio was calculated as compared with reference.

We analyzed the characteristics of 47 patients according to response on erlotinib after gefitinib failure (Table 5). In these patients, the significantly different response on erlotinib therapy was observed in patients who had shown SD for gefitinib therapy and those who had a PFS of more than 6 months during gefitinib treatment. Cho et al. [4] concluded that erlotinib seems to be a potential therapeutic option for the treatment of advanced NSCLC patients who had SD while receiving gefitinib. We believe that our results are also able to strengthen their conclusion. However, we could not clarify the mechanisms behind the effectiveness of erlotinib in this population. Several potential explanations were as follows: (1) erlotinib was administered at maximum-tolerated dose, whereas gefitinib was administered at approximately one of third of its maximum-tolerated dose. The standard dose of erlotinib and gefitinib are not biologically equivalent. (2) Difference in tumor sensitivity might be associated with the relative concentration of *EGFR* TKIs. (3) The IC_{50} value of erlotinib is much lower than that of gefitinib [5]. In the present study, no significantly different response on erlotinib therapy was observed in patients who had shown CR + PR or PD for gefitinib therapy. There is evidence of a strong association between *EGFR* mutations and objective response to both gefitinib and erlotinib [16,29]. However, a lack of correlation between response to erlotinib and *EGFR* mutations was observed in our study. Our result suggests that *EGFR* mutations are not positive predictors for erlotinib response after gefitinib failure. Moreover, erlotinib seems produce higher clinical benefits in patients who had shown SD for prior gefitinib treatment and had a PFS of long-term during gefitinib therapy.

Recently, several researchers described that most patients who did not benefit from prior gefitinib therapy had rapid progression on subsequent erlotinib therapy, whereas tumor response to prior gefitinib therapy can be used as predictive marker for subsequent erlotinib therapy [4,7,8]. Cho et al. [4] described that erlotinib seem to be a potential therapeutic option for the treatment of NSCLC patients with wild type *EGFR* who shown SD with prior gefitinib treatment. Lee et al. [7] also described that erlotinib should not be given routinely after gefitinib failure, but may be an option for patients who had benefited from prior gefitinib therapy. In *EGFR* mutated tumors to resistant to gefitinib, most patients were described to have no radiographic response by a switch to erlotinib [10]. *In vitro* study indicated that the common mechanisms of TKI resistance (T790M and MET amplification) are not inhib-

ited by clinically achievable doses of gefitinib or erlotinib [19,30]. T790M secondary mutation and MET amplification were commonly described among the mechanisms of acquired resistance to *EGFR* TKIs [19,30]. If tumor progression occurs in patients with gefitinib-responsive NSCLC with *EGFR* mutations, the tumor cell would have a high probability of resulting cross-resistant to erlotinib. However, other secondary mutations such as L747S or E884K have also been described, and they may result in different tumor response to gefitinib and erlotinib [31]. Experimental studies indicated that some irreversible and second-generation *EGFR* inhibitors could overcome the resistant T790M secondary mutation [10,19,32]. Recently, irreversible *EGFR* inhibitors or anti-MET agents are being developed for the treatment of NSCLC, and it will be dependent on the results of clinical trials whether these agents could be used as the therapeutic options for the patients with acquired resistant to *EGFR* TKIs [33,34].

Another observation in our pooled analysis was that of safety of erlotinib after prior gefitinib treatment. The most common toxicities were those of skin rash and diarrhea, which had been expected from the large phase III trial [1]. Most of the patients were described as mild toxicities and few patients had grade 3/4 skin toxicities. ILD was not observed in our study. In BR-21 trial, 9% developed grade 3–5 skin rash, 6% developed grade 3–5 diarrhea, and one of 485 patients was died due to pneumonitis [1]. Compared with the previous trial [1], the erlotinib-related adverse events were not severe in our study.

The limitation of this study must be addressed. Our study includes not only prospective phase II studies but also retrospective studies or case reports. Although all studies were discussed about the objective response of erlotinib after disease progression on gefitinib, the inclusion criteria were different among individual studies. Moreover, the status of *EGFR* mutations was not investigated in all of 106 patients, and we could not have the detailed information in all of 106 patients. Thus, this study has a bias against the effectiveness of erlotinib after gefitinib failure. Further clinical trials should be prospectively investigated in large sample sizes.

Our compilation of the 106 published patients who receive erlotinib after gefitinib failure revealed that erlotinib may produce clinical benefits in patients who had shown SD with a long-term duration (more than 6 months) for prior gefitinib therapy. Moreover, *EGFR* mutations were not positive predictors for erlotinib response after gefitinib failure. Our data supports the notion that *EGFR* mutated patients do not benefit significantly from "switching" to an *EGFR* TKI with higher biological doses once resistance (through EGFR-T790M or MET) develops on gefitinib. The adverse events for erlotinib treatment were also similar to previous reports. We believe that erlotinib should not be administered routinely after gefitinib failure, but the patients who benefited from prior gefitinib might be appropriately considered for erlotinib treatment.

Conflict of interest

We, all authors, have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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