

Re-administration after the failure of gefitinib or erlotinib in patients with advanced non-small cell lung cancer

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ABSTRACT

Objective: Few treatment options are available for advanced non-small cell lung cancer (NSCLC) patients who have failed of gefitinib or erlotinib treatment in second/third-line treatment. The aim of this study was to investigate the efficacy of re-administration of the same TKI after failure of gefitinib or erlotinib.

Patients and methods: The clinical data of 33 patients with advanced NSCLC were retrospectively analyzed. All of the patients were given the same TKI treatment after the failure of gefitinib or erlotinib. Survival analysis was evaluated by Kaplan-Meier method.

Results: Twenty patients (60.6%) were re-administration with gefitinib as the 2nd EGFR-TKI, and thirteen patients (39.4%) received erlotinib. One patient (3.0%) showed partial response (PR), 14 (42.4%) achieved stable disease (SD), and 18 (54.5%) had progressive disease (PD). The disease control rate was 45.5% and the median progression-free survival was 1.5 months (95% CI: 0.6-2.3 months). The PFS in patients who got disease control in the prior TKI was 2.2 and 1.2 months in the progression disease cases (P=0.29), the DCR was 54.5% and 27.3% in two group, respectively (P=0.26).

Conclusions: Re-administration of TKI seems to be a potential therapeutic option for treatment of selected advanced NSCLC patients after failure of gefitinib or erlotinib, especially for the patients with NSCLC who once responded from the prior TKI treatment.

KEY WORDS

Non-small cell lung cancer (NSCLC); erlotinib; gefitinib; retreatment; efficacy

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Introduction

Gefitinib, an oral small molecule agent that inhibits epidermal growth factor receptor (EGFR) tyrosine phosphorylation (1), is the first targeted agent to be approved for the treatment of the patients with advanced non-small cell lung cancer (NSCLC), which has demonstrated clinical efficacy in the second or third-line treatment of NSCLC, especially among never-smokers, females, East Asians, and patients with adenocarcinoma (2,3). Erlotinib, another EGFR-TKI, also has shown a survival benefit in second-line or third-line treatment for advanced NSCLC (4,5).

Despite the high objective response rate (ORR) and disease control rate (DCR) in the EGFR mutation patients with the

gefitinib or erlotinib treatment, most of cases would be with disease progression. For patients who previous treated with TKI and later showed tumor progression, currently, many patients with no further treatment options. Some studies have conducted trials to evaluate the efficacy of erlotinib after gefitinib failure in patients with NSCLC (6-11), but, few studies investigated the same EGFR-TKI re-administration and most of the data was from case report (12-17).

In the present study, we investigated the efficacy of re-administration of the same TKI after failure of gefitinib or erlotinib, and to explore which patients may benefit from re-administration.

Patients and methods

Patient eligibility

Six hundred and ninety-one consecutive, unselected NSCLC patients, who were admitted to Zhejiang Cancer Hospital from January 2007 to July 2011, were administrated with erlotinib or gefitinib treatment. NSCLC staging was performed for all

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the patients according to the 7th TNM classification. Inclusion criteria were as follows: (I) pathologically proven primary stage IIIB or IV NSCLC; (II) All the patients were supplied with the same TKI as subsequent salvage therapy after failure of gefitinib or erlotinib; (III) All patients received chemotherapy between the first TKI treatment and re-administration; (IV) The disease recurrence was confirmed using chest computed tomography (CT), brain MRI and bone scan as well as ultrasound examination and/or CT of the abdomen; (V) Without any local treatment like radiotherapy or interventional therapy during the period of gefitinib or erlotinib therapy; (VI) At least one measurable lesion and an Eastern Cooperative Oncology Group performance status of 0 to 3.

Response evaluation

All patients were followed up every 6 weeks with imaging examination during treatment with EGFR-TKIs or were evaluated early when significant tumor progression appeared. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). DCR was defined as the addition of objective response and stabilization.

Toxicity evaluation

The toxicity profile of EGFR-TKI was assessed by reviewing medical records including skin rash, diarrhea, liver toxicity, and radiological evidence of interstitial pneumonitis. Severity of adverse reactions was determined based on the requirements of dosage reduction or discontinuation of EGFR-TKI. All such toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0 (CTC 3.0).

Follow-up

All the patients were to be evaluated for tumor response and PFS. Follow-up rate was 100%. The last follow-up date was July 31, 2012. The median follow-up period was 30.2 months (6.7-56 months).

Statistical analysis

The Chi-square was applied to elucidate the differences between different treatment arms. PFS encompassed the time from the first day of TKI therapy to documented progression or death from any cause, or until the date of the last follow-up visit for patients who were still alive and who had not progressed. Survival analysis was conducted with a Kaplan-Meier analysis and log-rank test. A P-value of less than 0.05 was regarded as statistically significant. All

Table 1. Baseline characteristics of the study population (n=33).

Variables	Number	Percent
Gender		
Male	16	48.5
Female	17	51.5
PS		
0-1	22	66.7
2-3	11	33.3
Age		
Median	59.0	
Mean	57.9±10.6	
Smoking history		
Yes	10	30.3
No	23	69.7
Histology		
Adenocarcinoma	28	84.8
Non-adenocarcinoma	5	15.2
Staging		
IIIB	0	0
IV	33	100
Chemotherapy before re-treatment		
Yes	33	100
No	0	0
TKI		
Gefitinib	20	60.6
Erlotinib	13	39.4
Brain metastasis		
Yes	6	18.2
No	27	81.8

statistical tests were analyzed using the computer software SPSS version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

A total of 33 patients were included in the study and all of them were assessable for response and toxicity. There were 16 males and 17 females. PS 0-1 was present in 22 patients (66.7%) and PS 2-3 accounted for 33.3%. The median age of the patients was 57.9 years (range, 32-76 years). The majority of the tumors were adenocarcinoma (87.9%) and all of them were advanced stage on presentation. Thirty percent (10/33) had a smoking history. In 20 patients with adequate specimens for molecular analysis, 14 (70%) had EGFR mutations (8 with deletions within exon 19 and 6 with L858R messenger mutation in exon 21). All of the cases underwent cytotoxic chemotherapy between the first and second TKI therapy. Patients' characteristics are shown in Table 1.

Table 2. Response rate after treatment with gefitinib and retreatment.

	Initial treatment		Retreatment	
	Gefitinib	Erlotinib	Gefitinib	Erlotinib
PR, n [%]	9 [45]	4 [30.8]	0 [0]	1 [7.7]
SD, n [%]	4 [20]	5 [38.4]	9 [45]	5 [38.5]
PD, n [%]	7 [35]	4 [30.8]	11 [55]	7 [53.8]
ORR, n [%]	9 [45]	4 [30.8]	0 [0]	1 [7.7]
DCR, n [%]	13 [65]	9 [69.2]	9 [45]	5 [46.2]

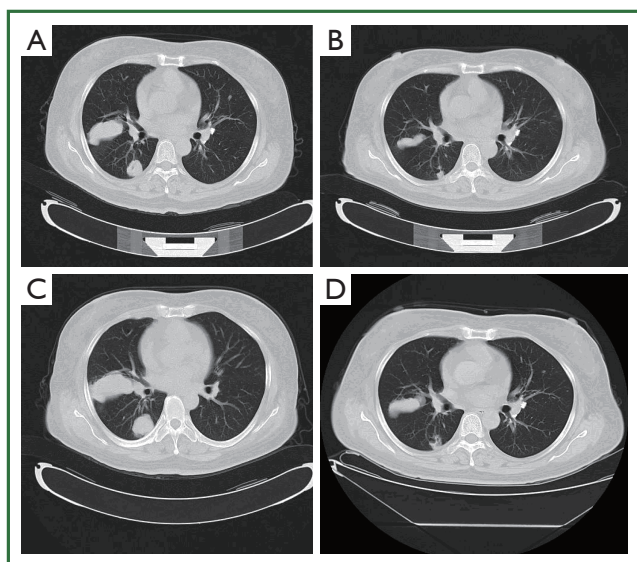


Figure 1. Chest CT scan of a patient who had a PR with retreatment of erlotinib. A. Chest CT scan before treatment with erlotinib; B. Chest CT scan 2 months after treatment with erlotinib; C. Chest CT scan before retreatment with erlotinib; D. Chest CT scan after retreatment with 2 months of erlotinib.

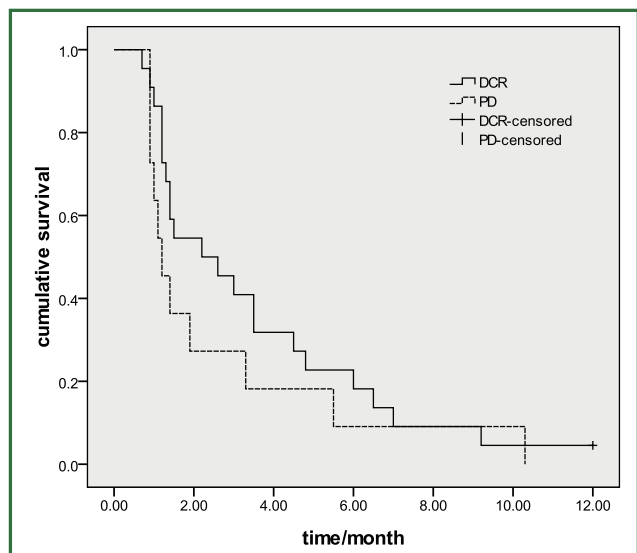


Figure 2. The retreatment PFS in patients who got disease control in the prior TKI and in the initial PD group ($P=0.29$).

Response data and survival analysis

Response data for gefitinib and erlotinib therapy are shown in Table 2. Thirteen patients had a PR and nine patients had SD in the initial gefitinib or erlotinib treatment, accounting for a DCR of 66.7%. There was only one patient with a PR to the retreatment (Figure 1), while 14 patients had SD and 18 patients had PD. No patients had PR and two with SD in the six patients with brain metastasis. Median PFS during initial gefitinib and erlotinib treatment was 8.9 months (95% CI: 5.0-12.8 months), but only 1.5 months during erlotinib or gefitinib retreatment (95% CI: 0.6-2.3 months). The median survival time for all patients was 27.5 months. The median OS from the beginning of the 2nd EGFR-TKI was 9.9 months (95% CI: 7.5-12.2 months).

The relationship between initial treatment and retreatment efficacy

The overall DCR in the retreatment group was 45.5% (15/33). The retreatment DCR was 54.5% (12/22) in patients who got disease control in the prior TKI and 27.3% (3/11) in the initial PD group ($P=0.26$), and the PFS was 2.2 and 1.2 months in two group, respectively, ($P=0.29$) (Figure 2). No difference was found of the PFS between the erlotinib and gefitinib group (1.9 vs. 1.4 months, $P=0.98$). The median PFS was 2.4 months in 12 patients with EGFR mutation and 1.2 months in EGFR wild-type patients ($P=0.09$).

Toxicities of treatment

Toxicity was evaluated in all the patients. The most common adverse event was skin toxicity in 15 patients (45.5%), including 3 patients with grade 3. Other common toxicity included diarrhea (eleven cases), fatigue (twelve cases). Two patients demonstrated hepatic function injuries after being retreated with erlotinib therapy. No dosage reduction was occurred. Overall, toxicity appeared similar to the previously published trials of gefitinib and erlotinib monotherapy (Table 3).

Discussion

To the best of our knowledge, our represents the largest data to assess whether gefitinib and erlotinib re-administration confers any clinical benefit in patients with advanced NSCLC. In our series, we obtained a DCR of 45.5% with a median duration of this control of 1.5 months with TKI re-administration. In particular, our study suggested that the overall DCR was 54.5% in patients who got disease control in the prior TKI, in contrast, the DCR was only 27.3% in the initial TKI PD group.

Riely *et al.* reported that in patients who develop acquired resistance, stopping gefitinib or erlotinib results in symptomatic

Table 3. Toxicities of gefitinib and erlotinib as initial and retreatment therapy for patients with advanced NSCLC.

Toxicity	Initial treatment, n=33 (%)		Retreatment, n=33 (%)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Rash	14 (42.4)	3 (9.1)	12 (36.4)	3 (9.1)
Fatigue	8 (24.2)	2 (6.1)	8 (24.2)	4 (12.1)
Diarrhoea	11 (33.3)	1 (3.0)	9 (27.3)	2 (6.1)
Nausea	10 (30.3)	1 (3.0)	10 (30.3)	2 (6.1)
Anorexia	6 (18.2)	1 (3.0)	6 (18.2)	3 (9.1)
Dyspnoea	3 (9.1)	2 (6.1)	3 (9.1)	2 (6.1)
Vomiting	5 (15.2)	1 (3.0)	7 (21.2)	1 (3.0)
Neurotoxicity	2 (6.1)	0 (0)	1 (3.0)	0 (0)
Cough	3 (9.1)	3 (9.1)	6 (18.2)	4 (12.1)
Stomatitis	3 (9.1)	1 (3.0)	3 (9.1)	3 (9.1)
Dry skin	5 (15.2)	3 (9.1)	1 (1.6)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic injure	2 (6.1)	1 (3.0)	3 (9.1)	2 (9.1)

Table 4. All the articles published about retreatment as a salvage treatment after failure of gefitinib or erlotinib.

Author	TKI sequence	No. of patients	Response to TKI		Response to 2 nd TKI		DCR to 2 nd TKI
			CR/PR/SD	PD	CR/PR/SD	PD	
Yokouchi H (12)	G-G	9	9	0	8	1	88.90%
Yoshimoto A (13)	G-G	1	1	0	1	0	100%
Yano S (18)	G-G	3	3	0	2	1	66.70%
Hashimoto N (19)	G-G	1	1	0	0	1	0%
Kurata T (17)	G-G	1	1	0	1	0	100%
Watanabe S (20)	G-G	3	3	0	2	1	66.70%
Guo RH (21)	G-G	1	1	0	1	0	100%
Asahina H (14)	G-G	16	16*	0	7	8	46.7%
Tomizawa Y (22)	G-G	20	20	0	13	7	65%
Guo RH (21)	E-E	1	1	0	1	0	100%
Becker A (23)	E-E	8	UK	UK	UK	UK	UK
Current study	G-G	20	13	7	9	13	45%
Current study	E-E	13	9	4	5	8	46.2%

*, including one patient can not evaluate efficacy; G, gefitinib; E, erlotinib; UK, unknown.

progression, and increased tumor size, while restarting EGFR-TKI results in a decreasing in tumor diameter, and improvement of symptoms (15). Ten patients who previously responded to erlotinib or gefitinib suggested that these patients continued to benefit from treatment with erlotinib or gefitinib despite progression of disease in Riely *et al.* study. At our knowledge, a total of 55 cases, treated with gefitinib after failure of gefitinib and only six cases with erlotinib after failure of erlotinib were described (12-14,16,17). Table 4 lists all the studies recently published with the same TKI retreatment, which showed promising results to re-administration of gefitinib and erlotinib.

Several studies have suggested a possible explanation for the clinical benefit of EGFR-TKI retreatment. Some cytotoxic agents have been reported to restore the sensitivity of NSCLC cells to gefitinib *in vitro* by increasing EGFR phosphorylation (24,25). It is also possible that chemotherapy during the EGFR-TKI-free interval could decrease EGFR-TKI resistant tumor cells. All of the previous patients including our cases were received chemotherapy between the first and TKI retreatment.

Another explanation may be contributed to T790M mutation in the EGFR gene and amplification of the MET gene, which are some of the mechanisms of the resistance to gefitinib and

erlotinib (26-28). However, the mechanisms of the resistance or re-sensitization to gefitinib or erlotinib have not been clearly defined. It may be explained the proportion of sensitive or resistant cells might have been modified or some genetic changes in EGFR associated resistance to gefitinib or erlotinib (17).

A limitation of this study was the retrospective design with its inherent shortcomings. In addition, EGFR mutation status is not fully available for the patients enrolled in our present study. However, with few cases in previous clinical studies, our retrospective study may also be considered to be meaningful.

In conclusion, our results indicated that re-administration of TKI could be consider as one of treatment option for the patients who responded to treatment of initial TKI. The erlotinib and gefitinib retreatment had a similar efficacy. It is necessary to explore the mechanisms induced resistance and re-sensitivity for EGFR-TKI.

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