Cancer Chemother Pharmacol (2009) 64:1123–1127
DOI 10.1007/s00280-009-0973-1

ORIGINAL ARTICLE

Erlotinib in advanced non-small-cell lung cancer after gefitinib failure

Zheng-Tao Zhou · Xin-Hua Xu · Qing Wei · Ming-qian Lu · Jie Wang · Cai-Hong Wen

Received: 22 November 2008 / Accepted: 16 January 2009 / Published online: 26 March 2009

Abstract
Purpose To evaluate the efficacy and safety of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib treatment.
Patients and methods Patients with advanced or metastatic NSCLC, who had progressed after gefitinib treatment, were included in this study; patients received erlotinib 150 mg/day until disease progression or intolerable toxicity.
Results Twenty-one patients were included in this study. Among them, 14 (66.7%) were male and 7 (33.3%) were female; median age was 63 years; 10 (47.6%) patients were smokers; 9 (42.9%)patients had squamous cell carcinoma subtype; 8 (38.1%) patients had adenocarcinoma subtype and 4 (19%) patients had the other NSCLC subtype. Out of 21 patients, 2 (9.5%) had PR and 4 (19.0%) had SD, giving an overall response rate of 9.5% and a disease control rate of 28.5%. The median TTP were 55 days, the median OS were 135 days. Two patients with PR to erlotinib treatment were female never smokers with adenocarcinoma histology and both had partial response to prior gefitinib treatment. Three of four patients with a SD to erlotinib treatment also had SD from prior gefitinib therapy. Smoking history, histology and response to erlotinib were significantly correlated with survival. The most common toxic effects were skin rash.
Conclusions Erlotinib may be an option for a more highly selected subset of patients, especially those who had already benefited from prior gefitinib treatment.

Keywords Erlotinib · Gefitinib · Non-small-cell lung cancer

Z.-T. Zhou (✉) · X.-H. Xu · M.-q. Lu · J. Wang · C.-H. Wen
Oncology Department, The First College of Clinical Medical Science, China Three Gorges University, Yichang, China
e-mail: ozzie@tom.com

Q. Wei
Pharmacy Department, The First College of Clinical Medical Science, China Three Gorges University, Yichang, China

Introduction

The epidermal growth factor receptor (EGFR) is a promising target for the therapy of non-small-cell lung cancer (NSCLC). Strategies for EGFR-targeted cancer therapies include inhibition of the intracellular tyrosine domain of the receptor by small molecules, such as gefitinib or erlotinib. Both agents are orally active, reversible EGFR tyrosine kinase inhibitors (TKIs) that block signal transduction pathways implicated in the proliferation and survival of cancer cells [1].

Gefitinib was the first oral EGFR TKI to become commercially available. It shown benefits in Asian patients in the ISEL study. Erlotinib was shown to prolong survival in chemotherapy pretreated patients in the phase III study (BR.21), Both agents are routinely used for the treatment of advanced NSCLC in Asian now [2].

Despite the excellent initial response, disease progression usually occurs after a median time of 4–6 months, after which no good treatment options exist for these patients.

Although their similar structures and mechanism of action suggest that erlotinib and gefitinib should have similar efficacies, the agents have somewhat different pharmacological properties. For example, erlotinib is less susceptible than gefitinib to metabolism by the cytochrome P450 pathway and therefore has a lower clearance rate and inhibits the activity of wild-type EGFR at lower concentrations

than gefitinib [3]. In addition, because the maximum-tolerated doses of gefitinib and erlotinib are 1,000 and 150 mg, respectively [4, 5], the usual dose of erlotinib 150 mg may be a higher biological dose than the usual dose of gefitinib 250 mg. These differences may account at least in part for the contradictory results of the two phase III studies, in which erlotinib, but not gefitinib, was found to prolong survival in previously treated patients [6, 7]. These findings suggested that salvage treatment with erlotinib may be an option for patients who fail gefitinib treatment.

There were several reports of clinical activity with erlotinib in NSCLC patients after failure of gefitinib treatment,

We conducted a phase II study of erlotinib in patients with advanced or metastatic NSCLC who showed disease progression on gefitinib treatment.

Patient and methods

Patients' eligibility

Patients aged 18 years or older with advanced or metastatic NSCLC, who received prior chemotherapy regimens and who had documented progressive disease on gefitinib treatment, were eligible for inclusion if they had at least one dimensionally measurable lesion, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, adequate organ functions [white blood cell 3,000/μl, platelets 100,000/μl, hemoglobin 9.0 g/dl, serum creatinine 1.5 × the upper limit of normal (ULN), bilirubin 1.25 × ULN, and serum aminotransferases 2.5 × ULN] and life expectancy of at least 3 months.

Patients were excluded if they had unresolved chronic toxicity from prior therapy, other active malignancies, uncontrolled brain metastases, or severe comorbid conditions. The study was approved by the institutional review board of the Yichang Central People's Hospital, and written informed consent was obtained from all enrolled patients.

Study design

Patients received erlotinib 150 mg once daily. One dose reduction per patient was permitted from 150 to 100 mg and erlotinib treatment could be interrupted for a maximum of 21 days. Therapy was continued until disease progression, intolerable toxicity, or withdrawal of consent.

Evaluation of response and adverse events

Baseline evaluations included a complete medical history, physical examinations, ECOG-PS, CBC, and biochemistries. Evaluation of treatment response by computed tomography scan was repeated every 4 weeks according to the response evaluation criteria in solid tumors (RECIST). Disease control was defined as the best tumor response of complete response (CR), partial response (PR), or stable disease (SD) that was confirmed and sustained for 60 days or longer. Time to progression (TTP) was defined as the period from the start of treatment to the date, when disease progression or death was observed. Overall survival (OS) was defined as the period from the start of treatment to the date of death. Adverse events were evaluated every cycle according to the National Cancer Institute Common Toxicity Criteria for adverse event (version 3.0).

EGFR mutation analysis

Formalin-fixed, paraffin-embedded tumor samples of the cases were obtained from the Departments of Pathology; DNA was extracted from 5 μm sections of each sample. Mutations in the tyrosine kinase domain (exons, 18–21) of EGFR were detected using partially denaturing high-performance liquid chromatography.

Statistical analysis

The primary objective was to assess the disease control rate (DCR; CR + PR+ SD $\geq$ 60 days) of erlotinib therapy. The secondary objectives were overall response rate, TTP, survival, and safety.

A Simon two-stage optimal design was chosen for definition of the total number of patients required for the phase II study. We set a response rate of 15% as the target activity level and 5% as the lowest response rate (objective response rate) of interest. The study was designed to have 80% power to accept the hypothesis and 5% significance to reject the hypothesis. With $\alpha = 0.05$ and $\beta = 0.2$, the estimated accrual number was 19 patients. Allowing for a 10% loss to follow-up rate, a total of 21 patients were planned to enroll.

DCRs were compared between demographic factors using Fisher's exact test, survival curves were constructed using the Kaplan–Meier method, and survival were compared using the Log-Rank test.

Results

Patient charactistics

Twenty-one patients were included in this study. Among 21 patients, 14 (66.7%) was male and 7 (33.3%) was female; median age was 63 years (range 48–78); 10 (47.6%) patients were smokers and 11 (52.4%) patients were never smokers; 9 (42.9%)patients had squamous cell carcinoma subtype, 8 (38.1%) patients had adenocarcinoma subtype and 4 (19%) patients had the other NSCLC subtype (two patients had

large cell carcinoma, one patient had mucoepidermoid carcinoma, one patient had bronchioloalveolar carcinoma).

EGFR mutation was detected in 7 (33.3%) patients.

Previously received 1 regimen chemotherapy 2 (9.5%) patients, 2 regimen 13 (61.9%) patients, >2 regimens 6 (28.6%) patients. Previously chemotherapy regimes include cisplatin + vinorelbine, cisplatin + gemcitabine, paclitaxel + carboplatin and docetaxel + cisplatin.

Out of 21 patients, 2 (9.5%) exhibited PR with gefitinib therapy, 8 (38.1%) of 21 patients exhibited SD with gefitinib therapy.

Patients' characteristics are shown in Table 1.

Efficacy

All patients were included in the response assessment.

Table 1 Patient characteristics

Characteristic	No.	%
Age		
Median	63	
Range	48–78	
Sex		
Male	14	66.7
Female	7	33.3
ECOG performance status		
0–1	1	4.8
2	13	61.9
3	7	33.3
Pathological type		
Squamous cell carcinoma	9	42.9
Adenocarcinoma	8	38.1
Others	4	19
Smoking history		
Smoker	10	47.6
Never smoker	11	52.4
EGFR mutation		
Positive	7	33.3
Negative	14	66.7
No. of prior chemotherapy regimen		
1	2	9.5
2	13	61.9
3	6	28.6
Best response to prior chemotherapy		
Complete or partial response	1	4.8
Stable disease	14	66.7
Progressive disease	6	28.6
Response to gefitinib therapy		
Complete or partial response	2	9.5
Stable disease	8	38.1
Progressive disease	11	52.4

Out of 21 patients, 2 (9.5%) had PR and 4 (19.0%) had SD, giving an overall response rate of 9.5% (95% CI: 5.5–19.6%) and a DCR of 28.5% (95% CI: 16.4–58.7%) (Table 2).

These two patents with PR to erlotinib treatment were female never smokers with adenocarcinoma histology and both had partial response to prior gefitinib treatment. In the four patients with a SD to erlotinib treatment, three patients also had SD from gefitinib treatment, one patient exhibited PD to prior gefitinib treatment.

DCRs were compared between erlotinib and gefitinib treatment using Fishers exact test, response to prior gefitinib therapy was correlated with DCR to erlotinib, patients who had response to prior gefitinib showed significantly higer DCR [5 (83.3%) of 6 vs. 1 (6.7%) of 15 in non-response patients; $P = 0.001$).

With a median follow-up duration of 150 days (range 18–270 days), the median TTP was 55 days (95% CI: 34–76 days) (Fig. 1). The median OS was 135 days (95% CI: 82–188 days) (Fig. 2).

By univariate analysis, the following variables were significantly correlated with survival: smoking history, histology, and response to gefitinib (Table 3).

Table 2 Responses

Response	No.	%
PR	2	9.5
SD	4	19.0
PD	15	71.4
Total	21	100
ORR	2	9.5 (95% CI: 5.5–19.6)
DCR	6	28.5 (95% CI: 16.4–58.7)

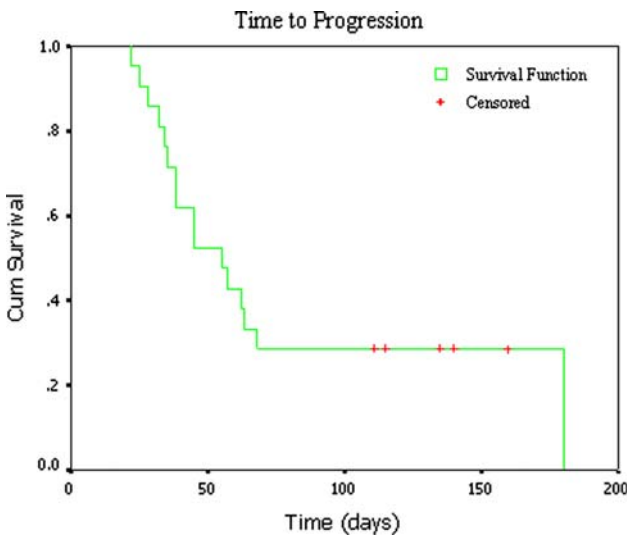

Fig. 1 Kaplan–Meiler curve of time to progression

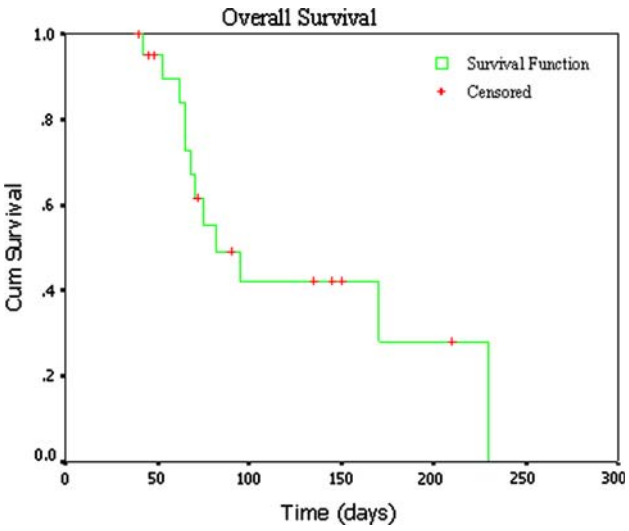

Fig. 2 Kaplan–Meiler curve of overall survival

EGFR mutations did not predict better DCR to erlotinib, 2 (290%) of 7 in EGFR mutants versus 4 (29%) of 14 in nonmutants.

Adverse events

The most common adverse event was grade 1/2 skin rash, which affected 75.0% of patients. Grade 3 skin rash occurred in one patient, whereas grade 1 diarrhea occurred in three patients. The other adverse events included prutitus, xerosis and elevation of transaminases were generally mild.

Discussion

Both erlotinib and gefitinib have been in routine use in Chinese patients with advanced or metastatic NSCLC for several years, but little is known about the efficacy of a second reversible EGFR TKI after disease progression on the first.

Several studies have observed that erlotinib confer benefits in NSCLC patients after gefitinib failure, especially in patients who had shown partial response or stable disease in prior gefitinib therapy. A case report by Garfield [8] showed response to erlotinib after gefitinib failure in a male smoker with squamous cell carcinoma, A recent publication of a phase II trial by Cho et al. [9] showed a DCR of 29.6% in NSCLC patients treated with erlotinib after gefitinib failure. It was reported that higher disease control and response rates with subsequent erlotinib were associated with patients who lacked EGFR mutations and achieved stable disease on gefitinib. Wong et al. [10] reported a retrospective analysis revealed DCR for erlotinib administered after progression on gefitinib was 35.7% (5 of 14). All patients who achieved disease control with erlotinib after progression on gefitinib were never smokers with adenocarcinoma subtype, who had prior disease control on gefitinib. Another phase II trial by Lee et al. [11] also showed patients benefited from erlotinib also benefited from prior gefitinib therapy. A recent publication by Costa et al. [12] also revealed erlotinib does not seem to be active after progression to gefitinib.

In our study, The DCR of erlotinib after gefitinib failure was similar to that in Cho's study. Most patients who benefit from erlotinib had also benefited from prior gefitinib treatment, but we did not observed the correlation between EGFR status and survival.

These results are surprising, because both EGFR TKIs share the same mechanism of EGFR blockade and maybe cross-resistant. It is difficult to clarify the mechanisms behind the effectiveness of erlotinib in this patient population.

Table 3 Univariate analysis of survival

Variables	Median survival (days)	*P*
Age		
<70	65	0.14
>70	85	
Sex		
Male	75	0.62
Female	95	
ECOG performance status		
0–1	42	0.07
2	170	
3	68	
Pathological type		
Squamous cell carcinoma	68	0.004
Adenocarcinoma	230	
Others	70	
Smoking history		
Smoker	75	0.014
Never smoker	110	
EGFR mutation		
Positive	70	0.67
Negative	95	
Best response to prior chemotherapy		
Complete or partial response	135	0.32
Stable disease	95	
Progressive disease	75	
Response to gefitinib therapy		
Complete or partial response	210	0.01
Stable disease	170	
Progressive disease	68	
Response to erlotinib therapy		
Complete or partial response	210	0.05
Stable disease	150	
Progressive disease	75	

One potential explanation is that the standard doses of 250 mg gefitinib and 150 mg erlotinib are not biologically equivalent. Erlotinib was administered at its maximum-tolerated dose, whereas gefitinib was administered at approximately one-third of its maximum-tolerated dose. However, we are reluctant to attribute the activity of erlotinib to the difference in dose, because of the lack of benefit from higher doses in previous ideal phase II studies [13].

Another possibility is the loss of acquired resistance after a "TKI-free interval". Conventional chemotherapy given after first-TKI failure may also result in reduction of TKI-resistant clones, leaving the TKI-sensitive ones to be further controlled by a second TKI "rechallenge" subsequently [14]. However, most of our patients had short time intervals from discontinuation of gefitinib to commencement of erlotinib, with some patients starting erlotinib immediately after progression on gefitinib treatment. In addition, response to subsequent chemotherapy was also poor.

Finally, some of the acquired gefitinib-resistant clones might be nonresistant or incompletely cross-resistant to erlotinib. Among the mechanism of acquired resistance to EGFR TKIs, T790M secondary mutation or amplification of the MET oncogene was reportedly common [15, 16]. However, other secondary mutations have also been reported [17, 18]. Of note, unlike T790M secondary mutation, some mutations, such as L748S or E884K mutation, may result in different sensitivities to gefitinib and erlotinib, resulting in different tumor responses to these two agents.

In conclusion, our results for disease control are consistent with other similarly designed trials such as Cho's and Costa's study. These findings suggested that erlotinib should not be given routinely after failure of gefitinib treatment, but may be an option for a more highly selected subset of patients, especially those who had already benefited from prior gefitinib treatment. We have contributed to the growing evidence for using multiple lines of oral TKI treatment in selected groups of lung cancer patients; further studies are warranted to evaluate the molecular mechanisms behind this evidence and clarify how to select patients for erlotinib treatment after failure of gefitinib therapy.

References

1. Jänne PA, Engelman JA, Johnson BE et al (2005) Epidermal growth factor receptor mutations in non-small cell lung cancer: implications for treatment and tumor biology. J Clin Oncol 23:3227–3234
2. Comis RL (2005) The current situation: erlotinib (Tarceva) and gefitinib (Iressa) in non-small cell lung cancer. Oncologist 10:467–470
3. Li J, Zhao M, He P et al (2007) Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res 13:3731–3737
4. Baselga J, Rischin D, Ranson M et al (2002) Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 20:4292–4302
5. Hidalgo M, Siu LL, Nemunaitis J et al (2001) Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 19:3267–3279
6. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al (2005) Erlotinib in previously treated non-small cell lung cancer. N Engl J Med 353:123–132
7. Thatcher N, Chang A, Parikh P et al (2005) Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomized placebo-controlled, multicenter study (Iressa survival evaluation in lung cancer). Lancet 366:1527–1537
8. Garfield DH (2005) Response to erlotinib after failure of gefitinib in a patient with advanced non-small cell lung cancer. J Clin Oncol 23:7738–7740
9. Cho BC, Im CK, Park MS et al (2007) Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol 25:2528–2533
10. Wong AS, Soong R, Seah SB et al (2008) Evidence for disease control with erlotinib after gefitinib failure in typical gefitinib-sensitive Asian patients with non-small cell lung cancer. J Thorac Oncol 3:400–404
11. Lee DH, Kim SW, Suh C et al (2008) Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment. Ann oncol 19:2039–2042
12. Costa DB, Nguyen KS, Cho BC et al (2008) Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. Clin cancer res 14:7060–7067
13. Baselga J, Arteaga CL (2005) Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. J Clin Oncol 23:2445–2459
14. Yokouchi H, Yamazaki K, Kinoshita I et al (2007) Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. BMC Cancer 7:51
15. Engelman JA, Zejnullahu K, Mitsudomi T et al (2007) MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316:1039–1043
16. Balak MN, Gong Y, Riely GJ et al (2006) Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. Clin Cancer Res 12:6494–6501
17. Costa DB, Halmos B, Kumar A et al (2007) BIM mediates EGFR tyrosine kinase inhibitor-induced apoptosis in lung cancers with oncogenic EGFR mutations. PLoS Med 4:1669–1679
18. Choong NW, Dietrich S, Seiwert TY et al (2006) Gefitinib response of erlotinib-refractory lung cancer involving meninges—role of EGFR mutation. Nat Clin Pract Oncol 3:50–57