original article

Annals of Oncology 19: 2039–2042, 2008
doi:10.1093/annonc/mdn423
Published online 21 July 2008

Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment

D. H. Lee, S.-W. Kim, C. Suh*, D. H. Yoon, E. J. Yi & J.-S. Lee

Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Received 14 May 2008; revised 11 June 2008; accepted 12 June 2008

Background: Both gefitinib and erlotinib are reversible epidermal growth factor receptor tyrosine kinase inhibitors, but they have somewhat different pharmacological properties. We conducted a phase II study of erlotinib after failure of gefitinib treatment in patients with non-small-cell lung cancer (NSCLC).
Patients and methods: Patients with advanced/metastatic NSCLC who had shown disease progression on gefitinib treatment were treated with erlotinib 150 mg/day until disease progression or intolerable toxicity.
Results: Between September 2006 and January 2008, a total of 23 patients were enrolled and all were assessable for response and toxicity. All patients were never smokers and all but one had adenocarcinoma. Of these 23 patients, one had a partial response and one stable disease, resulting in an objective response rate of 4.3% and a disease control rate of 8.7%. These two patients benefited from erlotinib for 6.2 months and 7.8 months, respectively; both had also benefited from prior gefitinib therapy. The most common toxic effects were skin rash and diarrhea.
Conclusion: Erlotinib should not be given routinely after failure of gefitinib treatment, but can be an option for more highly selected subsets, especially those who had benefited from prior gefitinib treatment. Identification of molecular markers in tumors is important to understand and overcome acquired resistance to gefitinib.
Key words: erlotinib, gefitinib, non-small cell lung cancer

introduction

Erlotinib and gefitinib are oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) widely used to treat patients with advanced or metastatic non-small-cell lung cancer (NSCLC). 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 is 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 [1, 2]. In addition, because the maximum-tolerated doses of gefitinib and erlotinib are 1000 and 150 mg, respectively [3, 4], 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 [5, 6]. These findings suggested that salvage treatment with erlotinib may be an option for patients who fail gefitinib treatment. We therefore carried out a prospective phase II study of erlotinib in patients with advanced or metastatic NSCLC who showed disease progression on gefitinib treatment.

patients and methods

eligibility

Patients with advanced or metastatic NSCLC who had documented progressive disease on gefitinib treatment were eligible for inclusion if they had at least one unidimensionally measurable lesion, an Eastern Cooperative Oncology Group performance status of zero to three, and adequate organ functions [white blood cell 3000/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]. Prior chemotherapy or radiotherapy was allowed. Brain metastases were also allowed if they were asymptomatic or controlled by supportive care. However, those patients with unresolved chronic toxicity from prior therapy, other active malignancies, uncontrolled brain metastases, or severe comorbid conditions were excluded. The study was approved by the institutional review board of the Asan Medical Center, and written informed consent was obtained from all enrolled patients. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

study design

This was an open-label, single-institution, phase II study. Patients received erlotinib 150 mg once daily. One dose reduction per patient was permitted

*Correspondence to: Dr C. Suh, Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Pungnap-2 dong, Songpa-gu, Seoul 138-736, South Korea. Tel: +82-2-3010-3209, Fax: +82-2-3010-6961; E-mail: csuh@amc.seoul.kr

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. Baseline evaluations included a complete medical history, physical and radiologic examinations, complete blood cell count, and biochemistry. The primary efficacy end point of this study was objective tumor response rate. Response assessments were carried out 4 ± 1 weeks after commencement of erlotinib therapy and then after every 8 ± 1 weeks unless clinically indicated, according to the Response Evaluation in Solid Tumors criteria; complete response (CR) is defined as the disappearance of all target lesions; partial response (PR) is defined as at least a 30% decrease in the sum of the longest diameter of target lesion, taking as reference the baseline sum longest diameters and/or the persistent of one or more nontarget lesion(s); progressive disease (PD) defined as at least a 20% increase in the sum of the longest diameter taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions; and stable disease (SD) defined as neither sufficient shrinkage to qualify the partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started. For patients with documented CR or PR, a confirmatory.

Progression-free survival (PFS) was defined as the interval between the date treatment started and the date of documented disease progression or death from any cause. Overall survival (OS) was defined as the interval between the date treatment started and the date of death from any cause. Patients lost to follow-up were censored at the last date of contact. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event version 3.0.

statistical consideration

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. For a total of 56 patients, 23 would be accrued during the first stage and 33 during the second stage. If one or no response was observed during the first stage, the study would be stopped early. If five or fewer responses were observed by the end of the study, no further investigation of the drug would be warranted.

patients' characteristics

Between September 2006 and January 2008, a total of 23 patients entered into the study and all were assessable for response and toxicity. All patients were never smokers and all but one had adenocarcinoma histology. Before starting therapy, we knew the mutation status of exons 18–21 of the *EGFR* gene in 10 patients (43.5%); three had exon 19 deletions, two had exon 18 substitutions, and five had no mutations. Fifteen patients (65.2%) had benefited from prior gefitinib therapy. Patients' characteristics are shown in Table 1.

response and survival outcome

Out of 23 patients, one had PR and one had SD, giving an overall response rate of 4.3% and a disease control rate of 8.7% (Table 2). These two patents were female never smokers with adenocarcinoma histology and both had a best response of OR to prior gefitinib treatment. In the patient with a PR to erlotinib treatment, an interval from discontinuation of gefitinib to administration of erlotinib was 7.4 months, her PFS during gefitinib treatment was 3.9 months, and her PFS during erlotinib treatment was 6.2 months, while in the patient with SD, the corresponding values were 1.4, 12.0, and 7.8 months, respectively. The remaining 21 patients showed PD to erlotinib treatment within 3 months.

Table 1. Patient characteristics

Characteristic	No. of patients	%
Total enrolled	23	
Age, years		
Median (range)	56 (41–73)	
Gender		
Male	4	17.4
Female	19	82.6
ECOG performance score		
0–1	12	52.2
2–3	11	47.8
Histology		
Adenocarcinoma	22	95.7
Neuroendocrine carcinoma	1	4.3
EGFR mutations in exons 18–21		
Mutation	5[a]	21.7
No mutation	5	21.7
Unknown	13	56.5
No. of prior chemotherapy, not including gefitinib therapy[b]		
0	2	8.7
1	12	52.2
2	3	13.0
≤3	6	26.1
Best response to gefitinib therapy		
PR	15	65.2
SD	2	8.7
PD	6	26.1
Interval from discontinuation of gefitinib to commencement of erlotinib		
<3 months	11	47.8
≤3 months	12	52.2

[a]Three had a mutations in exon 19 and 2 had a mutations in exon 18.
[b]All patients except two received at least one platinum-doublet.
ECOG, Eastern Cooperative Oncology Group; PR, partial response; SD, stable disease; PD, progressive disease.

Table 2. The tumor responses

Response	No.	(%)
PR	1	4.3
SD	1	4.3
PD	21	91.3
Total	23	100.0
ORR	4.3% (95% CI, <1% to 22%)	
DCR	8.7% (95% CI, 1% to 28%)	

PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; CI, confidence interval.

toxicity profile

The most common toxic effects were skin rash recorded in 14 patients (60.9%) and diarrhea in seven patients (30.4%). Two patients (8.7%) experienced grade 3 skin rash. Only one patient required a dose reduction of erlotinib due to grade 3 hyperbilirubinemia.

discussion

Both erlotinib and gefitinib are currently available in Korea and are used to treat patients with advanced or metastatic NSCLC in second- or third-line setting or sometimes in first-line setting for a specific subset of patients [7, 8]. Most patients treated with these agents, however, had progressive disease even after showing an initial dramatic response. Although gefitinib and erlotinib are thought to exhibit cross-resistance, their pharmacological differences as well as their distinct clinical outcomes suggest that erlotinib may be effective after failure of gefitinib treatment [9–12]. Two studies have shown that erlotinib after failure of gefitinib treatment yielded disease control rates of 35.7% (5 of 14) and 28.6% (6 of 21), respectively, [11, 12], although other studies, including ours, have shown contradictory results [13]. Of interest, most patients who benefit from erlotinib had also benefited from prior gefitinib treatment (Table 3) [9–12, 14], including the two patients in our study who benefited from erlotinib. In our study, of the 15 patients who benefited from gefitinib, two benefited from erlotinib treatment, yielding a disease control rate of 13.3% (2 of 15), which, however, was rather lower than those of 55.5 % (5 of 9) and 50.0% (5 of 10) in the prior two studies [11, 12]. This finding suggested that as a salvage treatment after failure of gefitinib treatment, erlotinib should be chosen very carefully in a more highly selective subset of patients.

Several explanations could be possible for the responsiveness to erlotinib after failure of gefitinib. Difference in tumor sensitivity, especially wild-type EGFR tumors might be associated with the relative concentration of EGFR TKIs. The IC_{50} value of erlotinib is much lower than that of gefitinib [2] and 8 of 10 patients benefiting from erlotinib had wild-type EGFR [14]. Most of these patients, however, had also benefited from prior gefitinib. In contrast, most patients who did not benefit from prior gefitinib treatment did not respond to subsequent erlotinib treatment. Another possibility may be that tumors may possess both EGFR TKI-sensitive and -resistant clones at the beginning of gefitinib treatment. During gefitinib treatment, only EGFR TKI-resistant clones can grow, but after discontinuation of gefitinib therapy and/or during subsequent chemotherapy, sensitive clones may grow faster or survive better than do resistant clones. Thus, subsequent erlotinib therapy could kill such TKI-sensitive clones, similar to the effectiveness sometimes observed following readministration of gefitinib [15]. However, most of our patients had short time intervals from discontinuation of gefitinib to commencement of erlotinib, with some patients

Table 3. Patient characteristics associated with benefits from erlotinib after failure of gefitinib treatment

Study	Gender	Smoking status	Histology	Gefitinib therapy		No. of prior chemotherapy	Erlotinib therapy
				DC	PFS		PFS
Garfield [9], case report	M	Former	NOS	N	1	2	7
Gridelli et al. [10]; case report	F	Never	Adeno	Y	18	0	13+
	F	Never	Adeno	Y	12	2	13+
	F	Never	Adeno	Y	24	2	7+
Wong et al. [11];	M	Never	Adeno	Y	6.5[a]	4	1.6[a]
retrospective study	F	Never	Adeno	Y	11.6[a]	3	1.6[a]
	F	Never	Adeno	Y	7.5[a]	0	7.8[a]
	M	Never	Adeno	Y	7.5[a]	1	3.2[a]
	F	Never	Adeno	Y	17.7[a]	3	6.5[a]
Cho et al. [12, 13];	F	Never	Adeno	Y	6.0	3	6.0
prospective study	M	Never	Adeno	Y	6.7	3	4.6
	F	Never	BAC	Y	18.1	3	4.9+
	F	Never	BAC	Y	22.4	NR	6.3
	F	Never	Adeno	Y	3.8	NR	3.3
	F	Never	Adeno	Y	17.7	0	12.8+
	F	Never	Adeno	Y	11.8	2	12.8+
	F	Never	Adeno	Y	23.5	2	6.9+
	M	Former	Adeno	Y	3.9	2	3.0
	F	Never	Adeno	Y	13.8	0	11.8+
	M	Former	Adeno	Y	8.9	1	17.8
	F	Never	Adeno	Y	16.3	3	3.6
	M	Current	SCC	Y	5.9	3	3.4
	M	Current	Adeno	N	2.0	2	3.3
	F	Never	Adeno	N	2.7	NR	3.2
	M	Former	Adeno	N	2.0	2	6.9+
Lee et al. (current);	F	Never	Adeno	Y	3.9	4	7.5
prospective study	F	Never	Adeno	Y	12.0	1	8.5

[a]Duration of disease control

DC, disease control = CR/PR + SD; PFS, progression-free survival; M, male; F, female; Adeno, adenocarcinoma; BAC, bronchioloalveolar carcinoma; SQCC, squamous cell carcinoma; NOS, not other wise specified; NR, not reported.

starting erlotinib immediately after progression on gefitinib treatment. In addition, response to subsequent chemotherapy was also poor [12, 15]. Finally, some of 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 [16, 17]. However, other secondary mutations have also been reported [18, 19]. 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 [14, 20]. Therefore, although half of patients could overcome the resistant T790M secondary mutation by empirical use of irreversible EGFR TKIs, identification of the mechanism of acquired resistance in each patient could guide the proper use of these two different EGFR TKIs.

In conclusion, our finding 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. However, identification of molecular markers in tumors is important to understand and overcome molecular mechanisms of resistance.

funding

Asan Institute for Life Science, Seoul, South Korea (07-432 and 08-432).

references

1. Li J, Zhao M, He P et al. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res 2007; 13: 3731–3737.
2. Sharma SV, Bell DW, Settleman J et al. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007; 7: 169–181.
3. Baselga J, Rischin D, Ranson M et al. 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 2002; 20: 4292–4302.
4. Hidalgo M, Siu LL, Nemunaitis J et al. 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 2001; 19(13): 3267–3279.
5. Shepherd FA, Rodrigues Pereira JR, Ciuleanu T et al. Erlotinib in previously treated non-small cell lung cancer. N Engl J Med 2005; 353: 123–132.
6. Thatcher N, Chang A, Parikh P et al. 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 2005; 366: 1527–1537.
7. Lee DH, Han JY, Lee HG et al. Gefitinib as a first-line therapy of advanced or metastatic adenocarcinoma of the lung in never-smokers. Clin Cancer Res 2005; 11: 3032–3037.
8. Lee DH, Hong JS, Han YH et al. A phase II study of erlotinib as a first-line therapy for non-small-cell lung cancer patients with favorable clinical predictors. J Thorac Oncol 2008; 3(Suppl 4): S70.
9. Garfield DH. Response to erlotinib after failure of gefitinib in a patient with advanced non-small cell lung cancer. J Clin Oncol 2005; 23: 7738–7740.
10. Gridelli C, Maione P, Galetta D et al. Three cases of long-lasting tumor control with erlotinib after progression with gefitinib in advanced non-small cell lung cancer. J Thorac Oncol 2007; 2: 758–761.
11. Wong AS, Soong R, Seah SBK et al. Evidence for disease control with erlotinib after gefitinib failure in typical gefitinib-sensitive Asian patients with non-small cell lung cancer. J Thorac Oncol 2008; 3: 400–404.
12. Cho BC, Im CK, Park MS et al. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol 2007; 25: 2528–2533.
13. Viswanathan A, Pillot G, Govindan R. Lack of response to erlotinib after progression on gefitinib in patients with advanced non-small cell lung cancer. Lung Cancer 2005; 50: 417–418.
14. Costa D, Schumer ST, Tenen DG et al. Differential responses to erlotinib in epidermal growth factor receptor (EGFR)-mutated lung cancers with acquired resistance to gefitinib carrying L747S or T790M secondary mutations. J Clin Oncol 2008; 26: 1182–1184; Cho BC, Kim JH. Author reply, 1184–1186.
15. Yokouchi H, Yamazaki K, Kinoshita I et al. Clinical benefit of readministration of gefitinib for initial gefitinib responders with non-small cell lung cancer. BMC Cancer 2007; 7: 51.
16. Kobayashi S, Boggon TJ, Dayaram T et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005; 352: 786–792.
17. Angelman JA, Zejnullahu K, Mitsudomi T et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007; 316: 1039–1043.
18. Balak MN, Gong Y, Riely GJ et al. Novel D761Y and common secondaryT790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. Clin Cancer Res 2006; 12: 6494–6501.
19. Costa DB, Halmos B, Kumar AS et al. BIM mediates EGFR tyrosine kinase inhibitor-induced apoptosis in lung cancers with oncogenic EGFR mutations. PLoS Med 2007; 4: e315.
20. Choong NW, Dietrich S, Seiwert TY et al. Gefitinib response of erlotinib-refractory lung cancer involving meninges—role of EGFR mutation. Nat Clin Pract Oncol 2006; 3: 50–57.