Cancer Chemother Pharmacol (2011) 67:35–39
DOI 10.1007/s00280-010-1280-6

ORIGINAL ARTICLE

Phase II study of erlotinib for chemotherapy-naïve patients with advanced or metastatic non-small cell lung cancer who are ineligible for platinum doublets

Dae Ho Lee · Sang-We Kim · Cheolwon Suh · Yun Hee Han · Jung-Shin Lee

Received: 8 July 2009 / Accepted: 9 February 2010 / Published online: 25 February 2010

Abstract
Purpose This phase II study evaluated efficacy of single-agent erlotinib for chemotherapy-naïve patients with advanced/metastatic NSCLC who were ineligible for platinum doublets.
Methods Chemotherapy-naive patients but ineligible for platinum doublets (aged 18–75 with an ECOG performance status [PS] 2–3; or aged 76 or older with an ECOG PS 1–3) were enrolled and treated with erlotinib 100 mg once daily till disease progression, unacceptable toxicity or patient's refusal.
Results Out of 24 patients enrolled, 5 reached a PR, giving an overall response rate of 21%, but all responders were never-smokers with adenocarcinoma. According to EGFR mutation status, PR was observed in two of three patients having mutant EGFR (67%) but in one of nine having wild-type EGFR (11%). With a median follow-up of 22.6 months, the median progression-free and overall survival was 1.5 months and 3.2 months, respectively. All responders to post-erlotinib chemotherapy had responded to prior erlotinib.
Conclusions For unselected chemotherapy-naïve Asian patients with NSCLC but ineligible for platinum doublets, empirical use of upfront erlotinib could not be recommended because of poor survival outcome. However, this can be given to selected subsets based on molecular or clinical predictors.

D. H. Lee · S.-W. Kim (✉) · C. Suh · Y. H. Han · J.-S. Lee
Department of Oncology,
University of Ulsan College of Medicine,
Asan Medical Center, 388-1 Pungnap-2 dong,
Songpa-gu, Seoul 138-736, Korea
e-mail: swkim@amc.seoul.kr

Keywords Erlotinib · Non-small cell lung cancer · Chemotherapy-naïve · Platinum doublet

Introduction

Platinum doublet chemotherapy has been a standard treatment for chemotherapy-naïve patients with non-small cell lung cancer (NSCLC), and addition of bevacizumab to a platinum doublet has shown survival benefit for a selected subset of those patients [1, 2]. However, platinum doublets with or without bevacizumab can be given in patient with a good performance status (PS) or Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1. Meanwhile, for the elderly or those with ECOG PS of 2, available data support only the use of single-agent chemotherapy [1].

Erlotinib, one of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), are widely accepted as standard treatment for previously treated patients with NSCLC. Considering its favorable efficacy and toxicity profile compared with cytotoxic chemotherapy in second-line setting, it can offer a potential treatment option for those who are chemotherapy-naïve but not eligible for a platinum doublet. The studies of gefitinib, another EGFR TKI, were disappointing in this clinical setting. For unselected patients of 75 years or older gefitinib showed rather low efficacy and high toxicity, especially interstitial lung disease [3]. Randomized phase II trials comparing gefitinib with single-agent vinorelbine in unselected chemotherapy-naïve Western patients of 70 years or older or with placebo in unselected chemotherapy-naïve Western patients with poor PS failed to show improvement in overall survival [4, 5]. However, erlotinib has rather different pharmacological properties and distinct clinical outcomes from gefitinib, suggesting that erlotinib might be more

effective than gefitinib [6–9]. Therefore, we undertook this phase II study to investigate the efficacy and tolerability of single agent erlotinib in unselected chemotherapy-naïve patients with advanced or metastatic NSCLC who were ineligible for a platinum doublet, and hoped to obtain preliminary information for further investigation comparing erlotinib with single-agent cytotoxic chemotherapy.

Methods

Eligibility criteria

Patients were required to have histologically documented NSCLC, stage IIIB with malignant pleural or pericardial effusion or stage IV and no history of prior cancer treatment including chemotherapy or radiotherapy. They were ineligible for platinum doublets defined as; either aged 18–75 with an ECOG PS of 2 or 3; or 76 years of age or older with an ECOG PS 1–3. The other inclusion criteria were as follows; at least one uni-dimensionally measurable lesion, and adequate organ functions (WBC $\geq$ 3,000/μL, platelets $\geq$ 100,000/μL, hemoglobin $\geq$ 9.0 g/dL, serum creatinine $\leq$ 1.5 $\times$ the upper limit of normal [ULN], bilirubin $\leq$ 1.25 $\times$ ULN, and serum aminotransferases $\leq$ 2.5 $\times$ ULN). Brain metastases were also allowed if they were asymptomatic or controlled by supportive care. However, those patients with severe co-morbid conditions, other active malignancies, or uncontrolled brain metastases 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 performed 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 100 mg once daily till disease progression, intolerable toxicity, or withdrawal of consent. The treatment could be interrupted for a maximum of 21 days. Baseline evaluations included a complete medical history, physical and radiologic examinations, CBC and biochemistry. The primary efficacy endpoint of this study was objective tumor response rate. Response assessments were performed 4 $\pm$ 1 weeks after commencement of erlotinib therapy and then repeated every 8 $\pm$ 1 weeks unless clinically indicated, according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.0. For patients with a documented complete response (CR) or partial response (PR), a confirmatory evaluation was performed at least after 4 weeks. Disease control was defined as the best tumor response of CR, PR, or stable disease (SD) that was confirmed and sustained for 8 weeks or longer.

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 NCI CTCAE version 3.0.

Statistical consideration

A Simon two-stage optimal design was chosen for definition of the total number of patients required for this phase II study. We set a response rate of 15% as the target activity level and 5% as the lowest 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.

Results

Patients' characteristics

Between October 2006 and January 2009, a total of 24 patients entered into the study and all were assessable for response and toxicity. All patients had stage IV disease and 3 had an ECOG PS of 3. Before starting therapy, we knew mutation status of exons 18, 19 and 21 of the *EGFR* gene in 12 patients (50.0%); 3 had an exon 19 deletion and 9 had no mutations. We could not carry out mutation analysis in 12 patients; insufficiency of tissue after cytologic diagnosis in 8 patients and unavailability of tissue due to referral from other hospitals in 4 patients. Patients' characteristics are shown in Table 1.

Response and survival outcome

Out of 24 patients, 5 had a PR and 1 had SD, giving an overall response rate of 21% (95% confidence interval [CI], 7–42%) and a disease control rate of 25%. Interestingly, the six responders were never-smokers with adenocarcinoma histology. Therefore, the response rate for 18 patients with adenocarcinoma histology was 28% and that for 12 never-smokers with adenocarcinoma was 42%. However, no response was seen in patients with squamous cell

Table 1 Patients' characteristics

Characteristic	No. of patients	%
Total enrolled	24	
Age (Year)		
Median (Range)	73 (47–86)	
Gender		
Male	10	42
Female	14	58
ECOG performance score		
1	3	13
2	18	75
3	3	13
Smoking status		
Ex-/Current smoker	12	50
Never smoker	12	50
Histology		
Adenocarcinoma	18	75
Squamous cell carcinoma	4	17
NSCLC, NOS	2	8
EGFR mutation in exons 18, 19 and 21		
Mutation	3	13
No mutation	9	38
Unknown	12	50

carcinoma or smoking history. For those having an activating *EGFR* gene mutation, the response rate was 67%, while that was 11% (1/9) for those having wild-type *EGFR* gene (Table 2).

After a median follow-up of 22.6 months, the median progression-free and overall survival was 1.5 months (95% CI, 0.8–2.3 months) and 3.2 months (95% CI, 1.3–5.1 months), respectively (Fig. 1).

Table 2 Tumor responses

	All patients (n = 24)		Adenocarcinoma (n = 18)		Never smokers with adenocarcinoma (n = 12)	
Response	No.	%	No.	%	No.	%
CR	0	0	0	0	0	0
PR	5	21	5	28	5	42
SD	1	4	1	6	1	8
PD	18	75	12	67	6	50
ORR	**5**	**21**	**5**	**28**	**5**	**42**
DCR	**6**	**25**	**6**	**33**	**6**	**50**

CR complete response; *DCR* Disease control rate; *ORR* Objective response rate; *SD* stable disease; *PD* progressive disease; *PR* partial response

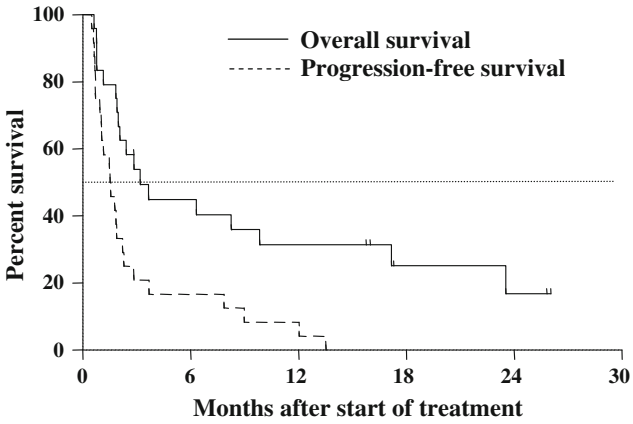

Fig. 1 Survival outcomes. *Tick marks* indicate censored data

Toxicity profile

The most common toxicities were skin rash (38%) and pruritus (38%). Severe or grade 3 toxicity was mucositis recorded in two patients and elevated liver enzyme in two patients, respectively, followed by skin rash in one patient. No grade 4 toxicity was observed (Table 3).

Post-discontinuation treatment

Six patients received gemcitabine and carboplatin after disease progression. Among them, four patients showed a PR, who had responded to prior erlotinib therapy, while the other two showed PD and they had also not responded to erlotinib at all. Two patients received pemetrexed as third-line therapy and responded again, that is, they responded erlotinib, gemcitabine and carboplatin, and pemetrexed.

Discussion

Considering its efficacy and favorable toxicity profile in previously treated patients compared with placebo, erlotinib

Table 3 Toxicity profile

Adverse effect	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia	15 (63)	6 (25)	3 (13)	0 (0)	0 (0)
Asthenia	21 (88)	1 (4)	2 (8)	0 (0)	0 (0)
Diarrhea	21 (88)	2 (8)	1 (4)	0 (0)	0 (0)
Mucositis	21 (88)	0 (0)	1 (4)	2 (8)	0 (0)
Pruritus	15 (63)	6 (25)	3 (13)	0 (0)	0 (0)
Paronychia	21 (88)	0 (0)	3 (13)	0 (0)	0 (0)
Rash	15 (63)	3 (13)	5 (21)	1 (4)	0 (0)
Elevated AST/ALT	18 (75)	4 (17)	0 (0)	2 (8)	0 (0)

can be a good option for those who were chemotherapy-naïve but ineligible for a platinum-doublet, but superiority or, at least, non-inferiority of erlotinib therapy to single agent chemotherapy, which is still accepted as standard treatment, is not proven yet.

In the current study, we observed rather a good response rate of 21% in unselected Asian elderly or poor PS patients and that of 42% in a selected subset, namely never-smokers with adenocarcinoma histology. Based on this promising preliminary result, we hoped to conduct a randomized phase III trial comparing erlotinib with single agent chemotherapy. However, we also observed rapid deterioration of PS and poor survival outcomes in non-responders, such as ever-smokers or those with non-adenocarcinoma histology, with the median PFS of 1.5 month and OS of 3.2 months. In addition, two recent studies of erlotinib for unselected PS 2 patients, although they were Caucasians, showed low response rates of 4 and 8% and short survival outcomes with median PFS of 1.9 and 2.1 months and median OS of 6.6 and 5 months, respectively [10, 11]. Therefore, although the response rate in the first stage exceeded in our expectations, we decided to stop the study earlier with a conclusion that we could not recommend empirical use of erlotinib for elderly or poor PS patients who were ever-smokers or had non-adenocarcinoma histology regardless of their ethnicity.

On the other hand, for Asian poor PS patients with EGFR mutations, a response rate for gefitinib was reportedly 66% with median PFS of 6.5 months and OS of 17.8 months, and for Western chemotherapy-naïve patients with EGFR mutation but good PS, a response rate for erlotinib was 82% with median PFS of 13.3 months [12, 13]. In addition, the result of a recent phase III trial reinforced the upfront use of EGFR TKI therapy for those with EGFR mutations, although this study has not proven yet that benefit of PFS will translate into better survival [14]. Interestingly, we observed from our study that responders to erlotinib therapy could receive post-erlotinib platinum doublet chemotherapy due to improved PS. Some might argue that since responders to post-erlotinib chemotherapy had responded to prior erlotinib therapy, they might benefit from first-line single-agent chemotherapy, instead of first-line erlotinib therapy. However, we have to keep in mind that platinum doublet chemotherapy is more effective than single agent chemotherapy in patients with a good PS of 0 or 1 [1]. Actually, we could hardly give a platinum doublet to the elderly, especially aged 75 or older, or those with a poor PS of 3 or even PS of 2 in clinical practice.

Another issue is whether we can give EGFR TKI therapy to a selected subset of poor PS patients based on clinical predictors, such as never-smoking status with adenocarcinoma histology. In the current study, we had known the mutational status in up to 50% of the patients enrolled before starting erlotinib therapy but this seems rather high. Due to insufficiency or unavailability of tumor tissue the mutational status before commencing a treatment, the mutational status might be unknown in more than half of patients, especially elderly or poor PS patients. We could not recommend empirical use of upfront erlotinib therapy because in general population, the average frequency of *EGFR* gene mutations in Western countries is reportedly 10–20%, and that in East Asian counties is 30–40%. However, the frequency increases up to 50–60% in enriched population such as never or light smokers with adenocarcinoma histology, regardless of their ethnicity [13–17]. So, as never-smoking status and adenocarcinoma histology can be a surrogate for mutation status, we could use these clinical predictors for selecting upfront treatment in this clinical setting [14, 18, 19].

In conclusion, like Western patients, we could not recommend routine use of upfront erlotinib therapy for unselected chemotherapy-naïve Asian patients with NSCLC because of poor survival outcome, even though they were ineligible for a platinum doublet. However, we can consider this upfront therapy for a selected subset of patients based on molecular or clinical predictors. Especially, if available, molecular markers are more important than clinical settings, poor PS or old age, in selecting treatment.

Acknowledgments This study was supported by grant 07-432 and 08-432 from the Asan Institute for Life Science, Seoul, Korea.

Conflict of interest The authors declare that no conflict of interest exists for any of the authors.

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