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ORIGINAL ARTICLE

A phase II trial of erlotinib in patients with EGFR wild-type advanced non-small-cell lung cancer

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Abstract
Purpose There is as yet no optimal treatment regimen for patients with epidermal growth factor receptor (EGFR) gene wild-type non-small-cell lung cancer (NSCLC) that has progressed despite cytotoxic chemotherapy. This trial was performed to evaluate the efficacy and toxicity of erlotinib, a tyrosine kinase inhibitor of EGFR, in Japanese patients with EGFR wild-type tumors.
Methods Patients with stage III/IV or postoperative recurrence of NSCLC whose tumors have wild-type EGFR were eligible. Erlotinib (150 mg/day) was administered until disease progression or unacceptable toxicity occurred. The primary end point was disease control rate (DCR).
Results Thirty-one patients (23 men and 8 women; median age, 71 years; range, 31–89) were enrolled between January 2008 and June 2011. Twenty-one had adenocarcinoma, nine had squamous cell carcinoma, and one had large cell carcinoma. Ten, nine, eight, and four patients showed performance status 0, 1, 2, and 3, respectively. Erlotinib was administered following the median 3.1 regimens of cytotoxic chemotherapies. One patient achieved complete response, four showed partial response, and eight had stable disease. Thus, response rate was 17.2%, and DCR was 44.8%. Skin rash was the most common side effect (80.6%). Two patients developed interstitial lung disease. Nevertheless, all of these events were reversible, and there were no treatment-related deaths. The median progression-free survival and survival times were 2.1 and 7.7 months, respectively.
Conclusion Erlotinib might be an alternative option for patients resistant to cytotoxic chemotherapy even in those with EGFR wild-type NSCLC.

Keywords Chemo-refractory · Salvage therapy · EGFR-sensitive mutation · Chemotherapy · NSCLC

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Introduction

Lung cancer is the leading cause of cancer-related death in Japan and throughout the Western world [1, 2]. Platinum-based doublet combinations are standard regimens for first-line treatment in advanced-staged non-small-cell lung cancer (NSCLC) and have provided only modest survival advantages [3, 4]. Tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) are promising therapeutic options for patients with NSCLC [5, 6], especially in Asia [7–12]. Erlotinib and gefitinib are selective EGFR-TKIs, and numerous clinical studies demonstrated favorable efficacy and toxicity profiles compared with

cytotoxic chemotherapy [7, 8]. The efficacy of EGFR-TKIs is associated with EGFR-sensitive mutation status in NSCLC [5–9]. A high response rate (RR) to EGFR-TKIs is observed in patients with EGFR-sensitive mutations, but the RR is 1.0–13.9% in wild-type EGFR [8, 13–15].

In the Iressa Survival Evaluation in Lung Cancer (ISEL) study, however, gefitinib failed to prolong survival in unselected patients with advanced NSCLC after failure of at least one prior chemotherapy regimen [16]. However, in the same clinical setting study (BR.21) [17], erlotinib showed a survival advantage of 6.67 months for erlotinib versus 4.70 months for the placebo. Thus, erlotinib is the only EGFR-TKI shown to provide a survival benefit for advanced unselected NSCLC patients. In addition, several clinical studies indicated that erlotinib could confer benefits in certain patients with NSCLC after gefitinib failure [18, 19]. Thus, erlotinib may have a higher biological activity and distinct clinical outcomes from gefitinib [20, 21]. Based on these findings, it is speculated that when treatment with cytotoxic chemotherapies fails in patients with wild-type EGFR, erlotinib may be a suitable option for salvage therapy. There is as yet no optimal treatment regimen for patients with EGFR wild-type NSCLC that has progressed despite several rounds of cytotoxic chemotherapy.

Therefore, we performed this prospective study to investigate the efficacy and tolerability of erlotinib monotherapy in Japanese patients with wild-type EGFR as a potential therapeutic option in heavily pretreated NSCLC patients with progressive disease after treatment with cytotoxic agents.

Patients and methods

Patient eligibility

Patients eligible for this study were required to have histologically or cytologically proven stage III/IV or postoperative recurrent NSCLC without EGFR-sensitive mutations (exons 18, 19, and 21). The other inclusion criteria were (1) age ≥20 years old; (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–3; (3) measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [22]; (4) no prior history of EGFR-TKI therapy; and (5) adequate hepatic and renal function. Patients were excluded from this study for any of the following reasons: (1) receiving systemic anticancer therapy within 4 weeks; (2) past history of hypersensitivity to drugs; (3) severe complications; (4) active infection; (5) interstitial lung disease (ILD) detectable on chest radiography; (6) pleural, pericardial, or peritoneal effusion requiring drainage; (7) active brain metastasis; or (8) pregnancy. This study was approved by the institutional review boards of the participating institutes and was conducted according to the principles of the Declaration of Helsinki. All enrolled patients gave their written informed consent.

Pretreatment evaluation

Before enrollment in this study, all patients underwent clinical and physical examination: PS, medical history, routine laboratory tests, electrocardiography, chest radiography, computed tomography (CT) scan of the chest and abdomen, and magnetic resonance imaging (MRI) scan of the whole brain. Positron emission tomography/CT and isotope bone scan were performed if medically indicated. Histological or cytological specimens containing tumor cells were examined for EGFR mutations by the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PNA-LNA PCR) clamp assay. This assay can detect mutated EGFR sequences with high specificity and sensitivity and is commercially available in Japan.

Treatment protocol

Erlotinib was taken orally at a dose of 150 mg daily. Erlotinib therapy was continued until disease progression (PD) or withdrawal of consent. Erlotinib was interrupted or a dose reduction considered in patients who developed grade 3 non-hematological toxicities or fever of ≥38.0°C. In addition, erlotinib was discontinued under any of the following conditions: (1) development of grade 1 ILD or any grade 4 toxicity and (2) interruption for over 2 weeks as a result of over grade 3 toxicity. During the trial, no other systemic anticancer treatment was permitted.

Toxicity and response evaluation

All toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [23]. Chest radiography or CT scan was performed every 2–4 weeks to assess the response. Complete and partial responses were confirmed by two observations not less than 4 weeks apart. Determination of stable disease (SD) required disease stabilization for at least 6 weeks in the present study.

Statistical considerations

The primary end point was the disease control rate (DCR). The expected DCR was 60%, and threshold DCR was 33%. We estimated that a total of 29 patients would be needed for the study to have a power of 90% to confirm the hypothesis with a two-sided significance level of 5%. Secondary end points were RR, toxicities, progression-free

survival (PFS), and overall survival (OS). OS was defined as the time from enrollment in this study until death from any cause. PFS was defined as the time from enrollment in this study to the first observation of PD or death from any cause. PFS and OS were analyzed by the Kaplan–Meier method and were compared using the log-rank test. The χ^2 test was used for comparisons between two groups.

Results

Patient characteristics

A total of 31 patients were enrolled between January 2008 and June 2011 from six institutes in Nagano prefecture, Japan. The clinical characteristics of the patients are summarized in Table 1. The median age was 71 years, with a range of 31–89 years. Most of the patients were men (74.2%) and were smokers (77.4%). Histological types included 21 cases of adenocarcinoma (67.7%), nine of squamous cell carcinoma (29.0%), and one of large cell carcinoma (3.2%). Ten, nine, eight, and four patients showed PS 0, 1, 2, and 3, respectively. Two patients were treated with erlotinib as the first-line chemotherapy because of advanced age (76 and 84 years old). Eleven patients were treated with erlotinib as second-line therapy, and nine cases were treated as third-line therapy. Nine patients (29.0%) in the present study were treated with erlotinib as fourth-line or later therapy.

Table 1 Clinical characteristics of all 31 patients

Characteristics	No.	%
Sex		
Male	23	74.2
Female	8	25.8
Age, years		
Median	71	
Range	31–89	
Smoking history		
Ever-smoker	24	77.4
Never-smoker	7	22.6
Histology		
Adenocarcinoma	21	67.7
Squamous cell carcinoma	9	29.0
Large cell carcinoma	1	3.2
Stage		
IIIA	1	3.2
IIIB	9	29.0
IV	14	45.2
Postoperative recurrence	7	22.6
Performance status (PS)		
0	10	32.3
1	9	29.0
2	8	25.8
3	4	12.9
No. of prior chemotherapy regimens		
0	2	6.5
1	11	35.5
2	9	29.0
3	4	12.9
≥4	5	16.1

Toxicity and treatment delivery

The adverse event profile is summarized in Table 2. The most common adverse events associated with erlotinib treatment were skin rash (80.6%) and diarrhea (38.7%). Two patients (6.5%) developed ILD, but they recovered with steroid treatment. Hematological toxicity was not observed in this study. There were no treatment-related deaths in the whole study population. Median treatment duration was 70 days with a range of 10–463 days. Two patients discontinued erlotinib treatment before response evaluation because of the development of ILD and patient refusal, respectively. Dose reduction of erlotinib was performed in five patients (16.1%) because of toxicities (eruption or diarrhea).

Table 2 The adverse event profile

Toxicity	Grade (No.)				All grade (%)
	1	2	3	4	
Interstitial lung disease (ILD)	0	2	0	0	6.5
Skin rash	3	17	5	0	80.6
Stomatitis	5	0	0	0	16.1
Diarrhea	9	2	1	0	38.7
General fatigue	3	3	0	0	23.1
Appetite loss	0	2	0	0	6.5
Liver dysfunction	2	3	0	0	16.1

Response and survival

The response to erlotinib was evaluated in all except two patients because of discontinuation of therapy before evaluation. The results are shown in Table 3. One patient achieved a complete response (CR), four showed a partial response (PR), and eight showed SD; thus, the RR was 17.2% (95% confidence interval (CI): 7.6–35.4%) and DCR was 44.8% (95% CI: 28.4–62.5%). We also analyzed the tumor response according to patients' characteristics and adverse effects. Patients with a skin rash of grade 2–3

Table 3 The response to erlotinib and duration of erlotinib administration

Parameter	No.	%
Total no. of patients	31	
Response		
Complete response (CR)	1	3.4
Partial response (PR)	4	13.8
Stable disease (SD)	8	27.6
Progressive disease (PD)	16	55.2
Not evaluated (NE)	2	
Duration of erlotinib administration, days		
Median	70	
Range	10–463	

showed a significantly higher DCR (57.1%) than those with grade 0 or 1 rash (12.5%, $P = 0.02$). There were no significant differences in DCR in adenocarcinoma and squamous cell carcinoma groups.

Survival was analyzed in all patients, and the survival curves are shown in Fig. 1. The median PFS and median survival time (MST) were 2.1 months (95% CI: 0.9–2.8 months) and 7.7 months (3.8–20.4 months), respectively. One-year survival rate was 44.2% (95% CI: 26.2–63.9%). The PFS and OS in patients with CR + PR + SD were significantly longer than in those with PD (Fig. 2). In addition, patients with PS 3 had significantly shorter PFS (0.4 months) and OS (0.9 months) than in those with PS 0–2 (PFS: 2.2 months, $P = 0.0002$ and OS: 10.3 months, $P = 0.0002$). No significance was observed in subgroups: gender, smoking history, and adverse effects. Patients with grade 2–3 rash showed longer PFS and OS than the group with grade 0 or 1 rash, but the difference was not significant (PFS, $P = 0.15$; OS, $P = 0.06$). Furthermore, survival tended to be longer in the adenocarcinoma group than the squamous cell carcinoma group, but the difference was not significant ($P = 0.11$).

Discussion

We prospectively evaluated the efficacy and toxicities of erlotinib in patients with EGFR wild-type NSCLC. In the present study, we found an objective RR of 17.2%, a median PFS time of 2.1 months, and MST of 7.7 months, along with manageable and non-fatal toxicities. As most patients enrolled in the present study had already received cytotoxic chemotherapy, the RR of 17.2% and DCR of 44.9% were encouraging results. Thus, we suggest that

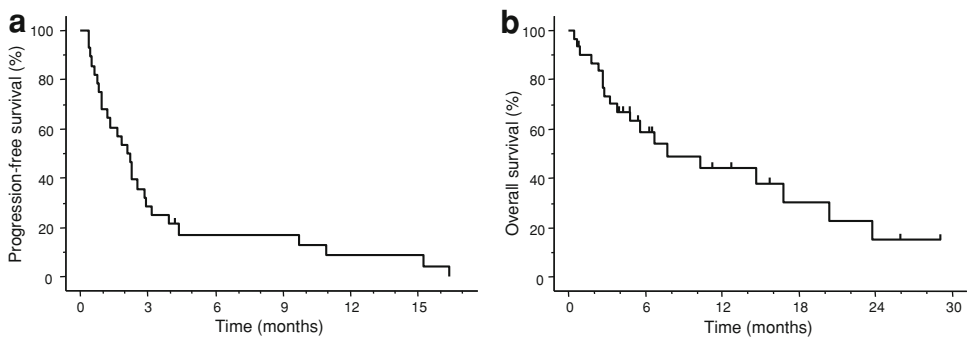

Fig. 1 Kaplan–Meier plot of progression-free survival (**a**) and overall survival (**b**) after enrollment in the study. The median period of progression-free survival was 2.1 months (95% CI: 0.9–3.1 months) and overall survival was 7.7 months (95% CI: 3.8–20.4 months)

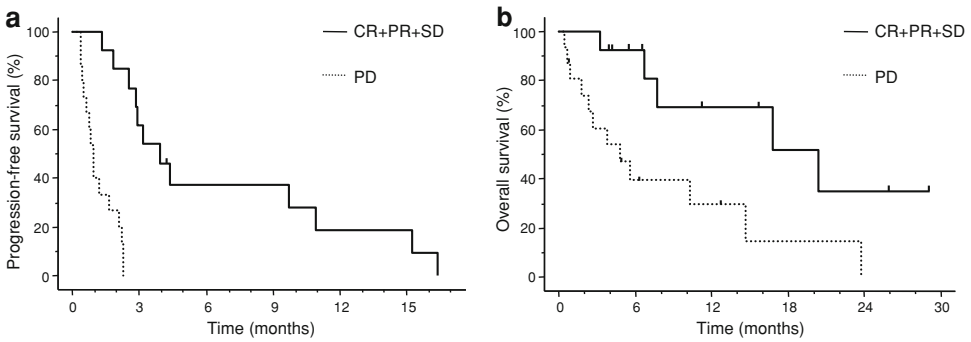

Fig. 2 Kaplan–Meier plot of progression-free survival (**a**) and overall survival (**b**) after enrollment in the study according to the response. Positive responders (CR + PR + SD) had longer median PFS (4.0 months, 95% CI: 2.6–10.9) than non-responders (0.9 months, 95% CI: 0.4–1.7, $P = 0.0001$). Positive responders also had longer median OS (20.4 months, 95% CI: 6.7–not reached) than non-responders (4.8 months, 95% CI: 1.7–14.6, $P = 0.009$)

EGFR-TKI using erlotinib may be an alternative option for patients resistant to cytotoxic chemotherapy, even in those with EGFR wild-type NSCLC.

Wu et al. [14] retrospectively summarized the effectiveness of erlotinib in patients with EGFR wild-type NSCLC and described the RR of 13.9%. In addition, Schneider et al. [15] also analyzed the patients from German Center in TRUST study [24] and reported a 3% response to erlotinib in EGFR wild-type cases. Yoshioka et al. [25] conducted a phase II study prospectively and reported RR of 3% and DCR of 60% to erlotinib in Japanese patients with EGFR wild-type NSCLC. Compared with these results, the response rate to erlotinib in the present study was somewhat higher, although DCR and PFS were almost identical to these previous reports. As the number of patients was small in all of these studies, including the present study, it is difficult to interpret the differences. Tumor tissues in NSCLC can include histologically heterogeneous components and detection of positive or resistant EGFR mutant tumor cells may vary among different tumor sites [26, 27]. As EGFR mutations were determined at initial diagnosis and not at initiation of erlotinib treatment, the biological features in the various sites of tumors may have changed somewhat during cytotoxic chemotherapies. Reevaluation of EGFR mutation may help to determine the variability in the tumors.

The DCR of 44.8% obtained here suggests that treatment with erlotinib would have a significant effect on the clinical course of patients with EGFR wild-type NSCLC. We cannot exclude the possibility that the efficacy of erlotinib observed in the present study may reflect the natural history of the disease rather than the efficacy of the drug. However, the duration of median PFS (4.0 months) in patients obtained over SD was substantial. The appropriate treatment in EGFR wild-type NSCLC resistant to several cytotoxic chemotherapies has yet to be determined. As we have encountered many patients with no further treatment options who have progressed despite receiving several cytotoxic chemotherapies, we emphasize that erlotinib may be a useful optional treatment for patients with EGFR wild-type tumors.

In a retrospective analysis comparing the effectiveness of erlotinib and gefitinib in patients with EGFR wild-type NSCLC, there are no differences in response rate or survival rate between the two regimens [14]. As the present study focused on the efficacy of erlotinib, the superiority or at least non-inferiority of erlotinib to gefitinib in cases resistant to multiple cytotoxic chemotherapy regimens was not determined.

It is difficult to clarify the molecular mechanisms underlying the effectiveness of erlotinib in this patient population. Recently, Chang et al. [28] analyzed the expression of amphiregulin, a novel molecular biomarker, in patients with EGFR wild-type NSCLC who were treated with EGFR-TKIs. They reported that, although the relationship with DCR was not statistically significant, positive amphiregulin status using immunohistochemical staining was associated with prolonged PFS and OS. Thus, amphiregulin could be a potential marker for the selection of EGFR-TKI treatment in patients with EGFR wild-type NSCLC. Thus, further studies are warranted to evaluate the molecular mechanism and clarify how to select patients for erlotinib treatment among those with EGFR wild-type NSCLC.

In conclusion, erlotinib is a potentially useful therapeutic option for advanced NSCLC patients with EGFR wild-type tumors showing resistance to cytotoxic chemotherapy. Although the molecular mechanisms underlying the observations of the present study remain unclear, the results presented here suggest that erlotinib has some clinical efficacy even in patients with EGFR wild-type NSCLC.

Conflict of interest None declared.

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