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Scientific Research

A Phase II Study of Erlotinib in Patients with Previously Treated Non-Small Cell Lung Cancer

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Abstract

Background: Erlotinib has been reported to be effective for the treatment of non-small cell lung cancer (NSCLC). To evaluate the efficacy and safety of erlotinib under conditions similar to daily clinical practice, a phase II trial was conducted in Japanese patients with previously treated NSCLC. Methods: The eligibility criteria were stage IIIB/IV NSCLC, a performance status (PS) of 0 - 2, and previous treatment with 1 - 2 non-EGFR-TKI regimens. Patients received erlotinib (150 mg/day) orally until disease progression or intolerable toxicity occurred. The primary endpoint was the objective response rate (ORR). In addition, the disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and *EGFR* gene mutation status were evaluated. Results: Thirty-eight patients were enrolled, and 37 patients were evaluated. The median age was 69 years (range, 50 - 80 years). Patient characteristics were as follows: 26 were male and 11 were female; 12 had a PS of 0, 20 had a PS of 1, and 5 had a PS of 2; and 26 had adenocarcinoma, and 11 had non-adenocarcinoma histology. The ORR and DCR were 21.6% (95% confidence interval [CI], 11.4% - 37.2%) and 54.1% (95% CI, 35.9% - 66.6%), respectively. Twenty-seven patients could be evaluated for *EGFR* gene status (12, mutated; 15, wild-type). The ORR for *EGFR*-mutated patients was 41.7%, while that for patients with wild-type *EGFR* was 13.3%. The median PFS was evaluated as 4.4 months (95% CI, 2.2 - 10.7 months). The median OS was 14.9 months (95% CI, 9.2 months - not reached). Common adverse events were tolerable skin toxicities, diarrhea, and stomatitis. In addition, interstitial lung disease occurred in 8.1% of patients. Conclusion: As efficacy and safety were similar to previous studies, erlotinib was found to be effective for Japanese patients with

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previously treated NSCLC in clinical practice.

Keywords

Non-Small Cell Lung Cancer; Phase II Study; Erlotinib; Previously Treated

1. Introduction

Lung cancer is currently the leading cause of cancer-related deaths in Japan [1] and worldwide [2], as it has been for years. Among lung cancer subtypes, non-small cell lung cancer (NSCLC) is the most common form (approximately 85%), with many patients presenting with advanced disease at initial diagnosis [3]. Advanced NSCLC is currently considered an incurable disease for which standard chemotherapy provides marginal improvement in overall survival. A combination of platinum chemotherapy with a third-generation agent has been established as a standard first-line regimen with a 1-year survival rate of approximately 33% [4]. Recent advances in chemotherapy and targeted therapy now provide new treatment options for the disease. One example is the orally administered epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) agent [5].

Erlotinib, an oral EGFR-TKI, demonstrated a significant survival benefit versus placebo in patients with previously treated advanced NSCLC in the pivotal trial BR.21 [6]. In that trial, erlotinib was associated with superior survival in unselected patients (6.67 months for erlotinib versus 4.70 months for placebo). Accordingly, erlotinib was approved by the Food and Drug Administration in 2004 for the treatment of patients with advanced NSCLC who have failed at least 1 prior chemotherapy regimen [7]. Thereafter, EGFR-TKIs, including erlotinib, have become promising therapeutic options for patients with advanced NSCLC [8], especially in Asian populations [9]-[11]. The efficacy of EGFR-TKIs is strongly associated with *EGFR*-sensitive mutation status in patients with NSCLC [7]-[11]. However, recent studies demonstrated that erlotinib showed modest but apparent beneficial effects in NSCLC patients with wild-type *EGFR* as well [12] [13]. It is important to understand the benefit of erlotinib under conditions similar to daily clinical practice, such as in a patient population with unselected *EGFR* gene status, unselected histology, and unlimited age. To date, a few prospective studies of erlotinib monotherapy for Japanese pretreated NSCLC patients have been reported [14]-[16]. Therefore, we performed this prospective, multicenter, phase II, open-label study to investigate the efficacy and tolerability of erlotinib monotherapy in Japanese patients with pretreated NSCLC, regardless of *EGFR* gene mutation status.

2. Patients and Methods

2.1. Patients Eligibility and Selection

Patients were required to fulfill the following eligibility criteria: pathologically (either cytologically or histologically) proven stage IIIB/IV NSCLC, measurable lesion(s) defined by Response Evaluation Criteria in Solid Tumors (RECIST), history of refractory treatment with 1 or 2 chemotherapy regimens but no prior EGFR-TKI therapy, age more than 20 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 - 2, and an expected survival of at least 3 months. In addition, other eligibility criteria with respect to organ function were as follows: adequate bone marrow functions (leukocyte count, 4000 - 12,000/μL; absolute neutrophil count, ≥1500/μL; and platelet count ≥100,000/μL), adequate respiratory function (arterial oxygen saturation, >90% while breathing ambient air), adequate liver function (levels of asparate aminotransferase and alanine aminotransferase, <2× upper limit of normal [ULN]; and total bilirubin, <1.5 mg/dL), and adequate renal function (serum creatinine, <1.5× ULN). Baseline chest computed tomography (CT) had to have been performed within 4 weeks before study registration. The study could not be initiated earlier than 3 weeks after the last dose of chemotherapy. Likewise, thoracic radiotherapy was required to have been completed at least 12 weeks prior to the study. Exclusion criteria were as follows: pregnancy, concomitant malignancy, pleural effusion requiring treatment, symptomatic cerebral involvement, history of using anti-HER2 agents, and prior and/or existing interstitial lung disease (ILD) including active radiation pneumonitis. Use of either concomitant anticancer treatment or preventive treatment for adverse events was not allowed. This study was performed in accordance with the World Medical Association Declaration of Helsinki (1964, amended in 2000). All enrolled patients provided

written informed consent. The protocol was approved by the Institutional Review Board of all participating institutions.

2.2. Treatment Regimen

Erlotinib was administered orally at a daily dose of 150 mg. Two-step reduction doses (first reduction, 100 mg/day; second reduction; 50 mg/day) were permitted per patient, according to treatment-related toxicities. For example when grade 3 or intolerable grade 2 rash or stomatitis occurred, treatment was withheld until symptoms improved to grade 1 severity or less, and erlotinib was resumed with a 1-step dose reduction. When grade 3 diarrhea occurred, treatment was stopped until improvement to grade 1 severity or less, and therapy was then resumed with a 1-step reduction. The therapy was continued until either disease progression or unacceptable toxicity occurred. No dose escalations were permitted. When either ILD of any grade or any other grade 4 toxicities occurred, erlotinib treatment was permanently discontinued.

2.3. Assessment of Antitumor Activity and Toxicity

Chest radiography, complete blood counts, and blood chemistry studies were performed at least every 2 weeks. CT for the assessment of target or non-target lesions was designed to be performed every 4 weeks. The RECIST was used to evaluate responses. Complete and partial responses were determined by 2 assessments not less than 4 weeks apart. A response designation of stable disease (SD) required tumor stabilization for at least 6 weeks. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

2.4. *EGFR* Analysis

EGFR gene mutation status was evaluated when suitable tumor tissues at initial diagnosis or surgery were available. Either paraffin-embedded tissues or fresh frozen samples were used for commercial analysis using either the cycleave polymerase chain reaction (PCR) method [17] or the real-time PCR-based peptide nucleic acid-locked nucleic acid PCR clamp method [18].

2.5. Statistics

This clinical trial was designed to assess the objective response rate (ORR) for erlotinib monotherapy as the primary endpoint. Secondary endpoints were the disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and toxicities. The sample size was calculated using Fisher's exact test. According to previous clinical trials of erlotinib for NSCLC in BR.21 [6] and in Japanese patients [14] [15], the response rate ranges from 8.9% to 28%. On the basis of a 1-sided calculation ($\alpha = 0.05$, $1 - \beta = 0.9$) with a null proportion of 0.28 and an alternative proportion of 0.089, the minimum sample number was assumed to be 34. Consequently, 38 patients were recruited to allow for patient dropouts. The 95% confidence interval (CI) for ORR and DCR was determined using the Clopper-Pearson method. The time-to-event variables were calculated using the Kaplan-Meier method. Statistical significance was evaluated using the log-rank test. $P < 0.05$ was considered significant. The best response and OS were estimated using logistic regression and Cox proportion hazards regression methods, respectively. This study was registered with the University Hospital Medical Information Network (UMIN) in Japan (number UMIN000002735).

3. RESULTS

3.1. Patient Characteristics

A total of 38 Japanese patients from 4 institutions were enrolled in this study between July 2009 and February 2011. Thirty-seven patients were evaluable for efficacy and safety. One patient was excluded because of protocol violation. The baseline clinical characteristics of the patients are summarized in **Table 1**. The median patient age was 69 years (range, 50 - 80 years), and 70.3% of the patients were male. Twenty-six patients (70.3%) had adenocarcinoma, and 14 patients (37.8%) had no history of smoking. Twenty-six patients (70.3%) had received only first-line chemotherapy.

Table 1. Summary of patient characteristics.

Number of patients	37
Age (years)	
Median (Range)	69.0 (50 - 80)
Sex	
Male	26 (70.3%)
Female	11 (29.7%)
Performance status	
0	12 (32.4%)
1	20 (54.1%)
2	5 (13.5%)
Histology	
Adenocarcinoma	26 (70.3%)
Squamous cell carcinoma	6 (16.2%)
Unclassified	5 (13.5%)
Stage	
IIIB	8 (21.6%)
IV	29 (78.4%)
Smoking history	
Never	14 (37.8%)
Current or former	22 (59.5%)
Uncertainty	1 (2.7%)
Number of prior chemotherapy regimen(s)	
1	26 (70.3%)
2	11 (29.7%)
EGFR gene status	
Mutated (sensitive mutation)	12 (32.4%)
Wild-type	15 (40.5%)
Unknown	10 (27.0%)

3.2. Clinical Outcome

The tumor response rates are shown in **Table 2**. Although no patients achieved complete response, 8 patients (21.6%) were assessed as having partial response (PR) and 12 patients (32.4%) were assessed as having SD. In 6 patients, the objective response could not be confirmed: in 4 cases, erlotinib was discontinued early after the initiation of therapy because of patient refusal, and in 2 patients, therapy had to be stopped because of either ILD or severe rash. The ORR was 21.6% (95% CI, 11.4% - 37.2%), and the DCR was 54.1% (95% CI, 35.9% - 66.6%). The median PFS was 4.4 months (95% CI, 2.2 - 10.7 months) (**Figure 1(a)**). The OS was determined based on information collected until the follow-up survey in February 2012. The median survival time from enrollment was 14.9 months (95% CI, 9.2 - not reached), and the 1-year survival rate was 56.6% (95% CI, 38.4% - 71.2%) (**Figure 1(b)**). As shown in **Figure 2**, the median survival times varied among cohorts: 23.2 months (95% CI, 2.3 - not reached) and 12.3 months (95% CI, 5.3 - not reached) in female and male patients ($P = 0.419$), Not reached (95% CI, 5.9 - not reached), and 11.4 months (95% CI, 3.8 - 16.3) in non-smokers and smokers (current or former) ($P = 0.0369$), and 23.2 months (95% CI, 9.2 - not reached) and 12.3 months (95% CI, not reached) in patients with adenocarcinoma and squamous cell carcinoma histology ($P = 0.018$), respectively. In some cohorts, survival times could not be determined because they were not reached during the observation period. These results suggested that patients with characteristics of female gender, non-smoking history, and adenocarcinoma histology showed better response rates than did others. As for previous chemotherapy regimens,

Table 2. Response assessment.

Partial response	8 (21.6%)
Stable disease	12 (32.4%)
Progressive disease	11 (29.7%)
Not evaluated	6 (16.2%)
Objective RR (95% CI)	21.6% (11.4 - 37.2)
Disease control rate (95% CI)	54.1% (35.9 - 66.6)
1-year survival	56.6% (38.4 - 71.2)
Median PFS (95% CI)	
Non-selected	4.4 months (2.2 - 10.7)
EGFR mutated	12.6 months (2.2 - 19.9)
EGFR wild-type	2.1 months (1.0 - 5.5)
EGFR unknown	3.9 months (1.0 - 11.0)
Median OS (95% CI)	
Non-selected	14.9 months (9.2 - NR)
EGFR mutated	NR (5.3 - NR)
EGFR wild-type	9.2 months (2.3 - 14.9)
EGFR unknown	10.5 months (1.1 - NR)

RR, response rate; CI, confidence interval; PFS, progression-free survival; OS, overall survival; NR, not reached.

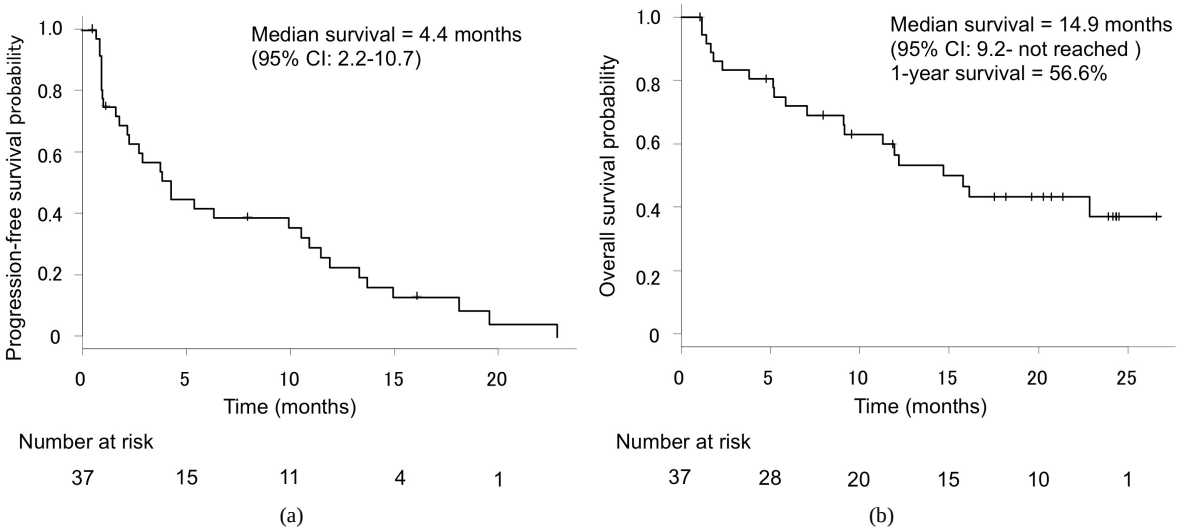

Figure 1. Progression-free survival (a) and overall survival (b) of all patients. The median PFS time, OS time, and 1-year survival rate were 4.4 months, 14.9 months, and 56.6%, respectively. CI, confidence interval.

our data showed no significant differences in either response rate or survival between patients with 1 prior regimen (n = 26) and those with 2 prior regimens (n = 11) (P = 0.13, data not shown).

3.3. Safety

As shown in **Table 3**, adverse events were observed in all patients. The most common adverse events were skin disorders (70.3%). Other adverse events, including stomatitis (35.1%) and diarrhea (24.3%), were often observed. Liver dysfunction was observed in 8.1% of patients; however, no patients showed elevation of transaminase levels of grade 3 severity or higher. Skin toxicities were well tolerated and reversible with either appropriate skin treatment or dose reduction. Six patients (16.2%) had dose reductions because of rash (n = 2) and diarrhea, fatigue, anorexia, or infectious enterocolitis. Unfortunately, 8 patients (21.6%) discontinued erlotinib therapy because of adverse events, including anorexia (n = 3), ILD (n = 2), rash (n = 2), and diarrhea (n = 1). Interestingly, a stratified Kaplan-Meier analysis demonstrated that patients with rash of grade 2 severity or

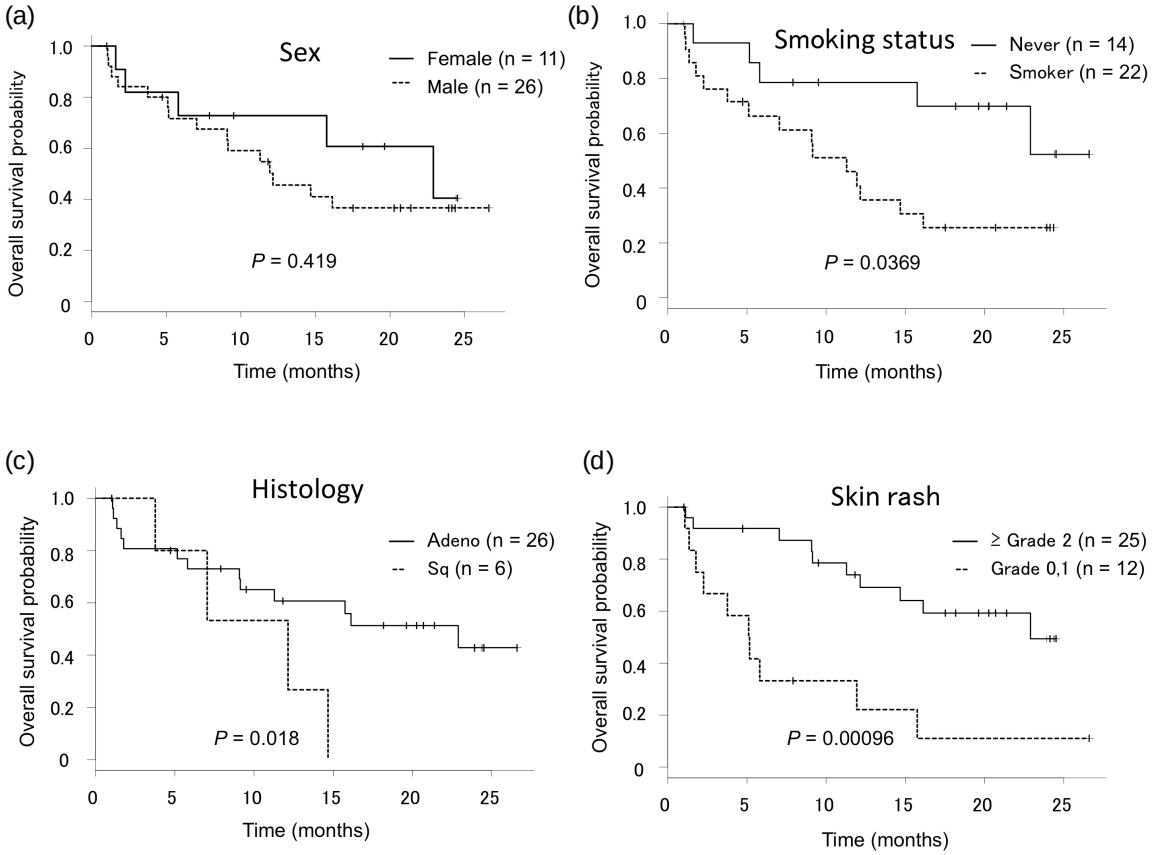

Figure 2. Overall survival curves according to clinical characteristics. (a) Sex (female versus male, $P = 0.419$). (b) Smoking status. Smokers include current smokers and former smokers (never smoker versus smoker, $P = 0.0369$). (c), Histology (adeno versus sq, $P = 0.018$). (d), Skin rash (grade 2 or higher versus grade 0 and 1, $P = 0.00096$). $P < 0.05$ was considered significant. Statistical analyses were performed using the log-rank test. adeno, adenocarcinoma; sq, squamous cell carcinoma.

higher (n = 25) showed significantly improved survivals compared with those with rash of grade 1 severity or those without rash (n = 12) ($P = 0.00096$) (**Figure 2(d)**). The median OS was 696 days (23.2 months) for those with severe rash and 157 days (5.2 months) for those with non-severe or no rash.

Regrettably, 3 patients (8.1%) experienced ILD events, and 1 of these patients died of acute respiratory failure. The characteristics of these patients are summarized in **Table 4**. All 3 patients were male, and their PS was 0 - 1. Two of these patients were former smokers, while 1 had no history of smoking. The patient who died of ILD was a 69-year-old man with adenocarcinoma; he had a 99-pack-year history (3 packs/day × 33 years). He discontinued erlotinib treatment on day 23 because of tumor progression. Despite treatment cessation, he developed ILD on day 36; a chest high-resolution CT scan revealed a pattern of acute interstitial pneumonia, compatible with drug-induced ILD. Immediate steroid pulse therapy was started, together with oxygen therapy plus ampicillin/sulbactam. An autopsy could not be performed. We considered this adverse event to be erlotinib related.

3.4. *EGFR* Analysis

In this study, a total of 27 samples (73%) were available for *EGFR* gene mutation analyses. All analyses were performed commercially as part of routine clinical practice. Fifteen patients (55.6%) had wild-type *EGFR* status, and 12 patients (44.4%) had mutated *EGFR* status. Of the 12 mutations (8 in male and 4 in female patients), 6 were exon 19 deletions, 5 were L858R point mutations in exon 21, and 1 was a double mutation of an exon 19 deletion plus a L858R point mutation. With regard to the association between responses and mutation types, patients with *EGFR* mutations showed various responses. Of the 6 patients with exon 19 deletions, the response was a PR in 1 patient, SD in 3 patients, progressive disease (PD) in 1 patient, and not evaluated (NE) in 1 patient.

Of the 5 patients with L858R, PR was noted in 3 patients and SD was noted in 2. The 1 patient with double mutations achieved PR. Taken together, the response in these patients with *EGFR* mutations was PR in 5 cases, SD in 5 cases, and NE in 1 case. Of the 12 cases, 11 (91.7%) were of adenocarcinoma and 1 was of unclassified NSCLC. Eight patients (66.7%) had no history of smoking, 4 patients (33.3%) were former smokers, and no patients were current smokers.

The PFS of patients with *EGFR* mutations was analyzed and compared with that of wild-type *EGFR* patients (**Table 2**). As expected, patients with *EGFR* mutations demonstrated longer survival times than did those with wild-type *EGFR*. The median PFS in *EGFR* mutation-positive patients was 12.6 months (95% CI, 2.2 - 19.9); meanwhile, PFS in patients with wild-type *EGFR* was 2.1 months (95% CI, 1.0 - 5.5), and that in patients with unknown-type *EGFR* was 3.9 months (95% CI, 1.0 - 11.1). A statistically significant difference in PFS was noted between patients with *EGFR* mutations and those with wild-type *EGFR* ($P = 0.00441$). However, no significant difference was detected between patients with unknown-type and wild-type *EGFR*.

We also evaluated OS in patients with *EGFR* mutations. As shown in **Figure 3**, Kaplan-Meier analysis revealed a survival advantage for patients with *EGFR* mutations, compared with patients lacking *EGFR* mutations. The median OS in patients with *EGFR* mutations was not yet reached: however, median OS in patients with wild-type and unknown-type *EGFR* was 9.2 months (95% CI, 2.3 - 14.9) and 12.3 months (95% CI, 1.1 - not reached), respectively (**Table 2**). Statistically significant differences in OS were detected between patients with and without mutations ($P = 0.0115$). However, no significant difference was noted between patients with unknown status and those with wild-type *EGFR*.

Table 3. Major treatment-related adverse events and grades.

Toxicity	Number of patients			
grade (CTCAE)	1	2	3	≥4
Skin disorder				
Rash	12 (32.4%)	14 (37.8%)	0	0
Acne-like rash	2 (5.4%)	5 (13.5%)	0	0
Dryness	6 (16.2%)	4 (10.8%)	0	-
Pruritus	4 (10.8%)	4 (10.8%)	0	-
Paronychia	2 (5.4%)	2 (5.4%)	0	0
Pyoderma	0	2 (5.4%)	0	0
Stomatitis	9 (24.3%)	3 (8.1%)	1 (2.7%)	0
Diarrhea	7 (18.9%)	1 (2.7%)	1 (2.7%)	0
Anorexia	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)
Fever	4 (10.8%)	0	0	0
Pneumonitis	2 (5.4%)	0	0	1 (2.7%)
Nausea	3 (8.1%)	0	0	0
Pharyngitis	3 (8.1%)	0	0	0
Liver injury	3 (8.1%)	0	0	0
Fatigue	0	1 (2.7%)	1 (2.7%)	0
Conjunctivitis	2 (5.4%)	0	-	-

CTCAE, common terminology criteria for adverse events.

Table 4. Characteristics of 3 cases showing treatment-related interstitial lung disease-like events.

Age/Sex	Smoking	PS	Histology	Onset (day)	Outcome
63M	Former	1	Ad	14	Recovered
69M	Former	1	Ad	21	Died (day 42)
70M	Never	0	Ad	262*	Recovered

*Causal relation to erlotinib is undeniable. PS, performance status; Ad, adenocarcinoma.

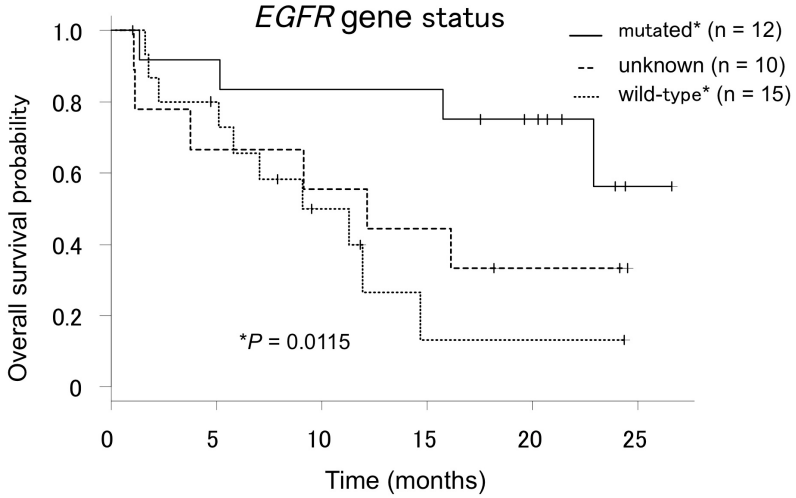

Figure 3. Kaplan-Meier survival plot according to *EGFR* gene mutation status (mutated, wild-type, unknown). The median OS in patients with *EGFR* mutations could not be determined, while that in patients with wild-type *EGFR* and unknown status were 9.2 months and 12.3 months, respectively. Statistically significant differences were observed between patients with and without mutations (P = 0.0115, log-rank test). CI, confidence interval.

4. Discussion

For the entire cohort, we observed an ORR of 21.6%, a DCR of 54.1%, a median PFS time of 4.4 months, and a median OS time of 14.9 months. To date, some phase II and phase III trials of erlotinib have been reported. Of these, 2 Japanese prospective phase II studies had similar concepts to our study [14] [15]. Compared with these 2 trials, our results showed similar favorable responses. In these past 2 studies, responses to erlotinib were as follows: ORR, 28.3% in both; DCR, 50.0% and 47.8%; median time to progression, 77 days and 75 days; and median OS, 14.7 months and 13.5 months, respectively. Patient characteristics were similar in these 2 studies, but patient characteristics in our study were different from these in some aspects. One of the major differences was the average age. On average, our patients were 9 years older, which likely explains the increased frequency of adverse events. Second, the proportion of patients with adenocarcinoma (70.3%) in this study was much lower than that in the previous 2 studies (92% and 87%). These differences might explain the discrepancies in the responses observed. Because sensitive *EGFR* gene mutations are generally seen in patients with adenocarcinoma, and because this is the most important prognostic factor for treatment with EGFR-TKIs [19] [20], a high proportion of patients with adenocarcinoma in the previous studies may have resulted in the better outcome observed. Despite such disadvantages, our results were as promising as previous Japanese studies. Compared with a previous Western study, our results were much more encouraging. In the BR.21 trial [6], the ORR, PFS, and OS were 8.9%, 2.2 months, and 6.7 months, respectively. These differences may depend on patient backgrounds; for examples, the percentages of Asian patients and adenocarcinoma cases in BR.21 were as low as 12.9% and 50.4%, respectively.

In a stratified analysis, the survival of patients with *EGFR* mutations was similar but slightly superior to that of a previous Japanese trial [16]. Our patients showed a median PFS of 12.6 months, and the median OS was not yet reached. Meanwhile, Yamada *et al.* [16] reported a PFS of 9.3 months (OS, not yet determined). Surprisingly, our PFS (12.6 months) in this previously treated group was as long as those observed not only in 2 first-line Japanese gefitinib trials [9] [11] (10.8 months and 9.2 months, respectively), but also in first-line Chinese and European erlotinib trials (13.1 months in OPTIMAL [21], 9.4 months in EURTAC [22]). As suggested, *EGFR* mutations have been strongly correlated with positive responses not only to gefitinib but also to erlotinib [23]. Meanwhile, our patients with wild-type *EGFR* had a median PFS of 2.1 months and a median OS of 9.2 months, which were very close to those reported by previous Japanese trials [12] [13], with a PFS of 2.1 months in both studies and an OS of 9.2 months and 7.7 months. Although the TOPICAL trial demonstrated that first-line erlotinib treatment for patients in a poor health condition is controversial [24] and the recent TAILOR trial in Italy

showed that second-line erlotinib treatment for patients with wild-type *EGFR* was not superior to standard chemotherapy [25]], our results indicate that erlotinib is beneficial for Japanese NSCLC patients even after failure of first-line therapy.

The toxicities commonly observed in this trial were mostly tolerable. In addition to diarrhea (24.3%), skin disorders (70.3%) and stomatitis (35.1%) were the main forms of erlotinib toxicity, which were mostly manageable, as previously reported [6] [8]. With respect to skin disorders, our data also suggested that development of severe rash during erlotinib therapy could be associated with improved survival, as previously reported [26]. Furthermore, severe hematological toxicities were not observed, and therefore, many patients could continue therapy for long periods and maintain their activities of daily life. For instance, 1 patient received erlotinib for as long as 490 days.

Importantly, 3 patients (8.1%) developed ILD, and unfortunately, 1 of these patients died. Two of these patients developed ILD within 3 weeks from the initiation of therapy. As previously reported [8], ILD is a relatively rare but potentially life-threatening complication, with an overall incidence of less than 1% in Caucasian patients and approximately 5% in Japanese patients, and ILD occurred within a month in most cases. An ILD occurrence of 8.1% in this study is relatively high, compared to 2 other Japanese phase II trials [14] [15], with incidences of 6.5% and 4.3%. This difference is probably due to the small sample size. Further studies may clarify the molecular mechanisms of the EGFR-TKI-induced ILD. Although the potential ILD risk in Japanese patients is not negligible, our results indicated that erlotinib has survival benefits as second- or third-line chemotherapy for *EGFR* non-selected NSCLC patients.

5. Conclusion

In summary, erlotinib was efficacious and well tolerated in Japanese patients with previously treated NSCLC. *EGFR* mutation status was the definitive predictive factor for erlotinib therapy. It is important to be especially aware of the risk of interstitial pneumonia for Japanese patients. Our results showed that erlotinib is a key drug for second- or third-line chemotherapy in patients with NSCLC.

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