Phase II Trial of Erlotinib in Elderly Patients with Previously Treated Non-small Cell Lung Cancer: Results of the Lung Oncology Group in Kyushu (LOGiK-0802)

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Abstract. *Background: As the incidence of lung cancer in the elderly is increasing worldwide, there exists a need to develop a clinically effective, less toxic therapy for this patient population. Although erlotinib has shown proven effectiveness against non-small cell lung cancer (NSCLC), few studies have prospectively investigated its application to elderly patients. Patients and Methods: Patients aged ≥75 years with advanced or recurrent NSCLC including wild-type EGFR who had previously received one or two chemotherapy regimens were enrolled in this trial. Erlotinib was initially administered at a dose of 150 mg/day orally until disease progression or unacceptable toxicities occurred. The primary endpoint was the objective response rate. Results: Forty patients were enrolled between May 2009 and January 2014. An objective response was observed in 8 patients (20%, 95%CI=9.1-35.7%), and the disease control rate reached 62.5% (95%CI=45.8-77.3%). After a median follow-up period of 12.2 months (range=1.4-47.2 months), the median progression-free survival period was 5.0 months (95%CI=2.3-7.6 months), and the median survival period was 12.2 months (95%CI=6.1-24.7 months). Major toxicities were skin disorders, fatigue, and anorexia. Most adverse events were grade 2 or less, but 13 patients (32.5%) required a dose reduction. Two patients developed interstitial lung disease, that was nevertheless reversible, and there were no treatment-related deaths. Conclusion: Although the percentage of patients requiring dose reduction seemed relatively higher than that in previous studies, erlotinib is a potentially useful therapeutic option for unselected elderly patients with previously treated advanced or recurrent NSCLC, as has been also shown for younger patients.*

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As the ratio of elderly people in the general population continues to increase, the incidence of lung cancer in elderly patients is now rising. In the USA, approximately 35% of lung cancer patients are more than 75 years old (1). Surprisingly, in Japan, almost half (48%) of all reported lung

cancers affect patients 75 years old or older (2), and 80-85% of cases have non-small cell histology.

Because the elderly tend to have impaired organ function and more co-morbidities than younger patients, they are more vulnerable to hematological and neuropsychiatric toxicity resulting from combination chemotherapy with cytotoxic drugs (3), and therefore single-agent chemotherapy using vinorelbine or docetaxel is considered the standard regimen for elderly patients with advanced or recurrent non-small cell lung cancer (NSCLC) (4, 5). However, the limited efficacy of such monotherapy means that elderly patients do not obtain sufficient clinical benefits. Moreover, few prospective studies have investigated the efficacy of second- or later-line treatments for this patient population. Therefore, there is a need to develop more effective, less toxic therapies for elderly patients with NSCLC in order to obtain clinical benefits in terms of overall survival (OS) and quality of life (QOL).

Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with lower toxicity than cytotoxic agents, and was reported to yield survival benefits with good tolerability in patients with pre-treated NSCLC in the pivotal randomized controlled trial BR.21 (6). Based on the sub-group analysis in the trial, it was revealed that elderly (≥70 years old) patients who received erlotinib had significantly better OS and QOL in comparison to the placebo group, similarly to younger (<70 years old) patients (7). Further subgroup analysis showed that patients with wild-type *EGFR* (*EGFR-wt*) might also benefit from erlotinib, although the difference was not significant (8). Therefore, we conducted a prospective trial to evaluate the efficacy and safety of erlotinib monotherapy in previously treated elderly patients with NSCLC.

Patients and Methods

Study design. This multicenter phase II trial was conducted to evaluate the efficacy and safety of erlotinib in elderly patients with previously treated NSCLC. *EGFR* mutations were analyzed as described below at each Institution beforehand as needed, although this was not mandatory. The primary endpoint was the objective response rate (ORR). Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), OS, and safety.

Eligibility. Patients with histologically or cytologically confirmed advanced NSCLC were eligible for study inclusion. Each patient was required to meet the following criteria: (i) clinical stage IIIB, IV, or postoperative recurrence; (ii) age ≥75 years; (iii) measurable tumor sites; (iv) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; (v) history of one or two lines of prior systemic chemotherapy but no prior EGFR-TKI therapy; (vi) appropriate organ functions (lung: SpO2 ≥90%, heart: normal 12-lead ECG, bone marrow: hemoglobin ≥9.0 g/dL, white blood cells ≥3,000/mm^3, neutrophils ≥1,500/mm^3, platelets ≥100,000/mm^3, liver: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2-times the upper normal limit, total bilirubin ≤1.5 mg/dL, kidney: serum creatinine ≤1.5 times upper normal limit); (vii) life expectancy of at least 3 months.

This study followed the ethical principles of the Declaration of Helsinki, and the study protocol was approved by the institutional review board at each participating institution. All patients provided written informed consent before study-related procedures were performed.

Study treatment. Patients received 150 mg of erlotinib orally per day until disease progression (PD) or unacceptable toxicity. In the event of treatment-related toxicity, dose reductions were permitted twice per patient (first reduction to 100 mg/day, second reduction to 50 mg/day), and interruption of dosing for up to 14 days was allowed. No dose escalations were permitted. For grade 3 or intolerable grade 2 skin disorder or stomatitis, treatment was discontinued until recovery to grade 1 or less, and then a treatment with reduced dose of erlotinib was started. For any other grade 3 treatment-related toxicities, treatment was interrupted until recovery to grade 1 or less, and then the same dose was administered. For interstitial lung disease (ILD) of any grade, or grade 4 toxicities, treatment was permanently discontinued. No systemic anticancer treatment, radiotherapy or pleurodesis was permitted during the trial. Salvage regimens were not restricted for patients after the discontinuation of protocol study.

All patients underwent comprehensive baseline assessments including clinical laboratory tests and imaging studies. Patients also received follow-up assessments and monitoring at regular intervals. Toxicity evaluations were based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE v3.0).

Assessment of tumor EGFR mutation status. EGFR mutations were analyzed at the contracted laboratory of each Institution beforehand. EGFR mutations were analyzed by polymerase chain reaction (PCR) invader assay (9), direct sequencing, or peptide nucleic acid-locked nucleic acid PCR clamp assay (10).

Evaluation of efficacy. Tumor response was evaluated every 4 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, and was confirmed by extramural review. PFS was defined as the period from enrollment until the date of confirmation of PD or the date of death from any cause, whichever was earlier. OS was defined as the period from registration until death due to any cause. Patients for whom there was no information about mortality or disease progression were censored at the date of the last progression-free assessment.

Statistical analysis. All patients who received at least one dose of the study treatment were included in the safety and efficacy analysis. A one-stage design using the binominal probability was used to determine the sample size. Assuming that a response rate of 25% would be expected, whereas a rate of 10% would be the lower limit of interest, and for α=0.05 (one-sided) and β=0.2, the estimated number of patients for accrual was 40. After assuming an inevaluability rate of <10%, we planned an accrual of 44 patients. Survival analysis was conducted on the full analysis set (FAS) using follow-up data available as of 31 January 2015. The survival curves were estimated using the Kaplan–Meier method, and differences in survival were compared by the log-rank test.

This study was registered with UMIN (University Hospital Medical Information Network in Japan), number UMIN000003271.

Results

Accrual started in May 2009 and stopped in January 2014 with 40 patients from 16 participating institutes. Although the number of patients enrolled was less than that initially planned, and the trial was closed because of slow accrual and reach of the estimated number of patients for analyzing the primary endpoint.

Patients' characteristics. The patients' characteristics are listed in Table I. Twenty-eight (70%) of the patients were male and nine (22.5%) were aged ≥80 years. The median patient age was 77 years (range=75-84 years). The median body surface area (BSA) was smaller than the standard for Japanese adults (1.73 m^2). The majority of patients were current or former smokers with adenocarcinoma, although seven patients (17.5%) with squamous cell carcinoma were also enrolled. *EGFR* mutations were detected in 10 patients (25%), exon 19 deletion in seven, exon 21 L858R in two, and other mutation in one.

Treatment delivery. Median treatment duration was 88 days (2.9 months) with a range of 4 to 1,069 days. Interruption of erlotinib treatment was necessary in 13 patients (32.5%), mainly due to skin disorders, fatigue and anorexia. The median duration of treatment interruption was 9 days (range=3-15 days). During the study period, the dose of erlotinib was reduced to 100 mg/day in 13 patients (32.5%) and a further second reduction (to 50 mg/day) was required in 5 of those patients (12.5%), mainly for the above-mentioned reasons. At the time of data analysis, the treatment had been discontinued in 39 patients including 21 whose disease had progressed.

Response and survival. The overall response rate for the patients is shown in Table II. Eight patients were assessed as having partial response (PR) and 17 as having stable disease (SD). The ORR was 20% (95%CI=9.1-35.7%) and the DCR was 62.5% (95%CI=45.8-77.3%). Patients with *EGFR* mutations tended to have a higher RR and DCR than those with *EGFR-wt* or unknown *EGFR* mutation. Only one of seven patients with squamous histology was able to achieve PR.

There was one exclusion from survival analysis because it was revealed that the patient had stage IIIA disease at the extramural review. At the point of data cut-off (January 2015), there had been 31 deaths, and 8 patients were confirmed to be alive, and no patient was lost to follow-up. After a median follow-up period of 12.2 months (range=1.4-47.2 months), the median PFS was 5.0 months (95%CI=CI 2.3-7.6 months) and the median OS was 12.2 months (95%CI=6.1-24.7 months) (Figure 1). We also analyzed PFS and OS according to *EGFR* mutation. As shown in Figure 2, PFS was longer in the patients who had *EGFR* mutation than those with *EGFR-wt* or unknown EGFR mutations. The presence of *EGFR* mutation was also associated with prolonged OS (log-rank test, p=0.0427).

Table I. *Patients' characteristics*.

Characteristics	N (%)
Total patients	40
Gender	
Male/Female	28/12
Age median, years (range)	77 (75-84)
BSA median, m^2 (range)	1.47 (1.16-1.76)
ECOG Performance status	
0	17 (42.5)
1	22 (55)
2	1 (2.5)
Histology	
Adenocarcinoma	33 (82.5)
Squamous cell carcinoma	7 (17.5)
Stage	
IIIB	3 (7.5)
IV	33 (82.5)
Other*	4 (10)
Smoking status	
Smoker (current or former)	26 (65)
Never smoker	13 (32.5)
Unknown	1 (2.5)
EGFR mutation	
Exon 19 deletion/Exon 21 L858R/ other	7/2/1 (25)
Wild type	19 (47.5)
Unknown	11 (27.5)
No. of prior chemotherapy	
1	32 (80)
2	8 (20)

BSA, Body surface area; ECOG, Eastern Cooperative Oncology Group. *Three patients with postoperative recurrence and one with stage IIIA.

Safety and toxicity. Toxicity was evaluated in all eligible patients (Table III). The most frequent toxicity was skin disorder including rash, pruritus, desquamation, xeroderma, dry skin, and paronychia. Five patients developed grade 3 skin disorder, but this toxicity was reversible with either an appropriate treatment interruption or dose reduction. Liver dysfunction was also common, but generally mild. Only one patient experienced ≥grade 3 elevation of the AST and ALT level. Eight patients had to terminate erlotinib treatment because of treatment or disease-related adverse events: two patients with skin disorder, two with ILD, one with intestinal perforation, one with ileus, one with liver dysfunction, and one with pneumonia. Other toxicities were generally tolerable, and no unexpected toxicities were observed. No treatment-related deaths occurred, although ILD was observed in two patients.

Table II. *Tumor response by baseline characteristics.*

	Overall (n=40)	*EGFR* mutation		Histology	
		Positive (n=10)	Wild-type or Unknown (n=30)	Ad (n=33)	Sq (n=7)
PR, n (%)	8 (20)	3 (30)	5 (16.67)	7 (21.21)	1 (14.29)
SD, n (%)	17 (42.5)	5 (50)	12 (40)	14 (42.42)	3 (42.86)
PD, n (%)	13 (32.5)	1 (10)	12 (40)	10 (30.3)	3 (42.86)
NE, n (%)	2 (5)	1 (10)	1 (3.33)	2 (6.06)	0 (0)
ORR, % (95% CI)	20% (9.1-35.7)	30% (6.7-65.3)	16.7% (5.6-34.7)	21.2% (9.0-38.9)	14.3% (0.4-57.9)
DCR, % (95% CI)	62.5% (45.8-77.3)	80% (44.4-97.5)	56.7% (37.4-74.5)	63.3% (45.1-79.6)	57.1% (18.4-90.1)

PR, Partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; CI, confidence interval; Ad, adenocarcinoma; Sq, squamous cell carcinoma.

Discussion

We performed a multicenter phase II trial to evaluate the efficacy and toxicity of erlotinib for previously treated elderly patients with NSCLC. In this trial, we obtained an ORR of 20%, a DCR of 62.5%, and a median PFS of 5.0 months (151 days), along with manageable toxicities, mainly skin disorder, in this population.

The American Society of Clinical Oncology Clinical Practice Guideline states that age alone should not be used to select chemotherapy for patients with stage IV NSCLC (11). Subset analyses in certain phase III trials have reported that platinum-doublet chemotherapies may be feasible and promising for fit elderly patients with good PS and adequate organ function (3, 12). Recently, a randomized controlled trial showed that combination chemotherapy, that is the standard-of-care for first-line treatment of non-elderly patients with advanced or recurrent NSCLC, yielded equivalent benefit in elderly patients (13). As a result, increase of the patient population and the development of less toxic regimen potentially provides the chances of receiving more treatments after failure of initial therapy for the elderly. However, little information is available on the impact of age on outcomes after treatment, especially in a second- or later-line setting for NSCLC, either with cytotoxic chemotherapy or EGFR inhibitors. Moreover, there are actually many elderly patients unable to receive further cytotoxic chemotherapy because of reduced organ function and multiple co-morbidities. In this situation, although the present trial did not meet the primary endpoint, an ORR of 20% and a median PFS of 5 months were encouraging results for such unselected elderly patients with NSCLC.

Several studies have reported that patient sensitivity to EGFR-TKI differs between Asian and non-Asian populations (6, 14), and that patients with Asian ethnicity may respond better to EGFR-TKI (15, 16). The Tarceva Lung Cancer Survival Treatment (TRUST) study, which is a large-scale global phase IV study of erlotinib in unselected patients with NSCLC, reported an ORR, DCR, and median PFS of 27%, 78%, and 5.78 months, respectively, in subgroup analysis of a East/South-East Asian population (17). The POLARSTAR (Post-Launch All-patient-Registration Surveillance in Tarceva-treated NSCLC patients) surveillance study conducted in Japan also reported a median PFS of 5.7 months (176 days) for patients aged <75 years, and 7.0

Table III. *Toxicities (N=40).*

Event (All grade)	N (%) (grade 3/4)	N (%) Grade	N (%)			
			1	2	3	4
Hematologic						
Anemia	32 (80)	0 (0)	21	11	0	0
Leucopenia	8 (20)	0 (0)	7	1	0	0
Neutropenia	4 (10)	0 (0)	3	1	0	0
Thrombocytopenia	7 (17.5)	0 (0)	7	0	0	0
Non-hematologic						
Rash	28 (70)	5 (12.5)	8	15	5	0
Fatigue	18 (45)	1 (2.5)	10	7	1	0
Xeroderma	17 (42.5)	1 (2.5)	8	8	1	0
Pruritus	16 (40)	1 (2.5)	11	4	1	0
Anorexia	16 (40)	2 (5)	8	6	2	0
Diarrhea	14 (35)	1 (2.5)	10	3	1	0
Paronychia	13 (32.5)	0 (0)	9	4	0	0
Erythema multiforme	13 (32.5)	3 (7.5)	5	5	3	0
Desquamation	11 (27.5)	0 (0)	7	4	0	0
Hand foot reaction	11 (27.5)	0 (0)	6	5	0	0
Stomatitis	7 (17.5)	0 (0)	5	2	0	0
Vomiting	3 (7.5)	0 (0)	2	1	0	0
Elevated AST	16(40)	1 (2.5)	15	0	1	0
Elevated ALT	12 (30)	1 (2.5)	10	1	1	0
Elevated total bilirubin	16 (40)	0 (0)	14	2	0	0
Elevated creatinine	16 (40)	0 (0)	11	5	0	0

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

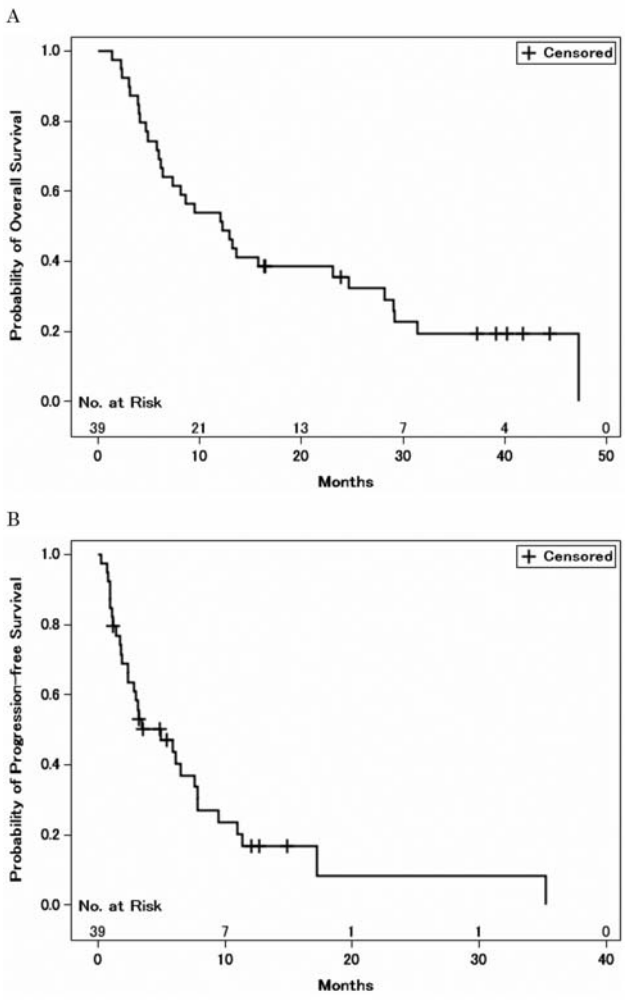

Figure 1. *Overall survival (A) and progression-free survival (B) (N=39).*

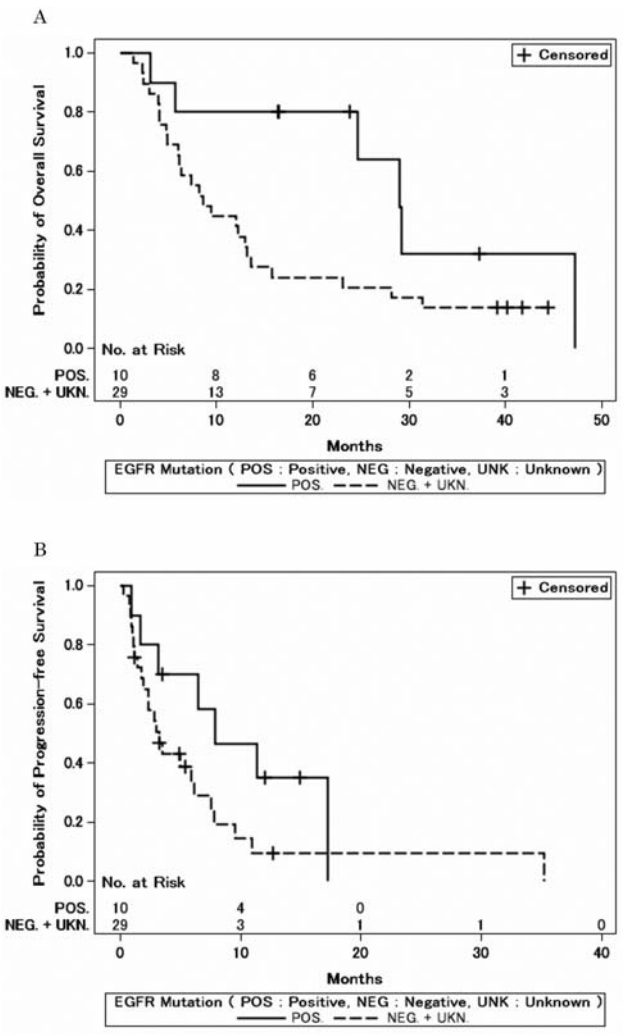

Figure 2. *Overall survival (A) and progression-free survival (B) by EGFR status. m, Months; CI, confidence interval.*

months (213 days) for patients aged 75-84 years, for those with clinical features associated with better EGFR-TKI efficacy (*i.e.* adenocarcinoma, non-smoker, ECOG PS 0-2, and second or third-line setting) who had not previously received gefitinib (18). The populations included in these Phase IV studies reflected patients who would be candidates for EGFR-TKI treatment in an actual clinical setting, and the patients included in our study were similar, except for the age requirement for accrual. Therefore, our present data are considered to demonstrate that unselected elderly patients aged ≥75 years can also benefit from erlotinib treatment, similarly to their younger counterparts.

In spite of the fact that the toxicity of erlotinib in our study compared favorably with that in other previous studies involving patients with NSCLC, including elderly patients, the rate of dose reduction in our study (13 patients; 32.5%) was higher than that reported previously (15%-20%) (7, 19-25). Before the adverse events meet the dose modification criteria defined beforehand, several patients required reduction of the erlotinib dose based on judgment by the attending physician, mostly because of grade 2 fatigue or anorexia. Although physicians consider early management of toxicities when treating the elderly especially, it may not always be easy to evaluate their physical condition objectively. The rate of dose reduction tends to be high in Japanese studies of EGFR-TKI compared to non-Japanese studies. Further studies are needed to clarify the influence of ethnic difference on the severity of erlotinib-induced toxicities.

It has been reported that the activity of enzymes that metabolize erlotinib (*i.e.* CYP3A4, CYP3A5, and CYP1A1)

might be reduced with increasing age (26, 27), and therefore a lower initial dose of erlotinib may be sufficient for elderly patients. A prospective study of low-dose erlotinib (50 mg/day) for frail or elderly patients is currently ongoing in Japan, and the results may be informative for future treatment planning.

In this study, the response rate of patients with *EGFR* mutation was somewhat lower than that reported previously (20, 21). In a phase II study involving unselected elderly patients with NSCLC, Jackman *et al*. reported that *EGFR* mutation status was closely correlated with DCR, and that the presence of an *EGFR* mutation was also associated with both survival and a longer time to progression. (19). Although our results are very similar, it remains unclear why the response rate in patients with EGFR mutation was lower in our study and that of Jackman *et al*. in comparison to other studies of patients with *EGFR* mutation. One possible explanation may be that the degree of tumor shrinkage may not directly affect the duration of response or survival in elderly patients. However, the result may just have been due to chance, as the numbers of patients with *EGFR* mutation in our study and that of Jackman *et al*. were only ten and nine, respectively.

In conclusion, although the percentage of patients in our study requiring for dose reduction seemed relatively higher than in previous reports, the toxicity profile was similar to that seen in other studies, and erlotinib was generally well tolerated. Erlotinib is a potentially useful therapeutic option for unselected elderly patients with previously treated advanced or recurrent NSCLC, as is the case for younger patients. However, further investigations to determine other factors in addition to *EGFR* mutations will be required in order to select patients who will benefit from erlotinib.

Conflicts of Interest

None declared.

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