Erlotinib as second- or third-line treatment in elderly patients with advanced non-small cell lung cancer: Keio Lung Oncology Group Study 001 (KLOG001)

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Abstract. The aim of this study was to assess the efficacy and safety of erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), as second- or third-line treatment for elderly Japanese patients with non-small-cell lung cancer (NSCLC). The patients eligible for this phase II trial were aged ≥70 years, had stage III/IV or recurrent NSCLC, and had previously received 1 or 2 chemotherapy regimens that did not include EGFR-TKIs. The patients received erlotinib at a dose of 150 mg/day. The primary endpoint was overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS) and toxicity. A total of 38 patients with a median age of 76 years were enrolled. The majority of the patients were men (66%), had an Eastern Cooperative Oncology Group performance status of 1 (58%), stage IV disease (66%) and adenocarcinoma (74%). Of the 35 patients, 13 (34%) had tumors with *EGFR* mutations. The ORR was 26.3% (95% confidence interval: 12.1-40.5%) and the disease control rate was 47.4%. The median PFS was 3.7 months and the median OS was 17.3 months. The grade 3 adverse events observed included rash (13%), diarrhea (5%), interstitial pneumonitis (5%), anorexia (3%) and gastrointestinal bleeding (3%). Grade 4 or 5 adverse events were not observed. The median OS did not differ significantly between patients aged <75 years (14.9 months) and those aged ≥75 years (19.0 months; P=0.226). Therefore, erlotinib was found to be effective and well-tolerated in elderly patients with previously treated NSCLC.

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). More than 80% of all lung cancers are non-small-cell lung cancers (NSCLCs) (2). Platinum-based chemotherapy has been widely accepted as the standard treatment for advanced NSCLC (3) and is appropriate for several patients with lung cancer. However, the use of traditional chemotherapeutic agents, such as platinum, has reached a therapeutic plateau.

Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is an effective standard second-line treatment for NSCLC, regardless of *EGFR* mutation status (4-8). In a previous phase III study (BR.21), erlotinib prolonged overall survival (OS) and progression-free survival (PFS) compared with placebo when used as second- or third-line treatment of NSCLC; the OS was 6.7 and 4.7 months [hazard ratio (HR)=0.61; P<0.001) and the PFS was 2.2 and 1.8 months (HR=0.70; P<0.001) in the erlotinib and placebo groups, respectively (4). According to certain reports, erlotinib may also be effective in Japanese patients with previously treated NSCLC, irrespective of their *EGFR* mutation status (7,8). However, driver oncogene-targeted therapy has met with great success (9-12) and EGFR-TKIs are generally more effective in patients with *EGFR* mutation-positive NSCLC. Approximately 35-50% of the NSCLCs in East Asian patients harbor *EGFR* mutations, which is higher compared with the percentage in Western populations (13,14). To accurately interpret the results of clinical trials, the proportion of patients with *EGFR* mutation-positive tumors should be taken into account.

Owing to the growing size of the aging population, the number of elderly patients with NSCLC is increasing (15). Although several clinical trials have demonstrated that

EGFR-TKIs are safe and effective, the safety and efficacy of these drugs specifically in elderly patients remains unclear. Evaluation of these drugs in such patients is necessary given the complications, organ dysfunction and metabolic changes that may accompany aging (16,17). A phase II trial of elderly NSCLC patients receiving erlotinib as second- or third-line treatment was performed by the Keio Lung Oncology Group (KLOG001). This trial included *EGFR* mutation-positive as well as *EGFR* mutation-negative tumors and was registered at the UMIN-CTR (study ID: UMIN000001873).

Patients and methods

Patient eligibility. Patients eligible for this study were aged ≥70 years and had confirmed stage III or IV or postoperative recurrent NSCLC. The patients were previously treated with 1 or 2 chemotherapy regimens that did not include EGFR-TKIs and had at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf). Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, life expectancy >3 months and adequate organ function. The main exclusion criteria were major surgery ≤4 weeks, thoracic radiation therapy ≤2 weeks, or chemotherapy ≤4 weeks prior to the trial, and the presence of active double cancer, active infection, interstitial lung disease, symptomatic brain metastasis, or severe comorbidities. This study was approved by the Institutional Review Board at Keio University School of Medicine. All the patients provided written informed consent.

Study design and treatment. This study was a single-arm multi-center phase II trial of second- or third-line erlotinib treatment in elderly patients with NSCLC. The primary endpoint was overall response rate (ORR) and the secondary endpoints were PFS, OS and toxicity. The estimated minimum sample size was 38, with an α error of 0.05 (one-sided) and a β error of 0.2. The threshold ORR was 10% (4,18) and the expected ORR was 25% (19). Assuming that ~5% of patients would not qualify, 40 patients were enrolled. Patients received erlotinib at 150 mg/day until the disease progressed, unacceptable toxicity developed despite dose reduction, or further treatment was refused. If grade 3 or 4 adverse events (AEs) occurred, treatment was withheld for up to 14 days and the dose was reduced. Two dose reductions were permitted per patient (first reduction to 100 mg/day, second reduction to 50 mg/day).

Evaluation. Tumor response was evaluated via computed tomography, magnetic resonance imaging and bone scintigraphy according to RECIST every 4 weeks until treatment cessation. To confirm a complete response (CR) or partial response (PR), a second assessment was conducted 28 days or more after the initial assessment. Stable disease (SD) was defined as disease control (absence of progression) maintained for ≥6 weeks. During this study, patients underwent physical and blood examinations and chest X-rays at least once every 2 weeks. AEs were graded according to the National Cancer Institute Common Terminology Criteria, version 4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). PFS and OS were estimated using the Kaplan-Meier method.

Results

Patient characteristics. Between April, 2009 and October, 2014, 40 patients were enrolled in this study. A total of 38 patients were eligible for treatment, whereas 2 patients were deemed ineligible owing to priorly receiving 3 chemotherapy regimens, or erlotinib treatment, respectively. The characteristics of the patients are summarized in Table I. The median patient age was 76 years (range, 70-83 years). The majority of the patients were men (66%) and had an ECOG PS of 1 (58%), stage IV disease (66%) and adenocarcinoma (76%). Biopsy samples from 35 patients were screened for gain-of-function *EGFR* mutations, and mutations were identified in 13 patients (34%): An exon 19 deletion in 5 patients and an L858R mutation in 8 patients. A total of 35 patients received platinum-based combination chemotherapy and 3 patients received monotherapy as first-line treatment. A total of 16 patients received chemotherapy (including gefitinib treatment in 2 patients) after this trial. A second biopsy was performed in 5 of the 13 patients with *EGFR* mutation-positive tumors (38%) and an *EGFR* T790 M mutation was identified in 3 of those 5 patients (60%).

Response. The efficacy results of this study are summarized in Table II. Among the 38 patients in the study, 10 had a PR, 8 had SD and 11 had progressive disease (PD). The ORR for all patients was 26.3% [95% confidence interval (CI): 12.1-40.5%] and the disease control rate (DCR), defined as CR+PR+SD/total number of patients, was 47.4% (95% CI: 31.2-63.6%). Among the 13 patients with *EGFR* mutations, 7 had a PR, 2 had SD and 2 had PD. The ORR for patients with *EGFR* mutations was 53.8% (95% CI: 26.2-71.4%) and the DCR was 69.2% (95% CI: 43.6-94.8%). Among the 22 patients with wild-type *EGFR*, 2 patients had a PR, 5 patients had SD and 9 patients had PD. The ORR for this group was 9.1% (95% CI: 0-21.3%) and the DCR was 31.8% (95% CI: 12.0-51.6%).

PFS and OS. All 38 patients in the study were included in the survival analysis, and the minimum follow-up time was 7 months. At the time of the analysis, 25 patients had succumbed to the disease, 11 patients remained alive, and 2 patients were lost to follow-up. The median PFS was 3.7 months (95% CI: 1.1-6.4; Fig. 1A) and the median OS was 17.3 months (95% CI: 13.3-21.3; Fig. 1B). The median OS was 14.9 months (95% CI: 9.7-20.1) in patients aged <75 years, and 19.0 months (95% CI: 13.7-24.2) in patients aged ≥75 years (log-rank test, P=0.226; Fig. 2).

The median PFS was 7.8 months (95% CI: 5.4-10.1) in patients with *EGFR* mutations and 2.1 months (95% CI: 1.6-2.6) in patients without *EGFR* mutations (log-rank test, P=0.07). The median OS was 25.1 months (95% CI: 20.1-30.0) and 14.9 months (95% CI: 2.5-27.4), respectively (log-rank test, P<0.05), and the median post-PD OS was 13.1 months (95% CI: 8.0-18.1) and 10.8 months (95% CI: 0-21.7), respectively (log-rank test, P=0.261).

Table I. Patient characteristics (all, <75 years and ≥75 years of age).

	Number of patients		
	All	<75 years	≥75 years
Total enrolled	38	15	23
Age (years), median (range)	76 (70-83)	72 (70-74)	79 (75-83)
Gender			
Male	25	9	16
Female	13	6	7
Smoking status			
Never-smoker	15	5	10
Current smoker or ever-smoker	23	10	13
Smoking index, median (range)	750 (0-2,600)	750 (0-1,800)	520 (0-2,600)
Performance status			
0	13	5	8
1	22	9	13
2	3	1	2
Stage			
IIIA	6	3	3
IIIB	3	0	3
IV	25	10	15
Postoperative recurrence	4	2	2
Histology			
Adenocarcinoma	29	13	16
Squamous cell carcinoma	6	2	4
Non-small-cell carcinoma-NOS	3	0	3
EGFR status			
Wild-type	22	10	12
Exon 19 deletion	5	2	3
L858R	8	3	5
Unknown/not examined	3	0	3
Prior chemotherapy			
One regimen	27	8	19
Two regimens	11	7	4
First-line treatment			
Platinum doublet	31	10	21
Platinum doublet + bevacizumab	4	4	0
Monotherapy	3	1	2

NOS, not otherwise specified; EGFR, epidermal growth factor receptor.

Toxicity. Erlotinib safety was assessed in all 38 patients in this study, and the AEs observed are summarized in Table III. The main AE was skin rash (76% of the patients). Grade 3 AEs occurred in 11 patients (29%) and included rash (13%), diarrhea (5%), interstitial pneumonitis (5%), anorexia (3%) and gastrointestinal (GI) bleeding (3%). Grade 4 or 5 AEs were not observed. A total of 10 patients (26%) discontinued erlotinib due to the following AEs: Rash (3 patients), elevated creatinine level and interstitial pneumonitis (2 patients), and anorexia, diarrhea and GI bleeding (1 patient). The dose of erlotinib was reduced in 10 patients (26%) due to rash (7 patients), anorexia (2 patients), or diarrhea (1 patient).

Discussion

This study investigated the efficacy and safety of erlotinib as second- or third-line treatment for elderly Japanese patients with NSCLC. The ORR, which was the primary endpoint of this study, was 26.3% (95% CI: 12.1-40.5%), which exceeded the threshold ORR (10%). This percentage (26.3%) was higher compared with those observed in the BR.21 phase III study of erlotinib as a second- or third-line treatment for NSCLC patients [8.9% for all patients (n=427) and 7.6% for elderly patients (aged ≥70 years, n=112)] (4,20). In a phase II trial of erlotinib as second- or third-line treatment for elderly (aged

Table II. Response assessment.

Type of response	No. of patients			
	Total	*EGFR* mutant	*EGFR* wild-type	Unknown or not examined
Complete response	0	0	0	0
Partial response	10	7	2	1
Stable disease	8	2	5	1
Progressive disease	11	2	9	0
Not evaluable	9	2	6	1
Total	38	13	22	3
Response rate (%)	26.3	53.8	9.1	
Disease control rate (%)	47.4	69.2	31.8	

EGFR, epidermal growth factor receptor.

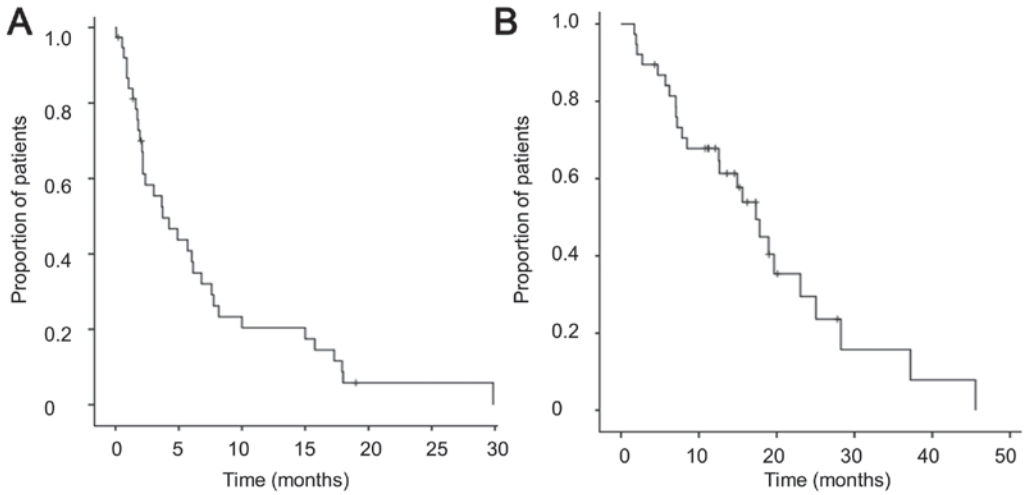

Figure 1. Kaplan-Meier curve analysis for (A) progression-free survival and (B) overall survival in all the patients.

≥65 years) Italian patients with advanced NSCLC (n=31), the ORR was 16% (6). We hypothesized that the higher ORR in our study reflects the inclusion of a higher proportion of patients with *EGFR* mutation-positive tumors. All the patients in our study were Japanese, and tumors with *EGFR* mutations are most common among Asian patients (9,13). In the BR.21 study, Asian patients (n=53) had a higher ORR compared with patients of other nationalities (n=374) (18.9 vs. 7.5%, respectively; P=0.02) (4). Other reported ORRs for erlotinib were similar to ours: 28.3% (95% CI: 17.5-41.4%) in a Japanese phase II study of 60 previously treated NSCLC patients of various ages (7), and 28.3% (95% CI: 16.0-43.5) in a Japanese phase II trial of 46 NSCLC patients (21). Both those studies were conducted on populations not selected for *EGFR* mutations. Overall, the elderly patients in our trial and the Japanese patients of all ages in previous trials had similar ORRs.

In a retrospective analysis of several Japanese studies, the efficacy of erlotinib in terms of survival and tolerability was not lower among elderly compared with younger patients. In a retrospective subgroup analysis of data collected from a population-based observational study, the PFS was similar in elderly (aged ≥75 years, n=74) and younger (aged <75 years, n=233) patients (median PFS, 62 vs. 46 days; 95% CI: 44-80 vs. 35-53 days, respectively; P=0.2475) receiving erlotinib for the treatment of NSCLC, regardless of treatment line or *EGFR* mutation status (22). In that study, OS was also similar between elderly (median, 170 days; 95% CI: 142-239 days) and younger patients (median, 146 days; 95% CI: 114-185 days, P=0.764). There was also no difference in the incidence of AEs between these groups, and all AEs were manageable. In a phase IV surveillance study of Japanese patients with previously treated NSCLC (the *EGFR* mutation status was not defined), the median PFS was 65 days for patients aged <75 years (95% CI: 62-68 days), 74 days for patients aged 75-84 years (95% CI: 69-82 days), and 72 days for patients aged ≥85 years (95% CI: 56-93 days) (23). Moreover, the toxicities were similar in all 3 age groups. In our study, the median OS was 17.3 months and was longer in patients aged ≥75 years compared with that in patients aged <75 years (19.0 vs. 14.9 months, respectively), although this difference was not statistically significant (P=0.226). Erlotinib was considered to be a tolerable and effective treatment for NSCLC patients, irrespective of their age.

Table III. Adverse events.

Toxicities	All-grade (%)	Grade 3 (%)	Grade 4/5 (%)
Rash	29 (76)	5 (13)	-
Stomatitis	10 (26)	-	-
Diarrhea	9 (23)	2 (5)	-
Fatigue	2 (5)	-	-
Anorexia	4 (11)	1 (3)	-
Elevated creatinine	4 (11)	-	-
Elevated bilirubin	3 (8)	-	-
Elevated hepatic transaminases	2 (5)	-	-
Gastrointestinal bleeding	2 (5)	1 (3)	-
Pneumonitis	2 (5)	-	-
Interstitial pneumonitis	2 (5)	2 (5)	-

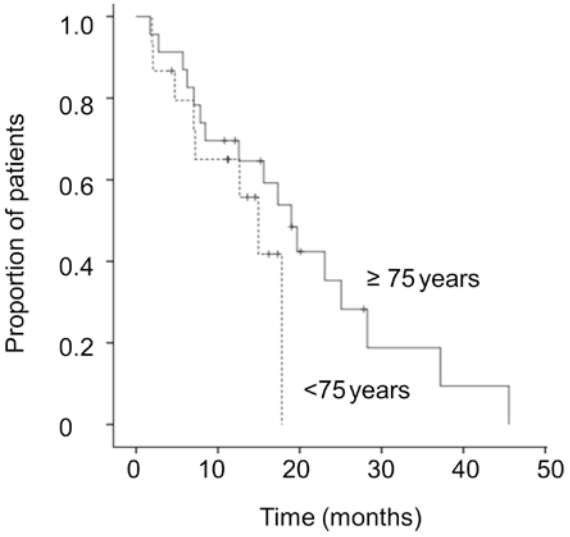

Figure 2. Kaplan-Meier curves for overall survival by age group (age <75 vs. ≥75 years).

In our study, the OS was significantly longer in patients with *EGFR* mutation-positive tumors compared with that in patients with *EGFR* mutation-negative tumors. The PFS and post-PD OS were also longer, although the difference was not statistically significantly. To date, 2 prospective trials have enrolled elderly NSCLC patients according to their *EGFR* mutation status: One was a phase II study of elderly patients (aged ≥75 years) with *EGFR* mutation-positive NSCLCs who received erlotinib as first- or second-line treatment (n=32). In that study, the ORR was 56.3% (95% CI: 39.4-72.0%) and the median PFS was 15.5 months (95% CI: 11.2-not reached) (24). The second prospective clinical trial examined elderly patients (aged ≥70 years) with *EGFR* mutation-negative tumors in the second- and third-line settings (25). This small phase II trial (n=16) reported an ORR of 0% (95% CI: 0-17.1%), a median PFS time of 1.7 months (95% CI: 1.3-2.2 months) and a median OS time of 7.2 months (95% CI: 5.6-8.7 months); however, it was terminated early as a phase III trial (26) found that docetaxel was superior to erlotinib in terms of PFS and ORR in patients with *EGFR* mutation-negative tumors. The results of the two prospective studies cited above (24,25) suggested that erlotinib should be administered only to patients with *EGFR* mutations, even in the second- and third-line settings. However, in our study, 2 of the 22 patients with *EGFR* mutation-negative tumors, and 1 of the 3 patients with tumors in which the *EGFR* mutation status was unknown, responded to erlotinib (ORR=12.0%; DCR=36.0%). These responses suggest that erlotinib remains a viable second- or third-line treatment option for elderly patients with NSCLC.

In the BR.21 study, elderly patients (aged ≥70 years) had more severe (grade 3 or 4) AEs compared with younger patients (aged <70 years) (35 vs. 18%, respectively; P<0.001) (20). In our study, 11 patients (29%) had grade 3 AEs, most of which were managed via dose reductions. Grade 4 or 5 AEs were not observed. Two patients had grade 3 interstitial pneumonitis and were treated with corticosteroid therapy. The frequency of AEs in our study was not higher compared with the previously reported frequencies (28.1-35%) (20,24). Therefore, erlotinib appears to be well-tolerated in elderly patients with previously treated NSCLC.

A limitation of our study was its small sample size, which precluded us from drawing definitive conclusions from the results of the main analysis and subset analysis. However, our study recruited a larger number of patients compared with previous prospective studies of elderly NSCLC patients in Japan (24,25). The definition of elderly patients varies across trials. For the present trial, age ≥70 years was used as an inclusion criterion, which was standard at that time (20,25). In accordance with the current standard definition for 'elderly' NSCLC patients (22,23), ≥75 and <75 years of age was used in our comparison of 'latter-stage elderly' and 'early elderly' patients, respectively. There were no significant differences in response, survival, or toxicity between these age groups.

In conclusion, our phase II study demonstrated the efficacy and safety of erlotinib as second- and third-line treatment for elderly patients with NSCLC, regardless of whether they were 'early elderly' or 'latter-stage elderly' patients.

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