Epidermal growth factor receptor-tyrosine kinase inhibitors for non-small-cell lung cancer patients aged 80 years or older: A retrospective analysis

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Abstract. The efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in elderly patients with non-small-cell lung cancer (NSCLC) remains uncertain. This retrospective study aimed to evaluate the efficacy and feasibility of EGFR-TKIs for NSCLC patients aged ≥80 years. We analyzed data from 21 NSCLC patients aged ≥80 years who were administered gefitinib and/or erlotinib between January, 2009 and December, 2014. The clinical characteristics, smoking status, type of *EFGR* mutation and the efficacy and toxicity of EGFR-TKIs were evaluated in these patients. In total, 14 (66.7%), 5 (23.8%) and 2 patients (9.5%) displayed partial response, stable disease and progressive disease, respectively. The median progression-free survival was 182 days, whereas the median overall survival was 371 days. Adverse events ≥grade 2 were as follows: skin toxicities, 12 patients; liver function test abnormalities, 7 patients; anorexia, 3 patients; and diarrhea, 2 patients. Dose reduction of EGFR-TKIs due to adverse events was required in 15 patients (71.4%). Although gefitinib and erlotinib therapy may be beneficial in patients aged ≥80 years, EGFR-TKI dose modification may be necessary according to the overall medical condition of elderly patients. Further studies are required to evaluate our findings.

Introduction

Lung cancer is one of the most common cancers worldwide, with non-small-cell lung cancer (NSCLC) accounting for ~80% of the cases (1,2). The risk of lung cancer clearly increases with advancing age and, with the prolongation of life expectancy, the number of elderly patients with lung cancer is expected to rapidly increase (3-5). According to the USA National Surveillance, Epidemiology and End Results database, approximately half of the patients with lung cancer were aged ≥70 years. In addition, 14% of the patients with lung cancer were aged at least 80 years (6,7). As a significant proportion of the NSCLC patients who are aged ≥80 years present with advanced disease, a poor performance status (PS) at diagnosis and several comorbidities, there is a need for the development of suitable chemotherapy for such patients.

Recently, several reports described the safety and efficacy of gefitinib in patients with epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC aged >70 years and/or with a poor PS (2-4,7-9). The safety and efficacy of erlotinib in elderly patients with NSCLC were also reported (10,11). Gefitinib and erlotinib are orally active EGFR-tyrosine kinase inhibitors (EGFR-TKIs), which have displayed notable efficacy in patients with advanced NSCLC (2,12-14). Since the hematological toxicity of EGFR-TKIs is lower compared to that of cytotoxic chemotherapy, they may be of value as treatment for elderly patients and/or patients with poor PS.

However, the efficacy and toxicity of EGFR-TKIs in NSCLC patients aged ≥80 years have not been fully evaluated. Whether standard anticancer therapy in extremely elderly patients with lung cancer is always safe in clinical practice remains unclear. In this study, we retrospectively assessed the value and safety of EGFR-TKIs in such patients.

Patients and methods

Patients. A total of 23 patients aged ≥80 years with NSCLC were treated with EGFR-TKIs between January, 2009 and December, 2013 at Kainan Hospital (Yatomi, Aichi, Japan). Two patients were excluded from this analysis, as they were administered EGFR-TKIs for only a few days and data on treatment efficacy and toxicity were not available. Accordingly, a total of 21 patients were included in this analysis. The gefitinib group included patients who were treated with gefitinib alone

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or with gefitinib followed by erlotinib. The erlotinib group included patients treated with erlotinib alone or with erlotinib followed by gefitinib. In the gefitinib group, the patients were treated with oral gefitinib 250 mg daily, 250 mg every other day, or 250 mg every 3 days. In the erlotinib group, the patients were treated with oral erlotinib 150, 100, or 50 mg daily. The administration of EGFR-TKIs was continued until worsening of the general status, the development of unacceptable toxicity regardless of dose reduction, or the patients' refusal to continue treatment.

This study was approved by the Ethics committee of Kainan Hospital, Aichi Prefectural Welfare Federation of Agricultural Cooperatives. Written informed consent was obtained from all the patients prior to the initiation of EGFR-TKI treatment.

Patient characteristics and evaluation of response to treatment and toxicity. The patient characteristics, including the type of *EGFR* mutation, were retrospectively obtained from medical records. *EGFR* mutations were analyzed using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (15) up to July, 2012. From August, 2012 onwards, EGFR exon 19 deletion was determined by fragment analysis and L858R point mutation was detected using the cycleave polymerase chain reaction technique (16). The patients were staged according to the 7th edition of the Union for International Cncer Control TNM classification prior to treatment initiation (17). The patients' adverse events, tolerance and response to treatment were retrospectively analyzed. Tumor response were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), in accordance with the Response Evaluation Criteria for Solid tumors, version 1.1 (18). Toxicities were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40)).

Statistical analysis. Progression-free survival (PFS) and overall survival (OS) rates were analyzed by the Kaplan-Meier method. PFS was measured from the date of initiation of gefitinib or erlotinib therapy to the date of progressive disease, death, or last follow-up. OS was defined as the time between the initiation of treatment and death or last follow-up. All the statistical analyses were performed with EZR statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics (19).

Results

Patient characteristics. The patients' characteristics are summarized in Table I. There were 8 male (38.1%) and 13 female (61.9%) patients, with a median age of 85 years (range, 80-96 years). A total of 8 patients (38.1%) had an Eastern Cooperative Oncology Group PS of 2-3, whereas the remaining 13 patients had a PS of 0-1. A total of 15 patients (71.4%) were never smokers and 6 (28.6%) were former smokers. Adenocarcinoma comprised the majority of the cancers (85.7%). *EGFR* status was analyzed in 20 patients and *EGFR* mutations were identified in 17 patients (81%). Of the 21 patients, 4 (19%) had clinical stage IIIA disease at diagnosis, whereas the remaining 17 (81%) had stage IV disease. A total of 5 patients received prior anticancer therapy; namely, 2 patients received cytotoxic chemotherapy (non-platinum-based chemotherapy), 2 patients received radiation therapy and 1 patient underwent surgery.

Table I. Patient characteristics.

Characteristics	Patient no. (n=21)
Age, years	85 (80-96)
Median (range)	
Sex	
Male	8
Female	13
ECOG performance status	
0	4
1	9
2	5
3	3
4	0
Smoking status	
Never	15
Former	6
Current	0
Histology	
Adenocarcinoma	18
Squamous cell carcinoma	2
Unknown	1
Clinical stage at diagnosis	
IIIA	4
IIIB	0
IV	17
EGFR mutation	
Exon 19 deletion	5
L858R	12
Negative	3
Unknown	1
Prior therapy	
None	16
Radiation	2
Cytotoxic chemotherapy	2
Surgery	1

ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.

Patient EGFR status, treatment and outcomes. The characteristics and outcomes of the enrolled patients are listed in Table II. Of the 21 patients, 18 were administered gefitinib and 3 were administered erlotinib. As regards *EGFR* mutations,

Table II. Patient characteristics and response to gefitinib or erlotinib therapy.

Case no.	Age (yrs)	Gender	*EGFR* mutation[a]	Type of EGFR-TKI	Dose reduction[b]	Response	Time to progression (days)	Survival (days)	Subsequent therapy	Beyond PD[c]
1	85	F	L858R	Gefitinib	Yes	PR	260	452	None	Yes
2	85	F	Wild-type	Gefitinib	No	PD	13	70	None	No
3	82	F	L858R	Gefitinib	Yes	PR	224	446	None	Yes
4	81	F	L858R	Gefitinib	Yes	PR	493	865	Pemetrexed	No
5	86	F	Unkown	Gefitinib	Yes	PR	159	192	None	No
6	81	F	Exon 19 del	Gefitinib	Yes	PR	223	371	None	Yes
7	81	M	L858R	Gefitinib	Yes	PR	96	183	None	Yes
8	85	F	Exon 19 del	Gefitinib	Yes	SD	733	854	None	Yes
9	88	F	L858R	Gefitinib	Yes	SD	851	965	None	No
10	83	F	Wild-type	Erlotinib	No	SD	63	99	None	No
11	81	F	Exon 19 del	Gefitinib	Yes	PR	188	734	Erlotinib	No
12	96	M	L858R	Erlotinib	Yes	PR	84	107	None	No
13	86	F	L858R	Gefitinib	Yes	PR	272	710	None	Yes
14	81	M	L858R	Gefitinib	No	SD	554	661	None	No
15	83	F	L858R	Gefitinib	Yes	PR	112	580	Erlotinib	No
16	80	M	Wild-type	Erlotinib	Yes	SD	55	361	Radiation	No
17	85	M	Exon 19 del	Gefitinib	No	PD	12	12	None	No
18	85	M	L858R	Gefitinib	No	PR	66	172	Erlotinib	No
19	90	M	Exon 19 del	Gefitinib	Yes	PR	166	341	Erlotinib	Yes
20	80	M	L858R	Gefitinib	Yes	PR	182	221	None	No
21	89	F	L858R	Gefitinib	No	PR	273	273	None	No

[a]L858R: leucine to arginine at codon 858 (exon 21). [b]Dose reduction of EGFR-TKIs due to EGFR-TKI-related adverse events; [c]First EGFR-TKI therapy beyond disease progression. M, male; F, female; PR, partial response; SD, stable disease; PD, progressive disease; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

12 patients carried the L858R mutation in exon 21 and 5 carried deletions in exon 19. The median treatment duration was 197 days (range, 12-965 days). No patients achieved CR, whereas 14 patients (66.7%) achieved PR. The disease control rate, defined as the percentage of patients who achieved CR, PR, or SD, was 90.5%. Dose reduction of EGFR-TKIs due to adverse events was required in 15 patients (71.4%). A total of 7 patients (33.3%) continued with the EGFR-TKI therapy beyond PD. In the gefitinib group, 4 patients received subsequent erlotinib therapy following termination of gefitinib therapy. The average follow-up duration was 413 days (range, 12-965 days). The median PFS was 182 days (Fig. 1) and the median OS was 371 days (Fig. 2). Of the 17 patients harboring *EGFR* mutations, 13 (76.5%) achieved PR and the median PFS and OS were 223 and 452 days, respectively.

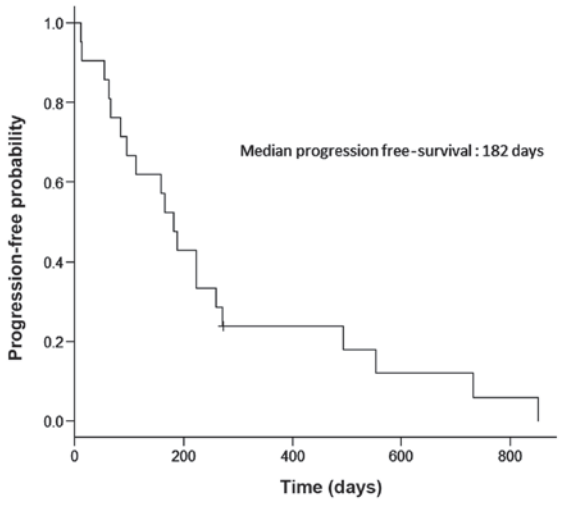

Figure 1. Kaplan-Meier curve for progression-free survival in the 21 patients treated with epidermal growth factor receptor-tyrosine kinase inhibitors. Median progression-free survival, 182 days.

Adverse events. The treatment-related adverse events are summarized in Table III. The most common adverse event associated with EGFR-TKIs was skin toxicities (57.1%). Skin toxicities ≥grade 2 were as follows: skin rash, 9 patients (42.9%); dry skin, 6 patients; (28.6%); pruritus, 5 patients (23.8%); and paronychia, 3 patients (14.3%). Liver function test abnormalities ≥grade 2 were observed in 7 patients (33.3%). Other adverse events ≥grade 2 were as follows: anorexia, 3 patients (14.3%); diarrhea, 2 patients (9.5%); general fatigue, 2 patients (9.5%); and anemia, leukopenia, elevated amylase and nausea, 1 patient each (4.8%). Adverse events ≥grade 4 or interstitial lung disease (ILD) were not observed in this study.

Table III. Adverse events.

Toxicity	Grade, no.				≥Grade 1, no. (%)	≥Grade 2, no. (%)
	1	2	3	4		
Skin rash	5	4	5	0	14 (66.7)	9 (42.9)
Dry skin	3	4	2	0	9 (42.9)	6 (28.6)
Pruritus	1	3	2	0	6 (28.6)	5 (23.8)
Paronychia	1	3	0	0	4 (19.0)	3 (14.3)
Diarrhea	7	2	0	0	9 (42.9)	2 (9.5)
Nausea	2	1	0	0	3 (14.3)	1 (4.8)
Vomiting	2	0	0	0	2 (9.5)	0 (0.0)
Anorexia	3	2	1	0	6 (28.6)	3 (14.3)
Stomatitis	3	0	0	0	3 (14.3)	0 (0.0)
Dysgeusia	2	0	0	0	2 (9.5)	0 (0.0)
Dry mouth	1	0	0	0	1 (4.8)	0 (0.0)
Elevated AST/ALT/ALP	4	4	3	0	11 (52.4)	7 (33.3)
Elevated amylase	0	0	1	0	1 (4.8)	1 (4.8)
Interstitial lung disease	0	0	0	0	0 (0.0)	0 (0.0)
Leukopenia	1	1	0	0	2 (9.5)	1 (4.8)
Anemia	0	1	0	0	1 (4.8)	1 (4.8)
Thrombocytopenia	0	0	0	0	0 (0.0)	0 (0.0)
Epistaxis	2	0	0	0	2 (9.5)	0 (0.0)
Increased creatinine	1	0	0	0	1 (4.8)	0 (0.0)
General fatigue	1	2	0	0	3 (14.3)	2 (9.5)
Leg edema	1	0	0	0	1 (4.8)	0 (0.0)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

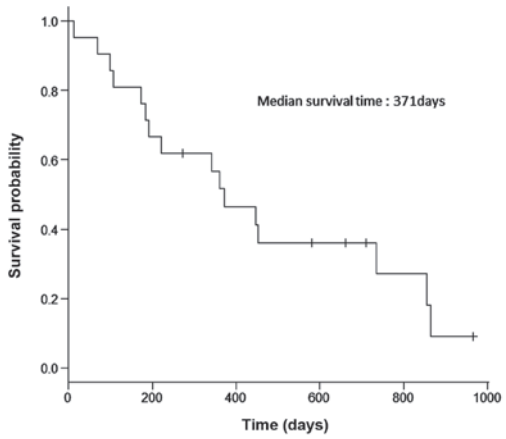

Figure 2. Kaplan-Meier curve for overall survival in the 21 patients treated with epidermal growth factor receptor-tyrosine kinase inhibitors. Median survival time, 371 days.

Discussion

Gefitinib and erlotinib have displayed acceptable efficacy in NSCLC patients aged ≥80 years. However, a dose reduction of EGFR-TKIs due to adverse events were required in >70% of our study subjects. To the best of our knowledge, this is the first study targeting extremely elderly patients with NSCLC who were treated with EGFR-TKIs.

Several recent studies described the efficacy of gefitinib and erlotinib for elderly patients with NSCLC (3,4,7-11,20,21). In studies of elderly patients not selected by *EGFR* mutation status, the overall response rates (RRs) were 10-25%, the median PFS was 2.7-4 months and the median OS was 7.6-11.9 months (4,7,10,11,20). By contrast, in studies of *EGFR* mutation-positive elderly patients, the overall RRs were 59-74%, the median PFS was 12.3-13.8 months and the median OS was 17.4-29.1 months (3,8,9,21). In our study, the overall RR was 66.7%, the median PFS was 6.1 months and the median OS was 12.4 months. A total of 17 patients (81%) had sensitive *EGFR* mutations in this study and, among these patients, PR was observed in 76.5% of patients and the median PFS and OS were 7.4 and 15.1 months, respectively. The high prevalence of *EGFR* mutation is considered to reflect that mutation-positive patients are more likely to receive gefitinib or erlotinib therapy compared to *EGFR* mutation-negative patients. As regards the efficacy of EGFR-TKI therapy, considering the age of our study population, the results of our study may be considered acceptable in comparison to those of previous studies.

Elderly patients with lung cancer prefer to receive less toxic anticancer chemotherapy (7). Such patients generally present with more comorbidities and more compromised organ functions compared to younger patients; even elderly patients with a good PS may be at higher risk of severe toxicity compared to younger patients (3,22). A subgroup analysis of the BR.21 study revealed that elderly patients with NSCLC who were

treated with erlotinib displayed similar efficacy as younger patients, but experienced more significant toxicity (3,23). In addition, advanced age has been reported to be a risk factor for ILD in Japanese subjects during gefitinib treatment (24). Therefore, extremely elderly patients who were treated with EGFR-TKIs should be carefully monitored for adverse events. In previous studies, dose reduction or discontinuation of EGFR-TKIs due to adverse events was observed in 19-51.5% of the patients (3,7,10,11,25,26), whereas in our study, 76.1% of the patients required dose reduction or discontinuation (dose reduction in 15 patients and treatment discontinuation in 1 patient, due to liver function test abnormalities). There were no fatal toxicities, including ILD, whereas almost all types of toxicity were manageable by dose modification in both EGFR-TKI groups. Satoh *et al* (25) reported that low-dose gefitinib was clinically comparable to standard-dose gefitinib for NSCLC in patients with sensitive *EGFR* mutations. Therefore, we may be able to suggest that reduced-dose gefitinib and erlotinib therapy may be suitable for extremely elderly patients.

The limitations of our study were the small sample size, retrospective nature, heterogeneity of the treatment regimens and being a single-arm study. As our study was based on clinical data from a small sample of patients in a single facility, larger prospective trials on patients aged ≥80 years treated with EGFR-TKIs should be conducted to reveal the true efficacy and toxicity of this treatment. In addition, as Togashi *et al* reported that 150 mg erlotinib daily was associated with more toxicity and less tolerability compared to 250 mg gefitinib daily (12), an independent research program regarding gefitinib and erlotinib therapy should be conducted.

In conclusion, reduced-dose gefitinib or erlotinib therapy may be an effective and tolerable regimen for NSCLC patients aged ≥80 years, particularly those with *EGFR* mutations. The information presented in our study may provide some directions for clinical research on the treatment of such patients. However, further large studies are required to validate our findings.

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