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A Retrospective Comparison of the Clinical Efficacy of Gefitinib, Erlotinib, and Afatinib in Japanese Patients With Non-Small Cell Lung Cancer

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Tyrosine kinase inhibitors (TKIs) are very effective against non-small cell lung cancer (NSCLC) caused by epidermal growth factor receptor (EGFR) mutation. Before the approval of osimertinib in March 2016, there were only three available EGFR TKIs (gefitinib, erlotinib, and afatinib) for the therapy of NSCLC in Japan. Osimertinib can be indicated only against $T790M^+$ lung cancer as a second-line therapy. However, whether gefitinib, erlotinib, or afatinib is most appropriate as a first-line therapy is still a controversial issue. The aim of this study was to compare the effectiveness of gefitinib, erlotinib, and afatinib. We retrospectively reviewed the records of 310 patients with the diagnosis of EGFR mutation-associated NSCLC including 147 patients treated with EGFR TKIs. Time to treatment failure and overall survival were evaluated. There were no significant differences in time to treatment failure (gefitinib: 9.2 months; erlotinib: 9.8 months; afatinib: 13.1 months) and overall survival (gefitinib: 27.3 months; erlotinib: 29.3 months; afatinib data not available) among NSCLC patients treated with the three different EGFR TKIs. Subgroup analysis showed that smoking status has a significant influence on both time to treatment failure and overall survival. In conclusion, this study showed comparable clinical efficacy of gefitinib, erlotinib, and afatinib in Japanese patients with NSCLC.

Key words: Gefitinib; Erlotinib; Afatinib; Non-small cell lung cancer (NSCLC); Epidermal growth factor receptor (EGFR) mutation; Adenocarcinoma; Japanese population

INTRODUCTION

Non-small cell lung cancer (NSCLC) is one of the major causes of death worldwide[1]. Therapy with cytotoxic drugs is associated with 20%–35% response rate and 10–12 months of median survival time among patients with advanced NSCLC[2]. Subsequent clinical trials have shown the significant efficacy of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in NSCLC associated with EGFR mutation[3,4]. Before the approval of osimertinib in March 2016, there were only three available EGFR TKIs (gefitinib, erlotinib, and afatinib) for the therapy of NSCLC in Japan. Phase III clinical trials have clearly demonstrated the superior efficacy of EGFR TKIs over standard chemotherapy for improving progression-free survival (PFS)[5–9]. Therefore, EGFR TKIs are presently recommended as first-line therapy of lung tumors caused by EGFR mutation[10]. However, whether gefitinib, erlotinib, or afatinib should be used as the first-line therapy still remains as a controversial issue.

A few prospective trials have demonstrated similar effects of gefitinib and erlotinib on PFS and superiority of afatinib over gefitinib to improve PFS[11–13]. The LUX-Lung 7 trial has shown that afatinib significantly prolongs PFS but not overall survival (OS) compared to gefitinib[12]. In addition, while the combined analysis of both LUX-Lung 3 and 6 has shown that afatinib is effective in tumors with Ex19 deletion but not in those with L858R mutation, the results of the LUX-Lung 7 trial demonstrated no difference in efficacy between tumors with Ex19 deletion and L858R mutation[8,12,14,15]. These previous contradicting reports underscore the importance of determining which of the EGFR TKIs should be the best indication as a first-line therapy for EGFR mutant-positive NSCLC.

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The aim of this retrospective study was to evaluate and compare the efficacy of gefitinib, erlotinib, and afatinib in NSCLC caused by EGFR mutation in a Japanese population.

MATERIALS AND METHODS

Patients

The electronic medical records of 310 EGFR mutation-related NSCLC patients who were diagnosed and treated at the Mie Prefectural General Medical Center and Matsusaka Municipal Hospital from January 2010 through April 2016 were evaluated. Among all patients, 162 received surgical treatment and 147 therapy with gefitinib ($n=83$), erlotinib ($n=36$), or afatinib ($n=28$), and 1 patient surgically treated received TKI because of tumor recurrence. The dose of gefitinib was 250 mg/day, erlotinib 150 mg/day, and afatinib 40 mg/day. Time to treatment failure (TTF) was the primary endpoint and OS the secondary endpoint (Fig. 1). In the subgroup analysis, TTF and OS were calculated after categorizing the patients by sex, smoking habit, EGFR mutation (Ex 19 del or L858R), and by the presence or absence of brain metastasis regardless of the EGFR TKI used for the treatment. Data collection was terminated on February 28, 2017. The study was approved by the Institutional Ethical Committee for Clinical Investigation of Matsusaka Municipal Hospital and Mie Prefectural General Medical Center (Approval date: April 2016; Approval No. 150401-1).

Genetic Testing

Genetic analysis to determine EGFR mutation was performed at LSI Medience Corporation (Tokyo, Japan) using the PCR clamp method.

Statistical Analysis

TTF was defined as the period from the day of starting induction therapy with any EGFR TKI to the day of its discontinuation for any cause. OS was calculated from the date of induction therapy with EGFR TKI to the date of death for any cause. Patients alive on February 28, 2017, were considered as censored cases. Survival curves were drawn using the Kaplan–Meier method, and statistical differences were calculated by the log-rank test. Values of $p<0.05$ were considered as statistically significant. All statistical analyses were performed using the SPSS software version 23.0 (IBM Japan, Ltd., Tokyo, Japan).

RESULTS

Characteristics of the Patients

Among 310 EGFR mutation-associated NSCLC patients, 147 were at clinical stage 3A/B or stage 4, and 1 with postsurgical recurrence received therapy with gefitinib, erlotinib, or afatinib. There was a significant difference in age between the treatment arms but not between other variables (Table 1).

TTF and OS in Patients Treated With Each TKI

The median TTF was not significantly different between patients treated with gefitinib (9.2 months), erlotinib (9.8 months), or afatinib (13.1 months) (Fig. 2A). The median OS was not significantly different between patients treated with gefitinib (27.3 months) and erlotinib (29.3 months) (Fig. 2B). The survival of the group of patients treated with afatinib could not be recorded, and thus the data were unavailable.

Subgroup Analysis

Smoking status significantly affected both TTF and OS, and the presence of brain metastasis was found to be significantly associated with worse survival (Fig. 3).

DISCUSSION

Gefitinib, a first-generation TKI, was approved in 2002 for use in patients with lung cancer in Japan. Early studies have shown cases with dramatic therapeutic response to gefitinib as well as cases without any response[3,4]. Subsequent large population clinical trials demonstrated that patients responsive to gefitinib with significant prolongation of

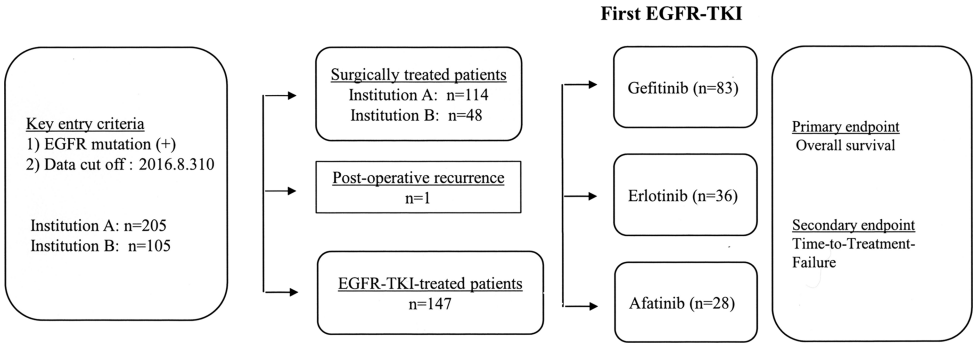

Figure 1. Flowchart of the patient selection process. Patients positive for EGFR mutation treated with tyrosine kinase inhibitors were included in the study.

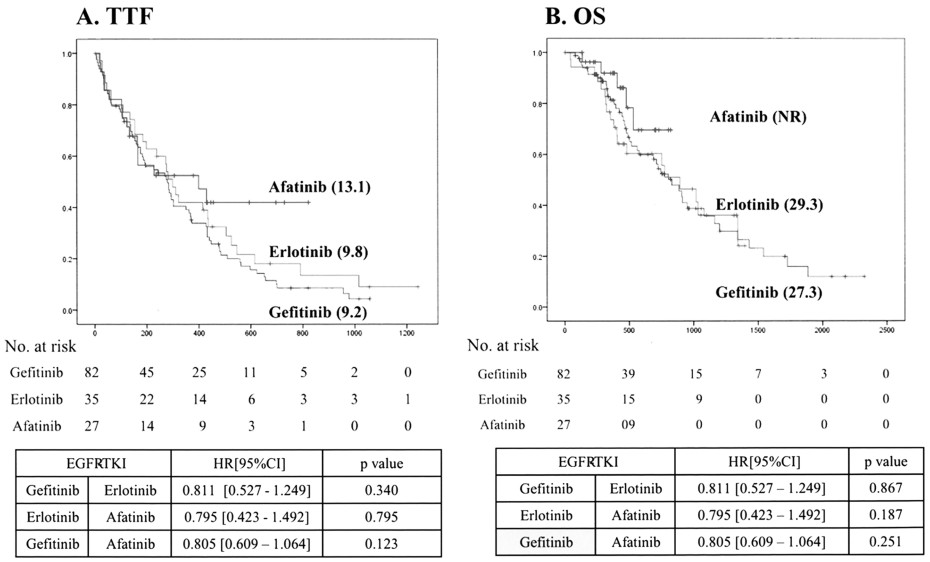

Figure 2. The time to treatment failure (TTF) and overall survival (OS) in patients treated with each tyrosine kinase inhibitor. The values of TTF (A) and OS (B) were not significantly different between the treatment groups.

PFS harbored a mutation in the EGFR gene[6,16]. Mutation of the EGFR gene occurs much more frequently in the Asian population, including Japan, than in Caucasians[17]. Among Japanese patients with lung adenocarcinoma, around 50% have the EGFR gene mutation[17]. Exon 19 deletion and L858R are the two major mutations. Takano et al. reported that therapy with gefitinib prolongs twice the medial survival time of patients with EGFR mutation[18]. The first-generation TKIs, gefitinib and erlotinib, and the second-generation TKI, afatinib, are currently available for use as first-line therapy in NSCLC patients[10]. Of the two first-generation TKIs, erlotinib can reach higher concentrations in blood and cerebrospinal fluid and shows more clinical efficacy in cases with leptomeningeal carcinomatosis than gefitinib[19,20]. Therapeutic effectiveness surpassing that of the first-generation TKIs has been expected from afatinib, the second-generation TKI, because afatinib has been reported to bind irreversibly

Table 1. Demographic Data of the Patients Treated With Tyrosine Kinase Inhibitors

Variables	Gefitinib ($n=83$)	Erlotinib ($n=36$)	Afatinib ($n=28$)	p Value
Median age [year (range)]	75 (50–95)	72 (52–87)	68 (37–82)	0.014
Sex				0.849
Female	54	22	19	
Male	29	14	9	
Smoking status				0.153
Never	58	18	22	
Former	14	13	5	
Current	9	2	1	
Unknown	2	3	0	
Histological subtype				0.120
Adenocarcinoma	78	33	23	
Squamous cell carcinoma	1	0	3	
Other	4	3	2	
Clinical stage				0.742
3A	20	10	8	
3B	5	3	3	
4	58	23	16	
Recurrent	0	0	1	

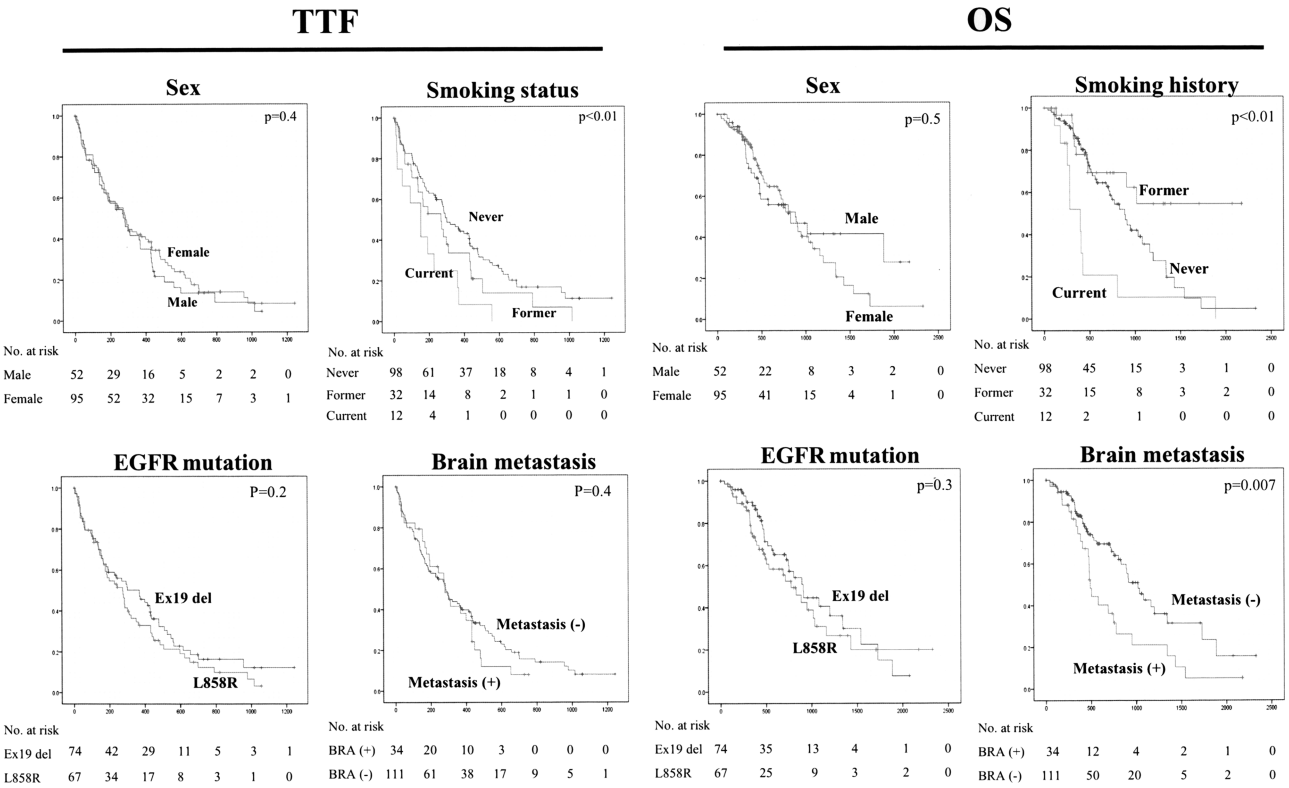

Figure 3. Subgroup analysis. Patients who smoked had significantly worse TTF and OS than nonsmokers, and there was a significant difference in TTF and OS between patients with and without brain metastasis.

to EGFR and to have strong antitumor activity in cancer cell lines positive for the T790M mutation[21].

In the present study, to get more information on the comparative efficacy of gefitinib, erlotinib, and afatinib, we retrospectively evaluated the clinical response to each TKI in the real-world clinical practice in the Japanese population. The selection of TKI was done by the attending physician based on the age, sex, constitution, performance status of the patients, and presence of adverse effects. Compared to patients treated with erlotinib and afatinib, patients treated with gefitinib were aged subjects and showed significantly less frequent and milder grade of adverse effects. However, comparable values of TTF and OS were observed in patients treated with gefitinib, erlotinib, or afatinib. These observations suggest that gefitinib tends to be used more commonly in the aging population than erlotinib or afatinib.

TTF tended to be longer in patients treated with afatinib than in those treated with gefitinib or erlotinib. Dose reduction of afatinib from 40 mg/day to 30 and 20 mg/day was also possible in many cases, although we have not performed a strict evaluation of the TKI dose. OS was assessed in patients treated with gefitinib or erlotinib, but not in those treated with afatinib because of the short observation period in the afatinib-treated group. In agreement with previous studies, never smokers had more prolonged OS than smokers[22]. OS, but not TTF, was significantly different between patients with and without brain metastasis. This may be explained by the frequent recurrence of the brain metastatic disease in patients with EGFR mutation despite several cycles of radiotherapy[23]. It is expected that

Table 2. Comparison With Results of Previous Studies

Variable	EGFR TKI	PFS (Months)	Reference
NEJ002	Gefitinib	10.8	15
WJOG3405	Gefitinib	9.2	6
LUX-Lung 7	Gefitinib	10.9	12
EURTAC	Erlotinib	9.7	7
OPTIMAL	Erlotinib	13.1	9
JO22903	Erlotinib	11.8	11
LUX-Lung 3	Afatinib	11.1	8
LUX-Lung 6	Afatinib	11.0	14
LUX-Lung 3 (Japanese)	Afatinib	13.8	5
LUX-Lung 7	Afatinib	11.0	12
Present study	Gefitinib	9.2	
Present study	Erlotinib	9.8	
Present study	Afatinib	13.1	

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; PFS, progression-free survival.

osimertinib, the third-generation TKI that has been recently approved in Japan for use against T790M mutation-associated lung tumors, will significantly improve OS in patients with EGFR mutation and brain metastasis[24].

No definite conclusions can be drawn from the present study due to limitations such as the retrospective nature of the study, small sample size, selection bias, and the insufficient follow-up of the patients. However, consistent with the results of our present study, previous meta-analysis also reported comparable clinical efficacy of gefitinib, erlotinib, and afatinib (Table 2)[13,25].

In brief, the results of the present retrospective study showed comparable clinical efficacy of gefitinib, erlotinib, and afatinib in Japanese patients with NSCLC.

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