Lung Cancer 135 (2019) 175–180

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

A phase II study of low starting dose of afatinib as first-line treatment in patients with *EGFR* mutation-positive non-small-cell lung cancer (KTORG1402)☆

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ARTICLE INFO

Keywords:
Low starting dose
Afatinib
Epidermal growth factor receptor mutation
Non-small-cell lung cancer

ABSTRACT

Objectives: Afatinib is an effective treatment in patients who have epidermal growth factor receptor (*EGFR*) mutation-positive non-small-cell lung cancer (NSCLC), but its toxicities often require dose adjustment. Exploratory analyses of previous trials have suggested that reducing the dose of afatinib can decrease treatment-related adverse events without negatively affecting effectiveness. The aim of this study was to assess the efficacy and safety of low starting dose of afatinib with dose modification according to its toxicity in patients with *EGFR* mutation-positive NSCLC.

Materials and methods: This study was a multicenter, single-arm, open-label phase II trial. Treatment-naïve patients with advanced NSCLC positive for common *EGFR* mutations received afatinib starting in a dose of 20 mg/day. If tolerated, the dose was increased in 10-mg increments up to 50 mg/day. The primary endpoint was progression-free survival (PFS).

Results: From February 2015 through March 2016, 46 patients were enrolled. The median age was 73 years (range, 43–86), and 35 patients (72%) were women.*EGFR* mutation subtypes included exon 19 deletion (54%) and Leu858Arg point mutation (46%). Most patients had a performance status of 0 or 1 (91%) and a histological diagnosis of adenocarcinoma (98%). As of the data cut-off date of June 2017, the median follow-up was 18.9 months. The median PFS was 15.2 months (95% CI: 13.2–not estimable). The 1-year overall survival rate was 95.6% (95% CI: 89.7%–100%). The objective response rate was 81.8% (95% CI, 81.3%–98.6%). Adverse events of grade 3 or higher occurred in 14 patients (30.4%) and included rash/acne in 4 patients (8.7%), paronychia in 4 patients (8.7%), diarrhea in 2 patients (4.3%). There was no treatment-related death.

Conclusions: Low starting dose of afatinib therapy showed promising clinical efficacy and good tolerability. Further investigations are warranted.

☆ The protocol was registered at the website of the University Hospital Medical Information Network, Japan (protocol identification no. UMIN000016444).

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https://doi.org/10.1016/j.lungcan.2019.03.030
Received 7 January 2019; Received in revised form 28 February 2019; Accepted 28 March 2019

1. Introduction

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide. In recent years, several targetable oncogenic drivers, such as epidermal growth factor receptor (*EGFR)*, anaplastic lymphoma kinase (*ALK)*, and *ROS*-1, have been identified in NSCLC [1]. NSCLC harboring activating *EGFR* mutations is highly sensitive to *EGFR* tyrosine kinase inhibitors (TKIs) [2]. As compared with platinum-based chemotherapy, *EGFR*-TKIs provide higher objective response rates (ORRs) and more prolonged progression-free survival (PFS), while maintaining the quality of life (QOL) in patients with NSCLC [3–5].

Afatinib is a second-generation ErbB family blocker, which down-regulates ErbB signaling by covalently binding to *EGFR*, human epidermal growth factor receptor (HER) 2, and HER4 and irreversibly inhibits tyrosine kinase autophosphorylation. The broad spectrum of activity and irreversible inhibition might be more potent and prolonged than the activities of the reversible first-generation EGFR-TKIs [6,7]. First-line afatinib therapy has produced PFS and overall survival (OS) benefits as compared with chemotherapy in patients with previously untreated advanced *EGFR* mutation-positive NSCLC [8–10]. The LUX-Lung 7 trial, comparing afatinib with gefitinib in the first-line treatment of patients with *EGFR*-mutant advanced NSCLC, showed that afatinib significantly improves PFS and the time-to-treatment failure [11]. On the other hand, more serious drug-related adverse events were reported in afatinib group than in the gefitinib group.

Exploratory analyses of the LUX-Lung 3 and 6 trials have suggested that reducing the dose of afatinib can decrease treatment-related adverse events without negatively affecting effectiveness [12]. A standard afatinib dose of 40 mg daily sometimes causes serious adverse events. Initial low-dose afatinib therapy starting at a dose of 20 mg daily might be a better strategy for improving the efficacy and safety of afatinib.

2. Materials and methods

2.1. Study design

This study was a prospective multicenter, single-arm, open-label phase II trial conducted by the Kyoto Thoracic Oncology Research Group (KTORG), Japan to evaluate the clinical efficacy and safety of low starting dose of afatinib, given in an initial dose of 20 mg daily. The primary endpoint was PFS. Secondary endpoints were OS, objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and safety. The study was conducted in accordance with the Declaration of Helsinki after receiving the approval of the institutional review board of each participating center. All patients provided written informed consent. The study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry Identifier, UMIN 000,016,444.

2.2. Study population

Eligibility criteria for the study included a cytologically or histologically confirmed diagnosis of treatment-naïve NSCLC with a common activating *EGFR* mutation (exon 19 deletion [Del-19] or Leu858Arg [L858R]) detected by a commercially available polymerase chain reaction method. Eligible patients had to be at least 20 years of age and to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, a life expectancy of 3 months or longer, and adequate organ functions with assessable lesions according to RECIST, version 1.1. Patients were excluded if they had obvious interstitial lung disease on chest computed tomography (CT), uncontrolled pleural or pericardial effusion, symptomatic brain metastases, severe comorbidities such as liver cirrhosis or heart disease, or additional active malignancies diagnosed within the past 5 years.

2.3. Treatment

Patients initially received afatinib in a dose of 20 mg orally once daily. Investigators were able to increase the afatinib dose in 10-mg increments at any time when they judged it was adequate to increase the dose provided the patient did not have any drug-related adverse event (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [NCI CTCAE 4.0]) of grade 2 or higher after at least a treatment period of 21 days elapsed. After one dose increase in afatinib, investigators were able to further increase the afatinib dose if the patient did not have any drug-related adverse event of grade 2 or higher after at least a treatment period of 21 days elapsed from the last day of increase in afatinib dose. If patients had drug-related adverse events of grade ≥ 3 or selected prolonged grade 2 adverse events despite best supportive care, afatinib was withheld for no more than 21 days until recovery to grade 1 or less. The selected adverse events included diarrhea, rash, stomatitis, and nail effects. After recovery from the adverse events, afatinib was restarted at a 10-mg lower dose. The treatment dose of afatinib was adjusted within the range of 20 mg every other day (minimum dose) to 20 mg daily, 30 mg daily, 40 mg daily, or 50 mg daily (maximum dose). No dose re-escalation was permitted. In patients in whom the onset of any grade interstitial lung disease was induced by afatinib, treatment was discontinued. Treatment was continued until disease progression, unacceptable toxicity, or the withdrawal of consent.

2.4. Efficacy and safety assessments

Tumors were assessed by CT or MRI scanning every 8 weeks until 1 year and every 8–12 weeks thereafter until discontinuation of the study treatment. Patients who discontinued the study treatment without evidence of progressive disease were evaluated until disease progression. Adverse events were assessed according to NCI CTCAE 4.0.

2.5. Statistical analyses

We set the threshold median PFS at 9 months (corresponding to a 1-year PFS rate of 40%) and the expected median PFS at 14 months (corresponding to a 1-year PFS rate of 56%). Given an alpha error of 0.10 (one-sided), a beta error of 0.2, an enrollment period of 2 years, and an observation period of 1.5 years, the number of patients required to provide an 80% power was estimated to be 44. Given the possibility of ineligible patients, the sample size was set at 45 patients. The PFS and OS curves and 95% confidence intervals (CI) were estimated by the Kaplan-Meier method. Subgroup analyses were performed according to *EGFR* mutation type (Del-19 vs. L858R), age (≥ 75 years vs. < 75 years), brain metastasis (present vs. absent), sex (male vs. female), body surface area (BSA) ($\geq 1.5\ m^2$ vs. $< 1.5\ m^2$), and afatinib dose increase (yes vs. no). The PFS curves were compared using the log-rank test. P-values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed using R software (version 3.4.1; The R Foundation for Statistical Computing. 2017).

3. Results

3.1. Patients

From February 2015 through March 2016, 46 patients were enrolled and evaluated at 6 centers in Japan. The baseline characteristics are shown in Table 1. The median age was 73 years (range, 43–86). Thirty-three patients (72%) were female, and 32 (70%) were never-smokers. The *EGFR* mutation subtypes were Del-19 in 25 patients (54%) and L858R in 21 patients (46%). Most patients had a performance status of 0 or 1 (91%) and adenocarcinoma (98%).

Table 1
Patients Characteristics (N = 46).

	Number (%)
Age, years (median (range))	73 (43-86)
Sex	
Male	13 (28)
Female	33 (72)
Smoking history	
Never	32 (70)
Ever	14 (30)
ECOG performance status	
0/1	42 (91)
2	4 (9)
Stage	
IIIB/IV	3/38
Postoperative recurrence	5
Histology	
Adenocarcinoma	45 (98)
Non-small cell lung cancer	1 (2)
EGFR mutation status	
Exon 19 del.	25 (54)
Exon 21 L858R	21 (46)
Body weight, kg (median (range))	53.8 (34.7-77.8)

Abbreviations: ECOGEastern Cooperative Oncology Group; EGFRepidermal growth factor receptor.

3.2. Efficacy

As of the data cut-off date of June 2017, the median follow-up for all randomized patients was 18.9 months (range, 8.2–28.9). The median PFS was 15.2 months (95% CI: 13.2%–not estimable [NE]), and the 1-year PFS rate was 69.3% (95% CI, 57.1%–84.1%), meaning the study had met its primary endpoint (Fig. 1A). Median OS was not reached, and the survival rate at 1 year was 95.6% (95% CI, 89.7%–100.0%) (Fig. 1B).

A waterfall plot of maximum tumor shrinkage from baseline is shown in Fig. 2A. Two patients without measurable lesions were excluded, and the response to treatment was evaluated according to RECIST 1.1 in 44 of the 46 patients. Two patients had complete responses, 34 had partial responses, and 5 had stable disease. The ORR was 81.8% (95% CI, 67.3%–91.8%), and the disease control rate was 93.2% (95% CI, 81.3%–98.6%) (Table 2).

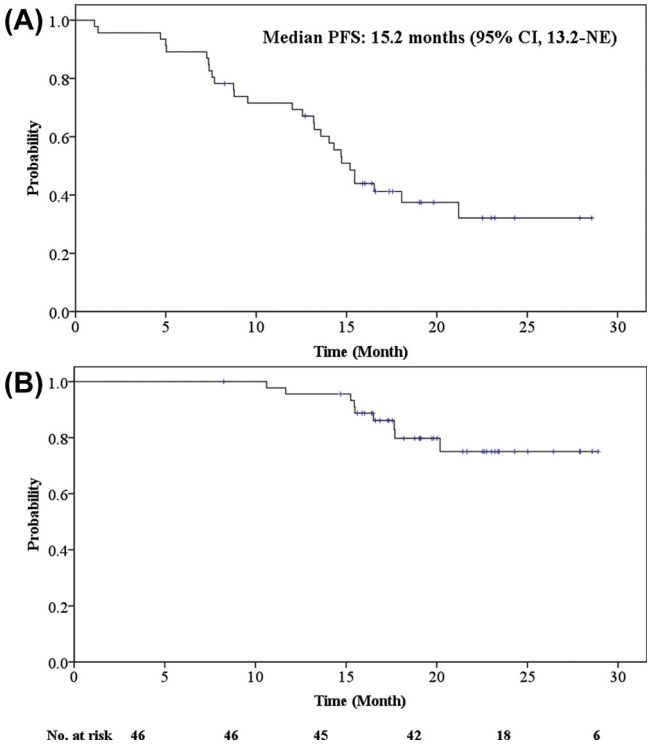

Fig. 1. Kaplan–Meier curves of progression-free survival (A) and overall survival (B).
PFS, progression-free survival; CI, confidence interval; NE, not estimable.

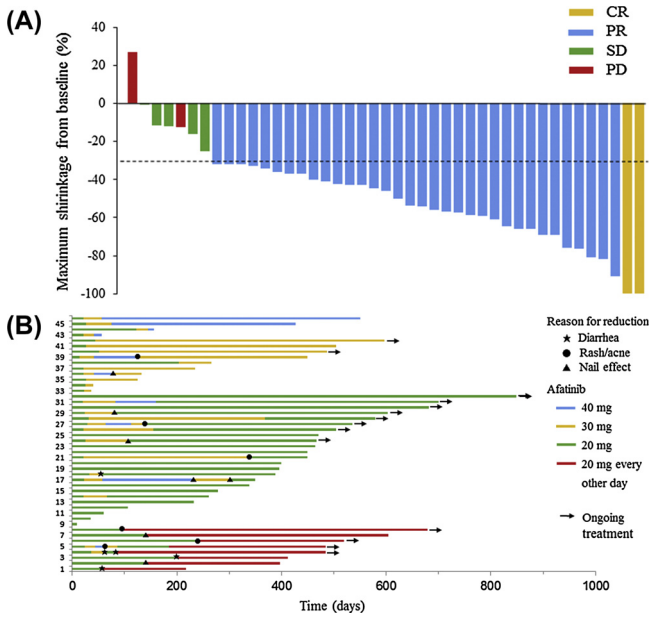

Fig. 2. A waterfall plot of maximum tumor shrinkage from baseline in the patients with measurable lesions (A) and a swimmer plot of treatment duration in all patients (B).
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

3.3. Drug delivery

The duration of treatment and the dose of afatinib are shown in Fig. 2B. The dose of afatinib was escalated to a maximum dose per day of 30 mg in 16 (35%) of the 46 patients and 40 mg in 10 (22%) of the 46 patients. At the cutoff date for data analysis, 21 patients (45.7%) had discontinued the study treatment because of disease progression and 5 patients (10.9%) had discontinued the study treatment because of afatinib-related adverse events. Fourteen patients (30%) continued to receive the study treatment.

3.4. Subgroup analyses

As for EGFR mutation status, the median PFS was 15.4 months (95% CI, 9.5-NE) in patients with Del-19 mutations (n = 25) and 14.0 months (95% CI, 14.3-NE) in patients with L858R mutations (n = 21) (p = 0.111) (Fig. 3A). As for the patients' age, the median PFS was 13.6 months (95% CI, 8.7-NE) in patients aged 75 years or older (n = 18) and 15.4 months (95% CI, 14.0-NE) in patients younger than 75 years (n = 28) (p = 0.192) (Fig. 3B). As for brain metastasis at study entry, the median PFS was 15.2 months (95% CI, 5.0–16.5) in patients with

Table 2
Objective Response.

Response	Number (%)
Complete response	2 (4.5)
Partial response	34 (77.3)
Stable disease	5 (11.4)
Progressive disease	2 (4.5)
Not evaluable	1 (2.3)
Total	44 (100)

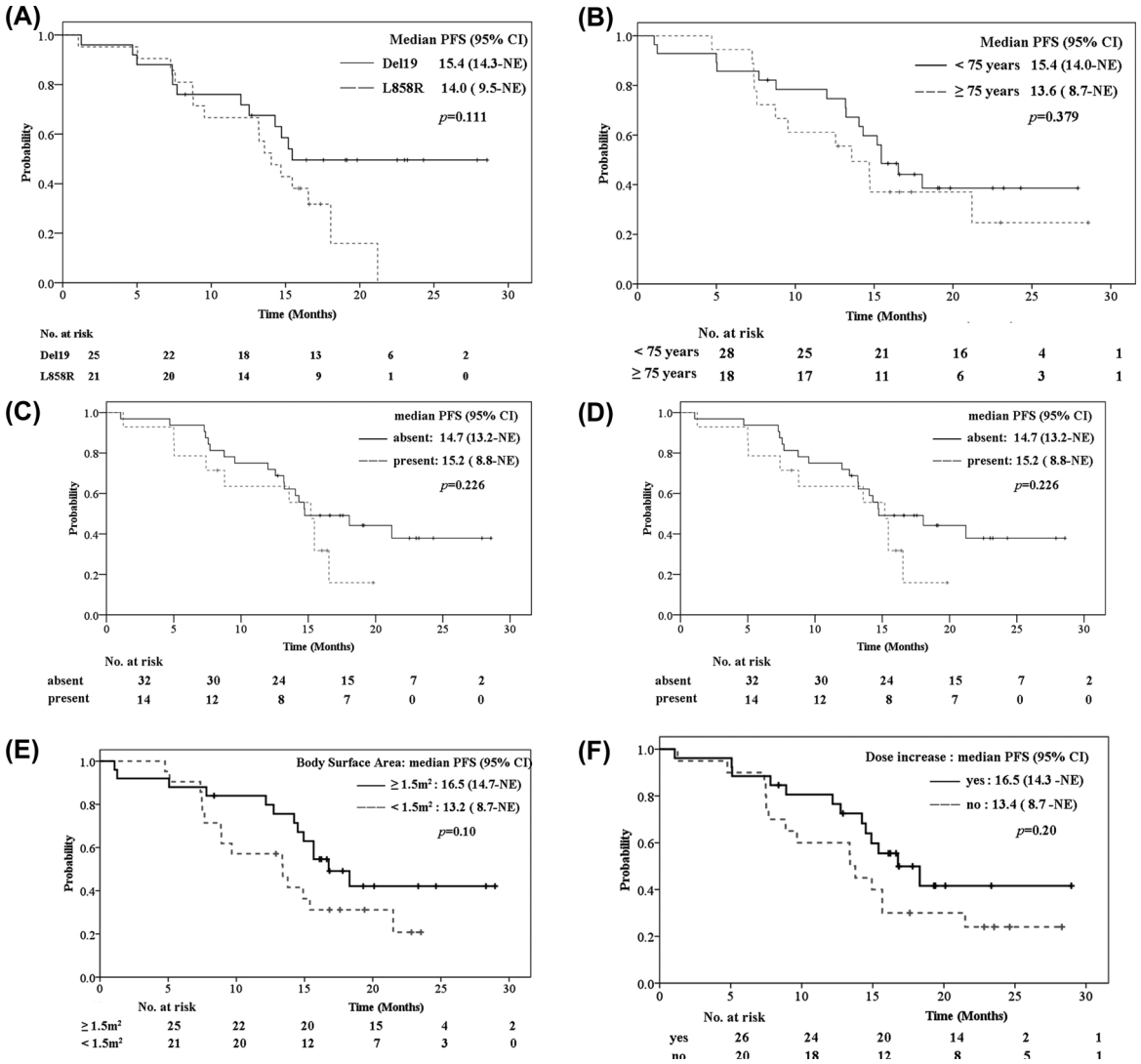

Fig. 3. Kaplan–Meier curves of progression-free survival according to EGFR mutation status (Del-19 or L858R) (A), age (patients aged 75 years or older or patient younger than 75 years) (B), brain metastasis (patients with or without brain metastasis at study entry) (C), sex (male or female) (D), BSA (≥ 1.5m2 or < 1.5 m2) (E), and afatinib dose increase (yes or no) (F).
CI, confidence interval; NE, not estimable; Del 19, exon 19 deletion; L858R, Leu858Arg; BSA, body surface area.

brain metastasis (n = 18) versus 14.7 months (95% CI, 12.6-NE) in patients without brain metastasis (n = 28) (p = 0.226) (Fig. 3C). As for sex, the median PFS was 14.7 months (95% CI, 13.2-NE) in male (n = 13) versus 15.4 months in female (95% CI, 12.0-NE) (p = 0.68) (Fig. 3D). As for BSA, the median PFS was 16.5 months (95% CI, 14.7-NE) in patients with BSA ≥ 1.5 m^2 (n = 25) versus 13.2 months (95% CI, 8.7-NE) in patients with BSA < 1.5 m^2 (n = 21) (p = 0.1) (Fig. 3E). As for afatinib dose increase, the median PFS was 16.5 months (14.3-NE) in patients experienced at least one afatinib dose increase (n = 26) versus 13.4 months (8.7-NE) in patients experienced no dose increase (n = 20) (p = 0.2) (Fig. 3F). Although no statistically significant differences were shown in PFS according to EGFR mutation status (Del19 vs. L858R), age (≥75 vs. < 75 years), brain metastasis (present vs. absent), sex (male vs. female), BSA (≥ 1.5 m^2 vs. < 1.5 m^2) and afatinib dose increase (yes vs. no), there was a trend to prolong PFS in patients with BSA ≥ 1.5 m2 and those experienced at least one afatinib dose increase.

3.5. Safety

An overall summary of treatment-related adverse events is shown in

Table 3
Adverse events with ≥10% frequency.

	Grade 1	Grade 2	Grade 3	Grade 4	≥ Grade 3 (%)	All Grade (%)
Patients with ≥1 event	46	39	14	0	30.4	100.0
Leukopenia	2	3	0	0	0	10.9
Anemia	13	5	0	0	0	39.1
AST elevation	10	0	1	0	2.2	23.9
ALT elevation	8	0	1	0	2.2	19.6
CRE elevation	7	1	0	0	0	17.4
Hypokalemia	5	2	0	0	0	15.2
Rash/acne	14	14	4	0	8.7	69.6
Stomatitis	17	7	1	0	2.2	54.3
Paronychia	12	16	4	0	8.7	69.6
Diarrhea	22	10	2	0	4.3	73.9
Anorexia	6	7	1	0	2.2	30.4
Nausea	6	2	0	0	0	17.4
Malaise	2	3	0	0	0	10.9

Abbreviations: AST, aspartate transaminase; ALT, aspartate aminotransferase; CRE, creatinine.

Table 3. Diarrhea (73.9%), rash/acne (69.6%), nail effects (69.6%), and stomatitis (54.3%) were frequently observed. Adverse events of grade 3 or higher occurred in 14 patients (30.4%). The most common grade 3 or higher adverse events were rash/acne in 4 patients (8.7%) and nail effects in 4 patients (8.7%). Drug-related grade 3 or higher adverse events occurred frequently in patients with dose escalations to 40 mg (5/10; 50%). There was no treatment-related death.

Four patients had drug-related interstitial lung disease (ILD) or an ILD-like event, and afatinib was discontinued. One patient with grade 3 ILD recovered after corticosteroid treatment. The ILD in the other patients (grade 1 in 2 patients and grade 2 in 1 patient) resolved without any treatment.

4. Discussion

To our knowledge, this is the first prospective study to investigate the efficacy of low starting dose afatinib at a dose of 20 mg daily in treatment-naïve patients who had NSCLC associated with common activating EGFR mutations. The median PFS was 15.2 months, which was similar to that in previous clinical trials of afatinib administered in a standard dose of 40 mg daily (approximately 14 months) [8,9,11]. The ORR was 81.8%, and few patients (2; 4.5%) had progressive disease at the first radiographic evaluation. Waterfall plots showed that most patients had deep responses.

The toxicities observed in this trial were generally mild. Although afatinib-related adverse events such as diarrhea, rash/acne, and nail effects frequently occurred, adverse events of grade 3 or higher developed in 14 patients (30.4%), and the incidence of such adverse events was lower than that (68.5%) in the Japanese subset analysis of the LUX-Lung 3 trial, in which patients received afatinib in a standard dose of 40 mg daily [13]. Half of the patients in whom the dose of afatinib was increased to 40 mg daily had adverse events of grade 3 or higher, suggesting that the dose should be carefully adjusted, especially when the dose of afatinib is increased up to 40 mg daily.

In patients with brain metastases at study entry, PFS was similar to that in patients with no brain metastasis. A previous study showed that a standard dose of afatinib is more effective than chemotherapy in patients with *EGFR*-mutation-positive NSCLC who had brain metastases (median PFS 8.2 versus 5.4 months, HR = 0.50, 95% CI: 0.27–0.95, $p = 0.0297$) [14]. In the present study, afatinib in a starting dose of 20 mg daily was also effective in patients with common *EGFR*-mutation-positive NSCLC who had asymptomatic brain metastasis. As for the patient's age, 18 (39.1%) of the 46 patients in this study were 75 years or older (older patients). The dose of afatinib was escalated in 7 (39%) of the 18 older patients. The dose was escalated up to 30 mg in 4 (22%) of the 18 older patients and up to 40 mg in 3 (17%) of the 18 older patients. The rate of dose escalation in the older patients was lower than that in the patients who were younger than 75 years (68%, 19 of 28 patients). Despite the difference in dose escalation, there was no significant difference in PFS between patients 75 years or older and those younger than 75 years ($p = 0.379$). Low starting dose afatinib therapy can thus be administered effectively and safely not only in low-risk patients, but also in high-risk patients with advanced age or brain metastasis.

There is a tendency to prolong PFS in patients with BSA ≥ 1.5 m^2. As for the influence of BSA on efficacy of Gefitinib (1^{st} generation EGFR-TKI) in patients with EGFR mutated NSCLC, Ichihara, et al reported that the median PFS of the patients with BSA ≥ 1.5 m^2 was significantly worse than that of those with BSA < 1.5 m^2 (10.4 vs. 18.0 months; p = 0.019, log-rank test) [15]. Our finding seems to be inconsistent with that of the gefitinib study. One of the reasons for this discrepancy may be the difference of dose setting in which gefitinib was administered at fixed dose of 250 mg/day and afatinib in this study was administered at adjusted dose according to the severity of its toxicities. In other words, gefitinib dose may be lower than ideal dose in some patients with higher BSA (≥ 1.5 m^2) because attending physicians are not permitted to increase gefitinib dose more than 250 mg/day even if they want to do it. Otherwise afatinib dose in this study can be modified according to the severity of toxicities defined by study protocol.

Regarding the influence of afatinib dose increase on efficacy, the PFS in patients experienced at least one afatinib dose increase tended to be better compared with that in those experienced no afatinib dose increase albeit no statistically significant difference. Although afatinib dose increase was not mandated by the study protocol even if the criteria of dose increase were met, the finding might indicate that attending physicians should not hesitate to increase the afatinib dose if adverse events are grade 1 or less after 3 weeks of treatment.

Trough concentrations of afatinib in plasma were reported to vary considerably among patients who received a 40-mg dose of afatinib, which indicates that it is difficult to estimate the adequate dose of afatinib on the basis of trough plasma concentrations in individual patients [12]. Starting afatinib therapy at an initial low dose of 20 mg daily with dose modification according to the severity of adverse effects is therefore considered a better strategy than standard afatinib treatment starting at a dose of 40 mg daily.

Our study had several limitations. First, this was a non-randomized trial with a small sample size. Second, the follow-up period was short, and we could not evaluate median OS at the data cutoff date. Finally, we did not assess serum afatinib concentrations to monitor pharmacokinetic profiles.

In conclusion, low starting dose afatinib therapy showed promising clinical efficacy and good tolerability. Further investigations are warranted.

Conflict of interest statement

Dr. Toshihide Yokoyama received personal fees from AstraZeneca, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd. and Eli Lilly, outside the submitted work.

Dr. Hiroshige Yoshioka received personal fees from AstraZeneca, Boehringer-Ingelheim, Chugai pharmaceutical Co., Ltd., Ono pharmaceutical Co., Ltd., Eli Lilly Japan, Taiho pharmaceutical Co., Ltd., MSD, NOVARTIS, Bristol-Myers Squibb, Pfizer, and Takeda pharmaceutical Co., Ltd., outside the submitted work.

Dr. Daichi Fujimoto received personal fees from Boehringer-Ingelheim and Chugai Pharmaceutical Co., Ltd., and grants and personal fees from AstraZeneca, outside the submitted work.

Dr. Keisuke Tomii received personal fees from Boehringer Ingelheim, Astra Zeneca, Eli Lilly, Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd. and MSD, outside the submitted work.

Dr. Mariko Kogo received a grant from AstraZeneca.

Dr. Katsuya Hirano received personal fees from AstraZeneca, Chugai Pharmaceutical Co., Ltd., Eli Lilly, Boehringer Ingelheim, Ono Pharmaceutical Co., Ltd., Pfizer, Taiho Pharmaceutical Co., Ltd. and Novartis, outside the submitted work.

Dr. Yasuharu Nakahara received personal fees from Boehringer Ingelheim Co., Ltd., outside the submitted work.

Dr. Tadashi Ishida received personal fees Chugai Pharmaceutical Co., Ltd., AstraZeneca and MSD, outside the submitted work.

Dr. Young Hak Kim received personal fees from AstraZeneca, Boehringer-Ingelheim, Chugai Pharmaceutical Co., Ltd., BMS, Eli Lilly, Kyowa-Hakko-Kirin, MSD and Novartis, and grants and personal fees from Ono Pharmaceutical Co., Ltd., Pfizer and Taiho Pharmaceutical Co., Ltd., outside the submitted work.

Dr. Toyohiro Hirai received grants from Chugai Pharmaceutical Co., Ltd. and Kyowa-Hakko Kirin Co., Ltd., outside the submitted work.

All remaining authors have declared no conflicts of interest.

Acknowledgements

The authors appreciate the participating patients and the investigators of KTORG. We thank Hironobu Tokumasu and Kaori Tanaka

for data management.

As for funding, none declared.

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