ORIGINAL ARTICLE

Clinical analysis of *EGFR*-positive non-small cell lung cancer patients treated with first-line afatinib: A Nagano Lung Cancer Research Group

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Abstract

Background: In the LUX-Lung 3 and LUX-Lung 6 trials, afatinib improved overall survival in previously untreated patients with *EGFR* 19del mutated non-small cell lung cancer (NSCLC) compared to chemotherapy. The appropriate management of adverse events and dose reduction of afatinib are important for *EGFR*-positive NSCLC patients. We conducted a retrospective and observational study of patients treated with first-line afatinib for *EGFR*-positive NSCLC in Nagano prefecture, Japan, focusing on efficacy and toxicities.

Methods: We retrospectively collected the medical records of NSCLC patients initially treated with afatinib between May 2014 and March 2018.

Results: A total of 62 patients with a median age of 67 years and a median body surface area (BSA) of 1.57 m^2 were included. The overall response rate was 87.7% and median progression-free survival (PFS) was 15.7 months. The median PFS was similar between standard initial dose (40 mg) and reduced initial doses (30 and 20 mg) (15.7 vs. 14.2 months; $P = 0.978$). The frequency of dose reduction and the discontinuation rate in the 40 mg daily dose group was higher in patients with BSA < 1.58 m^2 (100%) compared to BSA ≥ 1.58 m^2 (68.2%) ($P = 0.014$). The frequency of diarrhea was higher in patients with BSA < 1.58 m^2 (93.5%) compared to BSA ≥ 1.58 m^2 (71.0%) ($P = 0.02$).

Conclusion: In real-world clinical practice, first-line afatinib was well managed and was equally as effective as in previous clinical trials of *EGFR*-positive NSCLC. BSA is considered a predictive marker for appropriate afatinib dose reduction.

Introduction

Many clinical studies have demonstrated the efficacy of EGFR-tyrosine kinase inhibitors (TKIs) in patients with non-small cell lung cancer (NSCLC) positive for *EGFR* mutations.[1–4] In comparison to platinum-doublet chemotherapy, first-generation EGFR-TKIs, such as gefitinib and

erlotinib, prolong progression-free survival (PFS)[1–4] but not overall survival (OS).[5] Afatinib, a second-generation EGFR-TKI, is an orally available irreversible inhibitor of the ErbB family of tyrosine kinases and was approved for first-line treatment of *EGFR*-positive NSCLC in Japan in May 2014.[6] The LUX-lung 3 and LUX-lung 6 trials showed that afatinib improved overall survival (OS) in previously untreated patients with *EGFR* 19del mutations compared to chemotherapy.[7] In the LUX-Lung 7 trial, afatinib significantly improved PFS and the time to treatment failure compared to gefitinib.[8] However, higher rates of severe adverse events (AEs), such as diarrhea, skin rash, paronychia, and stomatitis, were reported compared to first-generation EGFR-TKIs.[9] Appropriate management of AEs and dose reduction of afatinib are important for *EGFR*-positive NSCLC patients. Post hoc analyses of the randomized LUX-Lung 3 and 6 trials suggested that patients with a lower body surface area (BSA) were more likely require dose reduction.[10] The final afatinib doses for patients with baseline BSA < 1.8 versus ≥ 1.8 m^2 in the LUX-Lung 3 and LUX-Lung 6 trials were 40 mg (38.3% vs. 65.9% and 62.3% vs. 71.9%, respectively).[10] However, the median PFS was similar between patients with and without dose reduction during the first six months of afatinib treatment (11.3 vs. 11.0 months, respectively).[10] There have been few real-world studies regarding the clinical efficacy and AEs associated with afatinib in Japan. We conducted a retrospective and observational study in patients administered first-line afatinib treatment for *EGFR*-positive NSCLC in Nagano prefecture, Japan, focusing on the efficacy and AEs of afatinib therapy.

Methods

We retrospectively collected and reviewed the medical records of chemotherapy-naïve NSCLC patients initially treated with afatinib in associated hospitals in Nagano prefecture, Japan, between May 2014 and March 2018. During this period, a Nagano Lung Cancer Research Group observational study (NAGANO-ALPS, a prospective observational study without intervention) began in June 2016 with the aim of verifying the existing state of clinical practice and prognosis for NSCLC with driver mutations at associated hospitals in Nagano prefecture. We retrospectively reviewed the records of *EGFR*-positive chemotherapy-naïve NSCLC patients treated with first-line afatinib until 2016 and then collected data from the prospective observational study. A questionnaire survey was conducted among physicians in each associated hospital in Nagano prefecture. Institutional review board approval from each individual hospital was not required because of the observational and retrospective nature of the study. An electronic clinical record search was performed in each hospital, and the clinical characteristics, response to afatinib, and toxicities during treatment were examined in the selected subjects.

Patient privacy was protected when using individual patient information. The histological diagnosis and NSCLC stage were based on the World Health Organization classification, version 7. Performance status (PS) was estimated according to the Eastern Cooperative Oncology Group classification. The response to afatinib therapy was evaluated using Response Evaluation Criteria in Solid Tumors version 1.1. Objective response rates (ORRs; complete response [CR] plus partial response [PR]) and disease control rates (DCRs; CR + PR + stable disease [SD]) were calculated. Toxicities associated with afatinib therapy were graded according to Common Terminology Criteria for Adverse Events version 4.0. Afatinib was administrated orally once daily and treatment was continued until progressive disease (PD) or intolerable toxicity. The attending physicians determined the initial dose, reduction (or temporary interruption), and discontinuation. If first-line afatinib therapy showed PD, patients were permitted any subsequent treatments required, including the continuation of afatinib treatment. PFS and OS were defined as the time from initiation of afatinib to the documentation of PD, and as the interval from the initial date of afatinib to the date of death or the last follow-up visit, respectively.

Statistical analysis

Kaplan–Meier plots were used for PFS and OS analyses, and the median and 95% confidence intervals (CIs) were determined. Differences between the groups were compared using log-rank statistics. The cutoff date for follow-up was 31 March 2018. Statistical analyses were performed using SPSS version 19. Comparisons were performed using Fisher's exact test and $P < 0.05$ was taken to indicate statistical significance. The research ethics committee of Shinshu University School of Medicine approved this retrospective study (Approval number: 3407).

Results

Patient characteristics

The study population consisted of 62 patients with *EGFR* mutations. The clinical characteristics of the patients are listed in Table 1. Twenty-six patients were male, 36 were female, at a median age of 67 years (range: 46–85 years), and a median body surface area of 1.57 m^2 (range: 1.23–2.05 m^2). Thirty-five patients had a PS of 0 (56.5%), 22 patients had a PS of 1 (35.5%), three patients had a PS of 2 (4.8%), one patient had a PS of 3, and one patient had a PS of 4. Thirty-five patients (56.5%) were never-smokers. The histological type in most patients was adenocarcinoma. According to the tumor node metastasis (TNM) classification, 5 patients had stage I–IIIA disease, 4 patients had stage

Table 1 Patient characteristics

Category	N = 62 (%)
Gender	
Male	26 (41.9)
Female	36 (58.1)
Median age (range), years	67 (46–85)
ECOG PS	
0	35 (56.5)
1	22 (35.5)
2	3 (4.8)
3	1 (1.6)
4	1 (1.6)
Median body surface area, m^2	1.57 (1.23–2.05)
Histopathology	
Adenocarcinoma	61 (98.4)
Unclassified	1 (1.6)
Smoking history	
Never	35 (56.5)
Ever	27 (43.5)
Staging	
I–IIIA	5 (8.1)
IIIB	4 (6.5)
IV	40 (64.5)
Postoperative recurrence	13 (21.0)
EGFR mutation	
19del	42 (67.7)
L858R	15 (24.2)
G719X	3 (4.8)
G719S	1 (1.6)
L858R · T790M	1 (1.6)

ECOG PS, Eastern Cooperative Oncology Group performance status.

IIIB disease, 40 patients had stage IV disease, and 13 patients experienced postoperative recurrence. *EGFR* mutations, including 19del, L858R, uncommon mutations, and L858R plus T790M, were detected in 42 (67.7%), 15 (24.2%), 4 (6.5%), and 1 (6%) patient, respectively.

Treatment and efficacy

The doses and response rates are summarized in Tables 2 and 3. The starting dose was 40 mg daily in 40 patients, 30 mg daily in 11 patients, and 20 mg daily in 11 patients. In patients with BSA < 1.58 m^2 ($n = 31$), the starting dose was 40 mg daily in 17 patients (54.8%), 30 mg daily in 5 patients (16.1%), and 20 mg daily in 9 patients (29.0%). The final dose was 40 mg daily in no patients (0.0%), 30 mg daily in 8 patients (25.8%), and 20 mg daily in 15 patients (48.4%). Adverse events requiring the discontinuation of afatinib were diarrhea ($n = 3$), interstitial lung disease (ILD, $n = 2$), paronychia ($n = 1$), colitis ($n = 1$), and diarrhea + hand-foot syndrome ($n = 1$). In patients with BSA ≥ 1.58 m^2 ($n = 31$), the starting dose was 40 mg daily in 23 patients (74.2%), 30 mg daily in 6 patients (19.4%), and 20 mg daily in 2 patients (6.5%). The final

Table 2 Dose and efficacy of afatinib

Category	Number (%)
Starting dose	
40 mg	40 (64.5)
30 mg	11 (17.7)
20 mg	11 (17.7)
Dose reduction	
None	23 (37.1)
Once	23 (37.1)
Twice	16 (25.8)
Best overall response	
Complete response	5 (8.1)
Partial response	45 (72.6)
Stable disease	5 (8.1)
Progressive disease	2 (3.2)
Not evaluable	5 (8.1)
Overall response rate	87.7 (95% CI 79.2–96.2)
Disease control rate	96.5 (95% CI 91.7–100)

CI, confidence interval.

dose was 40 mg daily in 7 patients (22.6%), 30 mg daily in 9 patients (29.0%), and 20 mg daily in 14 patients (45.2%). The dose reduction and discontinuation rates in the 40 mg daily starting group were 100% in BSA < 1.58 m^2 and 68.2% in BSA ≥ 1.58 m^2 ($P = 0.014$).

With regard to response rate, five subjects were excluded: no evaluable lesions in three cases and early discontinuation as a result of skin rash in two. Thus, the response rate was evaluated in 57 patients. Five patients achieved CR, 45 patients achieved PR, 5 patients showed SD, and 2 patients showed PD. Thus, the ORR was 87.7% (95% CI 79.2–96.2%) and the DCR was 96.5% (95% CI 91.7–100%). Survival curves are shown in Figures 1 and 2. The median PFS was 15.7 months (95% CI 11.9–19.5) (Fig 1a). The median PFS in 19del, L858R, and uncommon mutations were 17.3 (95% CI 10.6–24.1), 12.0 (95% CI 7.3–16.7), and 17.3 months, respectively. The median PFS in the postoperative recurrence group has not yet been reached (Fig 1b). There were no differences in PFS between

Table 3 Treatment status according to BSA

Dose	BSA < 1.58 m^2 ($n = 31$) N (%)	BSA ≥ 1.58 m^2 ($n = 31$) N (%)
Starting dose		
40 mg	17 (54.8)	23 (74.2)
30 mg	5 (16.1)	6 (19.4)
20 mg	9 (29.0)	2 (6.5)
Final dose		
40 mg	0 (0.0)	7 (22.6)
30 mg	8 (25.8)	9 (29.0)
20 mg	15 (48.4)	14 (45.2)
Treatment failure	8 (25.8)†	1 (3.2)‡

†Diarrhea: 3; interstitial lung disease (ILD): 2; paronychia: 1, colitis: 1, diarrhea + hand-foot syndrome: 1. ‡ILD: 1. BSA, body surface area.
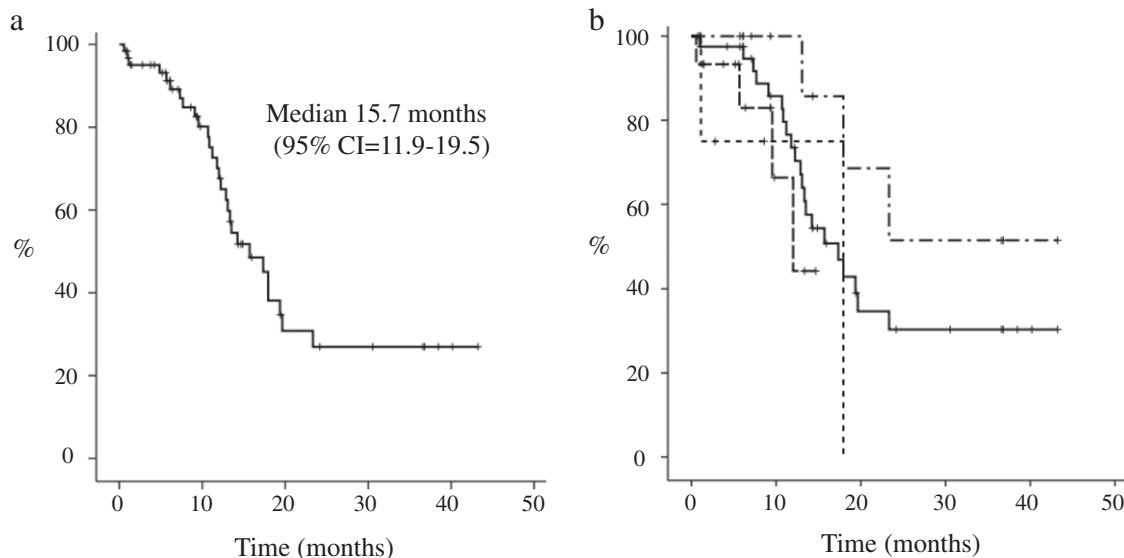
Figure 1 Kaplan–Meier analyses of progression-free survival (PFS) in (**a**) all patients and in (**b**) 19del, L858R, uncommon mutation, and postoperative recurrence groups. The median PFS in all patients was 15.7 months (95% CI 11.9–19.5), while the median PFS periods in 19del, L858R, uncommon mutation, and postoperative recurrence groups were 17.3 (95% CI 10.6–24.1), 12.0 (95% CI 7.3–16.7), 17.3 months, and not yet reached, respectively. – – – Post-operative recurrence, —— Del19, – – – L858R, ------ Uncommon mutation.

the groups with initial doses of 40 mg and < 40 mg (30 and 20 mg) (15.7 vs. 14.2 months, respectively; $P = 0.978$) (Fig 2). The median OS has not yet been reached, and the estimated OS rate at 24 months was 72.8%. In univariate analyses, no significant differences in PFS were observed according to gender, age (< 70 vs. ≥

Figure 2 Kaplan–Meier curves of progression-free survival (PFS) according to the initial dose. PFS was similar between the groups with a standard initial dose (40 mg) and reduced initial dose (30 mg + 20 mg). The median PFS periods were 15.7 and 14.2 months, respectively (log-rank $P = 0.978$). —— Standard group of initial doses (40 mg), ------ Reduction group of initial doses (30 mg + 20 mg).

70 years), BSA (< 1.58 vs. ≥ 1.58), or *EGFR* mutations (19del vs. L858R) (Table 4).

Toxicity

Toxicities were evaluated in all patients and are summarized in Tables 5 and 6. The most common AE associated with afatinib was diarrhea (82.3%), followed by rash/ache (80.7%), paronychia (56.5%), and stomatitis (54.9%). The grade ≥ 3 toxicities were diarrhea (24.2%), paronychia (9.7%), rash/ache (8.1%), stomatitis (6.5%), hepatic impairment (3.2%), and dry skin (1.6%). Toxicities were compared between patients with BSA < 1.58 m^2 and BSA ≥ 1.58 m^2. The frequency of diarrhea was higher in the BSA < 1.58 m^2 group compared to the BSA ≥ 1.58 m^2 group ($P = 0.020$ [$P < 0.05$]). However, there were no significant differences in rash/ache ($P = 0.199$), paronychia ($P = 0.793$), or stomatitis ($P = 0.610$) according to BSA. There were no cases of treatment-related death.
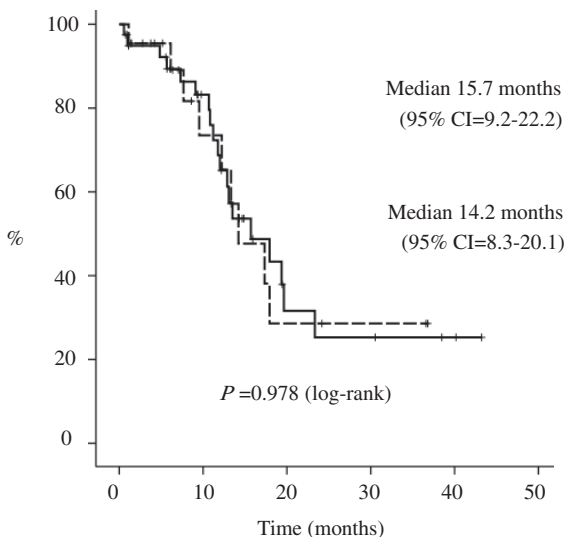
Second-line treatment

Twenty-eight patients discontinued afatinib therapy because of PD and toxicities. The second-line treatments administered in 22 patients (81.5%) are summarized in Table 7. The most commonly selected regimens were platinum doublet regimens (including pemetrexed ± bevacizumab) in 13 patients. Among the 22 patients who underwent re-biopsy, 8 (36.4%) were positive for T790M. In total, 31.8% of re-biopsies were performed on

Table 4 Prognostic factors associated with PFS as determined by univariable analyses

Factor	N	Median PFS (months)	HR (95% CI)	*P*
Gender				
Male	26	15.7	1.881	0.394
Female	36	17.3	(0.440–8.044)	
Age				
< 70 years	41	14.2	1.166	0.740
≥ 70 years	21	17.9	(0.471–2.886)	
BSA				
< 1.58 m^2	31	14.2	2.121	0.300
≥ 1.58 m^2	31	15.7	(0.512–8.775)	
EGFR				
19del	42	17.3	0.575	0.337
L858R	15	12.0	(0.186–1.780)	

BSA, body surface area; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Table 5 Toxicities according to BSA

Toxicity	Body surface area (BSA)	Grade (%)				
		0	1	2	3	4
Diarrhea	≥ 1.58 m^2 (n = 31)	2 (6.5)	12 (38.7)	9 (29.0)	7 (22.6)	1 (3.2)
	< 1.58 m^2 (n = 31)	9 (29.0)	11 (35.5)	4 (12.9)	7 (22.6)	0 (0.0)

BSA, body surface area.

Table 6 Toxicities

Adverse event	Any grade (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Diarrhea	51 (82.3)	23 (37.1)	13 (21.0)	14 (22.6)	1 (1.6)
Rash/ache	50 (80.7)	20 (32.3)	25 (40.3)	5 (8.1)	0 (0.0)
Paronychia	35 (56.5)	12 (19.4)	17 (27.4)	6 (9.7)	0 (0.0)
Stomatitis	34 (54.9)	19 (30.7)	11 (17.7)	4 (6.5)	0 (0.0)
Nausea	6 (9.7)	2 (3.2)	4 (6.5)	0 (0.0)	0 (0.0)
Dry skin	6 (9.7)	2 (3.2)	3 (4.8)	1 (1.6)	0 (0.0)
Hepatic	5 (8.1)	1 (1.6)	2 (3.2)	2 (3.2)	0 (0.0)
ILD	4 (6.5)	0 (0.0)	4 (6.5)	0 (0.0)	0 (0.0)

ILD, interstitial lung disease.

pulmonary lesions, followed by pleural or pericardial effusion, blood biopsy, cerebrospinal fluid, and lymph node biopsy. All T790M-positive patients had *EGFR* 19del.

Discussion

We summarized a real-world retrospective cohort study of *EGFR*-positive NSCLC patients treated with afatinib as first-line treatment in Nagano prefecture. The ORR and median PFS were 82.3% and 15.7 months, respectively. Afatinib toxicity was well managed using dose reduction during treatment. We found that the frequency of diarrhea

Table 7 Second-line chemotherapy administered after disease progression

Second-line chemotherapy after PD	N = 28 (%)
Platinum doublet	
Platinum + PEM ± BEV	13 (46.4)
Other	2 (7.1)
EGFR-TKIs	
Osimertinib	4 (14.3)
Gefitinib	1 (3.6)
Erlotinib	1 (3.6)
Erlotinib + BEV	1 (3.6)
BSC	1 (3.6)
None (beyond PD)	1 (3.6)
Unknown	4 (14.3)

BEV, bevacizumab; BSC, best supportive care; PD, progressive disease; PEM, pemetrexed; TKIs, tyrosine kinase inhibitors.

and dose reduction of afatinib in the group administered 40 mg daily were significantly higher in the lower BSA (< 1.58 m^2) than in the higher BSA (≥ 1.58 m^2) subgroup. In addition, PFS in patients treated with an initial daily dose of < 40 mg afatinib was not inferior to PFS in the 40 mg group.

With regard to efficacy, the median PFS in our study was 15.7 months, which was comparable to those in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 prospective randomized studies (11.1, 11.0, and 11.0 months, respectively).[7,8] The ORR in our retrospective study was 87.7%, which was slightly higher than those in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials (69%, 66.9%, and 70%, respectively).[7,8] The median PFS in the 19del and L858R groups were 17.3 and 12.0 months, respectively. In subgroup analysis of Japanese patients in the LUX-Lung 3 trial, the median PFS in 19del and L858R groups were 16.4 and 13.7 months, respectively.[7,8,11,12] Thus, although our analysis was retrospective and no central review of the response criteria was performed, our results suggest that first-line afatinib was useful for *EGFR*-positive NSCLC in clinical practice.

The study population included 10 elderly patients (≥ 75 years) and the ORR and PFS in these patients were 70.0% and 17.3 months, respectively. The initial daily dose was 40 mg in four patients, 30 mg in two patients, and 20 mg in four patients. The final dose was 20 mg daily in eight patients, and two patients discontinued afatinib because of ILD and diarrhea. Two cases of ILD occurred 11 and 103 days after the initiation of afatinib and were considered as drug-induced lung disease resulting from afatinib because there were no other suspicious drugs. Although no prospective analysis was performed for elderly *EGFR*-positive NSCLC patients, our data suggest that first-line afatinib in elderly patients is effective. However, the starting dose and/or reduction of afatinib in elderly patients should be considered.

We found that patients with postoperative recurrence had significantly longer PFS compared to those with medically advanced/metastatic NSCLC. The clinical backgrounds, including mean age, and PS, were similar between the groups. Although NSCLC patients with postoperative recurrence are generally regarded as having a good prognosis compared to patients with medically metastatic diseases,[13] no clinical studies have examined the differences in therapeutic effects of EGFR-TKIs between medically advanced/metastatic disease and postoperative recurrence. The preliminary results presented here suggest that a prospective study to evaluate the effects of EGFR-TKIs on *EGFR*-positive recurrence in NSCLC patients is required.

Furthermore, our data included two patients with poor PS (i.e. PS 3/4). These two patients achieved PR and SD, and had PFS of 4.8 and 8.8 months, respectively. Afatinib was used until PD without the need for discontinuation as a result of toxicity in both cases. In particular, a patient with a PS score of 4 initially started at a dose of 20 mg, which was eventually increased to 40 mg after improvement in the patient's general condition. Although the efficacy of afatinib has not been reported in patients with poor PS, our treatment experience of PS 3/4 patients suggests the usefulness of first-line afatinib in patients with *EGFR*-positive NSCLC. Several clinical trials are currently underway of *EGFR*-positive NSCLC patients with poor PS.

The frequency of toxicities in the present study, such as diarrhea, rash/ache, paronychia, and stomatitis, were comparable to those reported in the LUX-Lung 3, 6, 7, and 8 trials.[7,8,14] However, the frequency of afatinib discontinuation as a result of AEs in our study was high (14.5%).[3,7,8,10] Diarrhea was the most common and significant AE, with ≥ grade 3 diarrhea occurring in 24.2% of patients. Of the nine patients that discontinued afatinib treatment, diarrhea was the cause in four (44.4%). In meta-analyses of clinical trials, the risk of afatinib-induced diarrhea was significantly higher with afatinib (91.7%) than with erlotinib (42.4%) or gefitinib (44.4%).[9] Numerous pollutant studies have focused on the relationship between afatinib dose and toxicity. We previously reported that lower BSA (< 1.50 m^2) was significantly associated with a higher frequency of grade > 2 diarrhea compared to higher BSA (≥ 1.50 m^2).[15] In pooled analysis of seven clinical trials, low weight (< 45 kg), female gender, and older age (≥ 60 years) were identified as major independent risk factors of severe (≥ 3) diarrhea.[16] The frequency of diarrhea in our study was also significantly higher in the BSA < 1.58 m^2 (lower BSA) group compared to the BSA ≥ 1.58 m^2 (higher BSA) group (*P* = 0.02). Patients with lower BSA administered the standard initial daily dose of 40 mg of afatinib had significantly higher incidences of dose reduction and discontinuation of afatinib compared to patients

with higher BSA (*P* = 0.014). These findings suggest that BSA could be a marker of possible afatinib dose reduction during treatment and could be a predictive marker for diarrhea.

In the RealGiDo study, which evaluated the impact of afatinib dose adjustment on efficacy and safety in a real-world setting, 31.1% of patients received an afatinib starting dose of < 40 mg.[17] The median time to progression (TTP) in all patients was 20.8 months and the median TTP in those who commenced at a dose of ≤ 30 mg of afatinib was 25.9 months. In a real-world cohort study in Taiwan, there was no significant difference in median PFS in the first six months between the 40 mg and < 40 mg groups (12.0 vs. 11.0 months, respectively).[18] In a retrospective analysis of the efficacy of 40 mg versus dose reduction to < 40 mg of afatinib, there were no significant differences between the groups in the median time to treatment failure (405 vs. 472 days, respectively; *P* = 0.2271).[19] In our study, the median PFS rates in the < 40 mg and 40 mg groups were 14.2 and 15.7 months, respectively. These results suggest that the effectiveness of afatinib is consistent, regardless of whether patients require dose reduction.

In the LUX-Lung 3, 6, and 7 trials, female patients and those positive for 19del responded to long-term afatinib.[20] We examined gender, age, BSA, and *EGFR* mutation as predictors of therapeutic effect; however, no factors correlated with PFS were observed. This is likely the result of our small patient sample.

During the observation period, 28 patients showed PD and 22 of these patients (78.6%) underwent re-biopsy. Eight patients (36.4%) were positive for T790M mutation. Seven of these patients (25%) were treated with osimertinib in subsequent therapy lines. In the REMEDY trial conducted in Japan, 61 of 236 patients (25.8%) were positive for T790M mutation, and 56 patients (23.7% in re-biopsy group) were treated with osimertinib.[21] As 7 of the 28 patients with PD (25.0%) in our study were treated with osimertinib, our clinical practice is equivalent to the REMEDY trial. Asian *EGFR*-positive NSCLC patients administered sequential afatinib and osimertinib in a real world clinical setting had overall median treatment durations of 27.6 and 46.7 months, respectively.[22] Sequential afatinib and osimertinib therapy prolonged the treatment duration in patients who acquired T790M. Therefore it is important to determine methods to improve the frequency of T790M detection.

In conclusion, real-world first-line afatinib data from Nagano Prefecture, Japan, demonstrated afatinib efficacy and tolerability similar to those reported in other clinical studies. First-line afatinib appeared to be a feasible therapeutic strategy for *EGFR* mutation-positive NSCLC patients in a real-world population. The initial dose setting

and dose reduction should be considered according to BSA and toxicities.

Acknowledgments

Disclosure

No authors report any conflict of interest.

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