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Intracranial Responses to Afatinib at Different Doses in Patients With *EGFR*-mutated Non–small-cell Lung Carcinoma and Brain Metastases

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Abstract

Afatinib is commonly used for advanced *EGFR*-mutated non–small-cell lung cancer, and dose reduction is frequently required. The effect of dose reduction on brain metastasis was seldom investigated. This retrospective multicenter study analyzed different daily doses of afatinib used in treatment-naive patients with *EGFR*-mutated non–small-cell lung cancer and brain metastases, which demonstrated that dose reduction may not affect intracranial responses to afatinib therapy.

Background: As the first-line treatment, afatinib is commonly used in patients with *EGFR*-mutated non–small-cell lung cancer (NSCLC). However, dose adjustments are frequently required. The optimal dose of afatinib for brain metastasis has seldom been investigated. **Patients and Methods:** From May 2014 to March 2017, treatment-naive patients with advanced *EGFR*-mutated NSCLC and brain metastases at diagnosis who received afatinib therapy were retrospectively enrolled. Clinical data was reviewed and analyzed, including age, gender, performance status, smoking history, *EGFR* mutation status, initial doses of afatinib, average daily doses of afatinib, and best intracranial treatment responses. **Results:** A total of 74 patients were included for analysis. The overall intracranial objective response rate (IORR) and intracranial disease control rate (IDCR) were 81.1% and 95.9%, respectively. For patients treated with afatinib alone (N = 45), no significant difference between an initial daily dose of 30 mg (N = 15) and 40 mg (N = 30) (30 mg vs. 40 mg, IORR: 86.7% vs. 80.0%; $P = .581$ and IDCR: 93.3% vs. 93.3%; $P = 1.000$, respectively). The IORRs were 75.0%, 91.7%, 80.0%, and 85.7% ($P = .707$), and the IDCRs were 93.8%, 100.0%, 90.0%, and 85.7% ($P = .638$) in patients with an average daily dose of 40 mg (N = 16), < 40 mg and > 30 mg (N = 12), 30 mg (N = 10), and < 30 mg and > 20 mg (N = 7), respectively. No significant differences in intracranial treatment responses between groups treated with afatinib alone or afatinib plus local treatments. **Conclusion:** Dose reduction may not affect intracranial treatment responses to afatinib therapy, either alone or combined with local treatments, in patients with advanced *EGFR*-mutated NSCLC and brain metastases.

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Keywords: Adenocarcinoma, Dose reduction, Epidermal growth factor receptor-tyrosine kinase inhibitor, Intracranial metastases, Lung cancer

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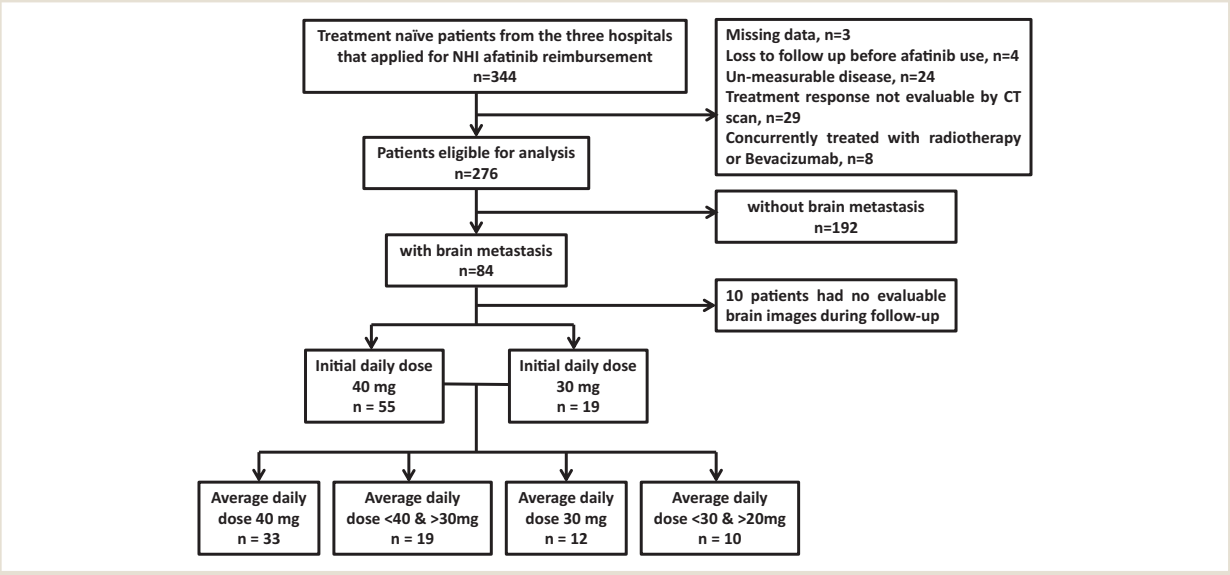
Figure 1 Flowchart of Patient Recruitment



Abbreviations: CT = computed tomography; NHI = National Health Insurance.

Introduction

Approximately 20% of patients with non−small-cell lung cancer (NSCLC) have brain metastases at diagnosis, which are often associated with neurological symptoms, poor quality of life, and worse prognoses.[1] Whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and brain tumor resection are frequently used for the treatment of brain metastases; however, individual treatment strategies are required.[2,3]

Patients with NSCLC harboring *EGFR* mutations are more likely to suffer from brain metastases compared with those without *EGFR* mutations.[4-6] Among patients with NSCLC treated with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), those with brain metastases at diagnosis had significantly higher total medical costs.[7] Previous studies demonstrated that first-generation EGFR-TKIs, including gefitinib and erlotinib, provided favorable intracranial responses in patients with *EGFR*-mutated NSCLC with brain metastases.[8-12]

In contrast, the effectiveness of afatinib, a second-generation EGFR-TKI, on brain metastasis in patients with NSCLC was less investigated. In 2 phase III trials using afatinib as the first-line treatment for *EGFR*-mutated NSCLC, subgroup analyses of patients with brain metastasis showed a systemic disease control rate of 89.3% and 95.0%.[13] However, the intracranial response rates were not reported. Hoffknecht et al demonstrated a cerebral response rate of 35% and a central nervous system disease control rate of 66% in pretreated patients with *EGFR*-mutated NSCLC who received afatinib therapy.[14]

The initial dose of afatinib was 40 mg daily in phase III clinical trials, which was recommended as the starting dose by the European Medicines Agency.[15,16] In a real-world setting, 29.6% to 38.3% of patients with *EGFR*-mutated NSCLC treated with afatinib required dose adjustments owing to intolerable adverse events.[17,18] However, dose reduction may lead to an insufficient concentration of afatinib in the cerebrospinal fluid and may result in a low efficacy against brain metastases. Recently, Tan and his colleagues performed a retrospective study included 42 patients with *EGFR*-mutated NSCLC with brain metastases, and concluded that a starting dose of afatinib at 40 mg/day was associated with a better progression-free survival (PFS) compared with those who had a reduced starting dose of 30 mg/day.[19] To examine intracranial responses to afatinib at different daily doses of afatinib in patients with *EGFR*-mutated NSCLC with brain metastases, this study and patient inclusion periods were extended from our previous study on the treatment effectiveness of afatinib at different average daily doses in patients with advanced lung adenocarcinoma.[20]

Materials and Methods

Patients

This multicenter retrospective study was conducted in 3 hospitals, including the National Taiwan University Hospital, the Far Eastern Memorial Hospital in northern Taiwan, and the E-Da Hospital in southern Taiwan. Treatment-naive patients with *EGFR*-mutated NSCLC and brain metastases at diagnosis who received afatinib as their first-line therapy between May 2014 and March 2017 were included retrospectively. The patient inclusion period is extended from our previous study[20] to include more patients with brain metastases for analysis. Some of the patients from the National Taiwan University Hospital were also included in another previous study on prognostic factors.[21] This study was approved by the institutional review boards of the 3 hospitals.

Data Collection and Response Assessment

Clinical data was collected and analyzed, including patient age, gender, smoking status, disease stage, metastatic sites, type of *EGFR*

Table 1 Clinical Characteristics of Patients With *EGFR*-mutated Lung Adenocarcinoma and Brain Metastasis (N = 84)

Characteristic	N (%)
Median age, y (range)	60.3 (35.7-82.1)
Gender	
Female	57 (67.9)
Male	27 (32.1)
Smoking history	
Never-smokers	65 (77.4)
Ex- or current smokers	19 (22.6)
ECOG performance status	
0-1	76 (90.5)
2-4	8 (9.5)
EGFR mutations	
Exon 19 deletion	50 (59.5)
Exon 21 *L858R*	14 (16.7)
Rare	11 (13.1)
Complex	9 (10.7)
Metastasis other than brain	
No	20 (23.8)
Yes	64 (76.2)
Metastatic sites other than brain	
Bone	41 (48.8)
Pleura	20 (23.8)
Adrenal gland	12 (14.3)
Liver	9 (10.7)
Others[a]	6 (7.1)
Initial daily doses	
30 mg	22 (26.2)
40 mg	62 (73.8)
Treatments in addition to afatinib	
WBRT	21 (25.0)
Stereotactic radiosurgery	7 (8.3)
Brain tumor resection	1 (1.2)
Brain tumor resection followed by WBRT	1 (1.2)
None	54 (64.3)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; WBRT = whole brain radiotherapy.
[a]The other metastatic sites included pericardium (N = 2), cervical lymph node (N = 1), spleen (N = 1), kidney (N = 1), and pancreas (N = 1).

mutation, Eastern Cooperative Oncology Group performance status (ECOG PS), and local treatments for brain metastasis. Local treatments for brain metastasis were defined as WBRT, SRS, or brain tumor resection within 1 month before or after the first dose of afatinib treatment. A rare mutation was defined as an *EGFR* mutation other than an exon 19 deletion or exon 21 L858R, and a complex mutation was defined as the coexistence of 2 or more distinct *EGFR* mutations. Afatinib was administered with an initial daily dose of 30 mg or 40 mg, according to the physician's clinical judgment. The average daily dose was calculated by dividing the summation of all doses of prescribed afatinib tablets by the total number of days of treatment.

Brain metastases were documented based on cranial contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). The baseline radiographic images were all taken within 1 month before the initiation of afatinib therapy, including a cranial enhanced CT or MRI for intracranial evaluation and a chest CT (including the liver and adrenal glands) for systemic evaluation. Patients were defined as evaluable if they had evaluable baseline image assessments (cranial and extracranial) prior to afatinib therapy and at least 1 evaluable cranial image assessment after afatinib therapy was initiated.

The intracranial treatment responses were assessed by cranial MRI or CT at an interval of 8 to 12 weeks or as needed, based on the physician's clinical judgment. This is the routine practice for evaluation of treatment response at all 3 hospitals. The best intracranial treatment responses were evaluated and analyzed, based on the response assessment criteria for brain metastases.[22] Intracranial complete remission (CR) was defined as the disappearance of all target lesions and with no new lesions occurring. Intracranial partial response (PR) was defined that the sum of the longest diameter (LD) of the target lesions decreased by at least 30% compared with the baseline sum of the LD, with no new lesions occurring. Intracranial progressive disease (PD) was defined as an increase of at least 20% in the sum of the LD of the target lesions, compared with the baseline sum of the LD. Intracranial stable disease (SD) was defined as neither sufficient shrinkage to qualify for intracranial PR nor sufficient increase to qualify for intracranial PD.

For those without measurable lesions, intracranial CR was defined as the disappearance of all nonmeasurable lesions. Intracranial PR was defined as the partial disappearance of intracranial lesions, whereas PD was defined as the increase in size or the number of lesions as assessed by the investigators or radiology reports, or the appearance of new lesions.[22] The intracranial objective response rate (IORR) was defined as the proportion of patients who had an intracranial PR or CR. The intracranial disease control rate (IDCR) was defined as the proportion of patients who had intracranial SD, PR, or CR.

The systemic treatment responses were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1.[23] The objective response rate (ORR) was defined as the percentage of patients who achieved a CR or PR. The disease control rate (DCR) was defined as the percentage of patients who achieved CR, PR, or SD. PFS was defined as the interval between the date of afatinib therapy started and the date that the first objective sign of disease progression was detected. The cutoff date for clinical information and follow-up data is April 30, 2018.

Statistical Analysis

Continuous variables were presented as the median (range), and categorical variables were presented as a number and percentage for analysis. The statistical differences between the responses among the patient groups of different daily doses were determined using the χ^2 test and Yates correction or the Fisher exact test for categorical variables and the Student test for continuous variables where appropriate. All tests for significance were 2-sided. A P value of $< .05$ was considered statistically significant. All analyses were done by using SPSS software (version 22 for Mac, SPSS Inc, Chicago, IL) and SAS (version 9.4, SAS Institute Inc, Cary, NC).

Table 2 Intracranial Responses to and Systemic Treatment Effectiveness of Afatinib Therapy, Alone or Plus Local Treatments, in Patients With *EGFR*-mutated Lung Adenocarcinoma and Brain Metastasis (N = 74)

	All Patients	Afatinib Alone (N = 45)	Afatinib Plus Local Treatments[a] (N = 29)	*P* Value
Intracranial treatment responses				
Complete response	32 (43.2, 32.0-54.5)	25 (55.6, 41.0-70.1)	7 (24.1, 8.6-39.7)	.008
Partial response	28 (37.8, 26.8-48.9)	12 (26.7, 13.7-39.6)	16 (55.2, 37.1-73.3)	.014
Stable disease	11 (14.9, 6.8-23.0)	5 (11.1, 1.9-20.3)	6 (20.7, 5.9-35.4)	.322
Progressive disease	3 (4.1, 0-8.5)	3 (6.7, 0.0-14.0)	0 (0.0, NA)	.275
IORR	60 (81.0, 72.2-90.0)	37 (82.2, 71.1-93.4)	23 (79.3, 64.6-94.1)	.755
IDCR	71 (95.9, 91.5-100.0)	42 (93.3, 86.0-100.0)	29 (100.0, NA)	.156
Systemic treatment effectiveness				
ORR	55 (74.3, 64.4-84.3)	33 (73.3, 60.4-86.3)	22 (75.9, 60.3-91.4)	.808
DCR	70 (94.6, 89.4-99.7)	43 (95.6, 89.5-100.0)	27 (93.1, 83.9-100.0)	.649
Median PFS (months)	12.9	11.7	15.0	.509

Data are presented as N (%, 95% confidence interval).
Abbreviations: DCR = disease control rate; IDCR = intracranial disease control rate; IORR = intracranial objective response rate; NA = not applicable; ORR = objective response rate; PFS =progression-free survival.
[a]Twenty (69.0%) patients received whole brain radiotherapy, 7 (24.1%) stereotactic radiosurgery, 1 (3.4%) underwent brain tumor resection, and 1 (3.4%) brain tumor resection followed by whole brain radiotherapy.

Results

Clinical Characteristics

From May 2014 to March 2017, 276 patients who had diagnosed advanced *EGFR*-mutated lung adenocarcinoma and received afatinib as the first-line therapy were enrolled in the 3 hospitals. Among them, 84 patients had brain metastases and were eligible for analysis (Figure 1). The demographic data is listed in Table 1. The median age of patients was 60.3 years. The majority of patients were females (67.9%), never-smokers (77.4%), and with an ECOG PS score of 0 to 1 (90.5%). The most common *EGFR* mutation was exon 19 deletion (59.5%), followed by exon 21 L858R (16.7%), rare mutations (13.1%), and complex mutations (10.7%).

Sixty-two patients (73.8%) were treated with afatinib at an initial daily dose of 40 mg, whereas 22 (26.2%) were treated at an initial daily dose of 30 mg. For brain metastases treatment, 30 patients received afatinib plus local treatments, including 21 (25.0%) WBRT, 7 (8.3%) SRS, 1 (1.2%) brain tumor resection, and 1 (1.2%) tumor resection followed by WBRT. Fifty-four (64.3%) patients received afatinib alone.

The clinical characteristics of patients who were treated with an initial daily dose of 30 mg or 40 mg, and those treated with afatinib alone or afatinib plus local treatment, are shown in Supplemental Tables 1 and 2 (in the online version).

Intracranial Responses to Afatinib Therapy

A total of 74 patients had evaluable radiography images of the brain during their follow-up. The intracranial treatment responses are listed in Table 2, including 32 (43.2%) CR, 28 (37.8%) PR, 11 (14.9%) SD, and 3 (4.1%) PD. The overall IORR was 81.0%, and the IDCR was 95.9%. In terms of different EGFR mutation types, the IORRs were 87.0% (40/46), 80.0% (8/10), 70.0% (7/10), and 50% (4/8) in patients with exon 19 deletion, L858R, rare mutations, and complex mutations, respectively.

Among these patients, 45 were treated with afatinib alone and 29 received afatinib therapy plus local treatments. No significant differences were found in the IORR and IDCR between the patients treated with afatinib alone and afatinib plus local treatments (IORR: 82.2% vs. 79.3%; $P = .755$ and IDCR: 93.3% vs. 100%; $P = .156$, respectively) (Table 2).

When looking at the individual treatment responses (Table 2), we found that patients with afatinib treatment alone had a higher proportion of CR (55.6% vs. 24.1%; $P = .008$) and a lower proportion of PR (26.7% vs. 55.2%; $P = .014$) than those with afatinib plus local treatments. Three (6.7%) patients in the afatinib alone group had PD, whereas none had PD in the afatinib plus local treatment group.

Intracranial Treatment Responses to Afatinib at Different Initial Daily Doses

The intracranial responses at an initial daily dose of 30 mg or 40 mg are listed in Table 3. For patients treated with afatinib alone (N = 45), no significant difference was found between the 30-mg (N = 15) and 40-mg (N = 30) treatment groups (30 mg vs. 40 mg, IORR: 86.7% vs. 80.0%; $P = .581$ and IDCR: 93.3% vs. 93.3%; $P = 1.000$, respectively). For patients treated with afatinib plus local treatments (N = 29), the intracranial responses were also similar in both the 30-mg (N = 4) and 40-mg (N = 25) treatment groups (30 mg vs. 40 mg, IORR: 100% vs. 76%; $P = .271$ and IDCR: 100% vs. 100%; $P = 1.000$, respectively). Figure 2 and Figure 3 show waterfall plots of the intracranial responses in the 30-mg and 40-mg treatment groups, respectively.

Intracranial Treatment Responses to Afatinib at Different Average Daily Doses

The intracranial responses to afatinib therapy at different average doses are shown in Table 4. In the groups treated with afatinib alone (N = 45), the IORRs were 75.0%, 91.7%, 80.0%, and 85.7% ($P = .707$), and the IDCRs were 93.8%, 100.0%, 90.0%, and 85.7% ($P = .638$) in patients with an average daily dose of 40 mg (N = 16), < 40 mg and > 30 mg (N = 12), 30 mg (N = 10),

Table 3 Intracranial Responses to and Systemic Treatment Effectiveness of Afatinib Therapy at Different Initial Daily Doses in Patients With *EGFR*-mutated Lung Adenocarcinoma and Brain Metastasis (N = 74)

Intracranial Responses	Afatinib Alone (N = 45)		*P* Value	Afatinib Plus Local Treatments[a] (N = 29)		*P* Value
	30 mg (N = 15)	40 mg (N = 30)		30 mg (N = 4)	40 mg (N = 25)	
Intracranial treatment responses						
Complete response	10 (66.7, 42.8-90.5)	15 (50.0, 32.1-67.9)	.289	1 (25.0, 0.0-67.4)	6 (24.0, 7.3-40.7)	1.000
Partial response	3 (20.0, 0.0-40.2)	9 (30.0, 13.6-46.4)	.722	3 (75.0, 32.6-100.0)	13 (52.0, 32.4-71.6)	.606
Stable disease	1 (6.7, 0.0-19.3)	4 (13.3, 1.2-25.5)	.651	0 (0.0, NA)	6 (24.0, 7.3-40.7)	.553
Progressive disease	1 (6.7, 0.0-19.3)	2 (6.7, 0.0-15.6)	1.000	0 (0.0, NA)	0 (0.0, NA)	1.000
IORR	13 (86.7, 69.5-100.0)	24 (80.0, 65.7-94.3)	.581	4 (100.0, NA)	19 (76.0, 59.3-92.7)	.271
IDCR	14 (93.3, 80.7-100.0)	28 (93.3, 84.4-100.0)	1.000	4 (100.0, NA)	25 (100.0, NA)	1.000
Systemic treatment effectiveness						
ORR	12 (80.0, 59.8-100.0)	21 (70.0, 53.6-86.4)	.475	3 (75.0, 32.6-100.0)	19 (76.0, 59.3-92.7)	.965
DCR	15 (100.0, NA)	28 (93.3, 84.4-100.0)	.306	4 (100, NA)	23 (92.0, 81.4-100.0)	.558
Median PFS (months)	9.1	12.9	.193	7.7	15.0	.963

Data are presented as N (%, 95% confidence interval).
Abbreviations: DCR = disease control rate; IDCR = intracranial disease control rate; IORR = intracranial objective response rate; NA = not applicable; ORR = objective response rate; PFS = progression-free survival.
[a]Twenty (69.0%) patients received whole brain radiotherapy, 7 (24.1%) stereotactic radiosurgery, 1 (3.4%) underwent brain tumor resection, and 1 (3.4%) brain tumor resection followed by whole brain radiotherapy.

and < 30 mg and > 20 mg (N = 7), respectively. Similarly, in the groups treated with afatinib plus local treatments, the IORRs were 88.2%, 57.1%, 100.0%, and 66.7% (P = .291), and the IDCRs were all 100.0% in patients with an average daily dose of 40 mg (N = 17), < 40 mg and > 30 mg (N = 7), 30 mg (N = 2), and < 30 mg and > 20 mg (N = 3), respectively.

Systemic Treatment Effectiveness of Afatinib

As for the systemic treatment effectiveness of afatinib, including ORR, DCR, and PFS, no significant differences were found between patient groups that received afatinib alone and afatinib plus local treatment (Table 2). There was also no significant difference found between patients groups that received an initial daily dose of afatinib at 30 mg and 40 mg, either alone or combined with local treatments (Table 3). Table 4 demonstrates the systemic treatment responses to afatinib at different average daily doses, either alone or combined with local treatments, which showed no significant differences among these patient groups.

Discussion

In this multicenter retrospective study, we reported the intracranial treatment responses to afatinib, alone or with local treatments, in patients with *EGFR*-mutated lung adenocarcinoma and brain metastases in Taiwan. The study showed comparable intracranial responses among the treatment groups at different daily doses. To the best of our knowledge, this is the first study on intracranial responses to afatinib at different daily doses as a first-line therapy against NSCLC.

The effectiveness of afatinib on brain metastases at different doses is seldom investigated. Post hoc analyses of the LUX-Lung 3 and 6 trials demonstrated that a tolerability-guided dose adjustment of afatinib reduced the incidence and severity of treatment-related adverse events without affecting efficacy.[15] Two retrospective studies reported similar effectiveness in patients receiving a daily dose of 40 mg or < 40 mg.[17,18] However, the efficacy of afatinib at different doses on brain metastases was not reported in these studies. In the present study, the intracranial responses to afatinib were similar among treatment groups of different daily doses when either initial or average dose was analyzed. This suggests that a modification of daily doses may not affect the intracranial disease control.

In clinical trials for afatinib, most subgroup analyses focus on the overall treatment efficacies for patients with brain metastases,[13,14] and data for the intracranial treatment efficacy of afatinib on brain metastases in patients with NSCLC is limited. A retrospective review of 28 patients with lung adenocarcinoma and brain metastasis, treated with afatinib monotherapy (N = 11) or afatinib with WBRT (N = 17), showed that the IORR and IDCR were both 81.8% for the afatinib monotherapy group and 88.2% and 94.1% for the combination group, respectively.[24] Further prospective studies with larger case numbers may be necessary to clarify the correlation between afatinib therapy and the intracranial progression-free period.

For those with brain metastases using EGFR-TKI as a first-line treatment, the addition of local treatments remains controversial. A retrospective study on patients with *EGFR*-mutated NSCLC with brain metastases concluded that the addition of WBRT to EGFR-TKI therapy showed no survival benefits compared with EGFR-TKI

Figure 2 Intracranial Responses to Afatinib Therapy at an Initial Daily Dose of 30 mg in Patients With *EGFR*-mutated Lung Adenocarcinoma and Brain Metastasis (N = 19)

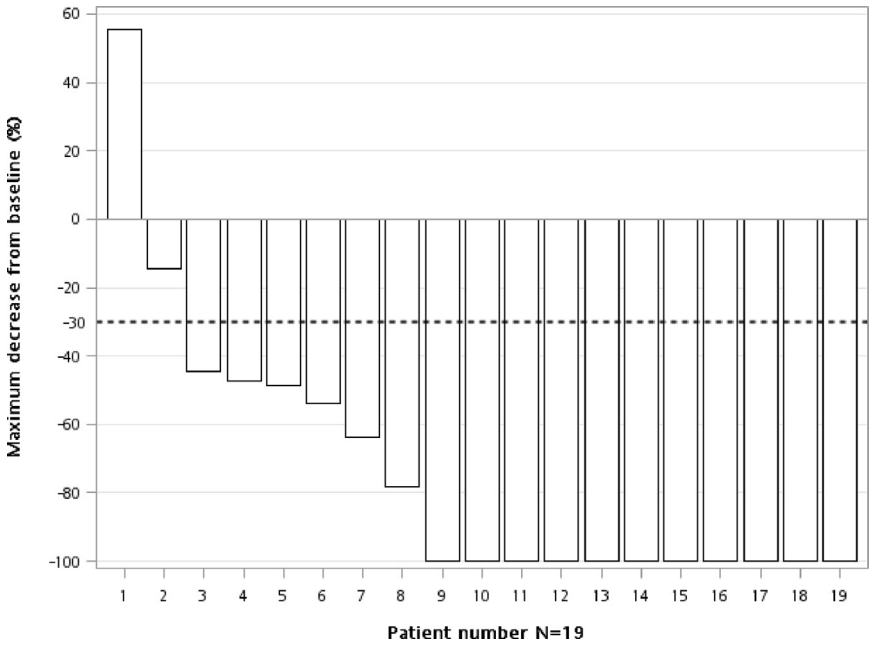


Figure 3 Intracranial Response to Afatinib Therapy at an Initial Daily Dose of 40 mg in Patients With *EGFR*-mutated Lung Adenocarcinoma and Brain Metastasis (N = 55). *Increased 66% in Size From Baseline

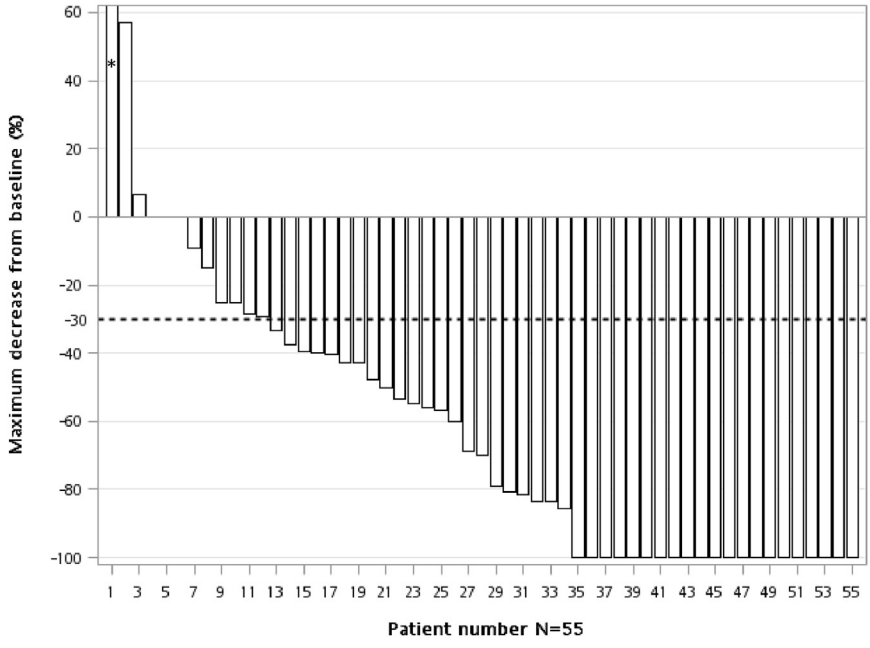


Table 4 Intracranial and Systemic Responses to Afatinib at Different Average Daily Doses in Patients With *EGFR*-mutated Lung Adenocarcinoma and Brain Metastasis (N = 74)

	Afatinib Alone (N = 45)					Afatinib Plus Local Treatments[a] (N = 29)				
	40 mg (N = 16)	< 40 mg and > 30 mg (N = 12)	30 mg (N = 10)	< 30 mg and > 20 mg (N = 7)	*P* Value	40 mg (N = 17)	< 40 mg and > 30 mg (N = 7)	30 mg (N = 2)	< 30 mg and > 20 mg (N = 3)	*P* Value
Intracranial responses										
Complete response	9 (56.3, 31.9-80.6)	6 (50.0, 21.7-78.3)	7 (70.0, 41.6-98.4)	3 (42.9, 6.2-79.5)	.693	6 (35.3, 12.6-58.0)	0 (0.0, NA)	1 (50.0, 0.0-100.0)	0 (0.0, NA)	.167
Partial response	3 (18.8, 0.0-37.9)	5 (41.7, 13.8-69.6)	1 (10.0, 0.0-28.6)	3 (42.9, 6.2-79.5)	.235	9 (52.9, 29.2-76.7)	4 (57.1, 20.5-93.8)	1 (50.0, 0.0-100.0)	2 (66.7, 13.3-100.0)	.973
Stable disease	3 (18.8, 0.0-37.9)	1 (8.3, 0.0-24.0)	1 (10.0, 0.0-28.6)	0 (0.0, NA)	.588	2 (11.8, 0.0-27.1)	3 (42.9, 6.2-79.5)	0 (0.0, NA)	1 (33.3, 0.0-86.7)	.291
Progressive disease	1 (6.3, 0.0-18.1)	0 (0.0, NA)	1 (10.0, 0.0-28.6)	1 (14.3, 0.0-40.2)	.638	0 (0.0, NA)	0 (0.0, NA)	0 (0.0, NA)	0 (0.0, NA)	1.000
IORR	12 (75.0, 53.8-96.2)	11 (91.7, 76.0-100.0)	8 (80.0, 55.2-100.0)	6 (85.7, 59.8-100.0)	.707	15 (88.2, 72.9-100.0)	4 (57.1, 20.5-93.8)	2 (100.0, NA)	2 (66.7, 13.3-100.0)	.291
IDCR	15 (93.8, 81.9-100.0)	12 (100.0, NA)	9 (90.0, 71.4-100.0)	6 (85.7, 59.8-100.0)	.638	17 (100.0, NA)	7 (100.0, NA)	2 (100.0, NA)	3 (100.0, NA)	1.000
Systemic responses										
ORR	11 (68.8, 46.0-91.5)	10 (83.3, 62.2-100.0)	7 (70.0, 41.6-98.4)	5 (71.4, 38.0-100.0)	.836	13 (76.5, 56.3-96.6)	5 (71.4, 38.0-100.0)	1 (50.0, 0.0-100.0)	3 (100, NA)	.623
DCR	14 (87.5, 71.3-100.0)	12 (100, NA)	10 (100, NA)	7 (100, NA)	.285	16 (94.1, 82.9-100.0)	6 (85.7, 59.8-100.0)	2 (100, NA)	3 (100, NA)	.803

Data were presented as N (%, 95% confidence interval).
Abbreviations: DCR = disease control rate; IDCR = intracranial disease control rate; IORR = intracranial objective response rate; ORR = objective response rate.
[a]Twenty (69.0%) patients received whole brain radiotherapy, 7 (24.1%) stereotactic radiosurgery, 1 (3.4%) underwent brain tumor resection, and 1 (3.4%) brain tumor resection followed by whole brain radiotherapy.

therapy alone.[25] Another retrospective study on patients with *EGFR*-mutant NSCLC and brain metastases demonstrated no significant survival difference in patients who received upfront radiotherapy compared with the deferral radiotherapy group (28.0 vs. 26.5 months; $P = .74$).[26] Notably, a meta-analysis demonstrated that EGFR-TKI alone exhibited superior intracranial PFS when compared with WBRT plus EGFR-TKI.[12]

In contrast, a retrospective multi-institutional analysis in patients with *EGFR*-mutant NSCLC and brain metastases demonstrated that patients who received SRS followed by EGFR-TKI therapy had the longest survival compared with those treated with WBRT followed by EGFR-TKI or with EGFR-TKI followed by SRS or WBRT at intracranial progression.[27] Another recent meta-analysis also demonstrated that patients with *EGFR*-mutated NSCLC with brain metastases had improved intracranial PFS and overall survival benefits when they received up-front radiotherapy and TKIs compared with those who received TKIs alone.[28] Our present study demonstrated that the intracranial responses were comparable in patients treated with afatinib alone or afatinib plus local treatments, including WBRT, SRS, and brain tumor resection.

There are several limitations to this study. First, it is a retrospective observational study. The dose selection of afatinib was based on the patient characteristics and physician's clinical judgment, which results in an inevitable selection bias. Second, the case number is relatively small; thus, these results need to be interpreted with caution. Nevertheless, it was relatively larger than those previously reported. Third, the intervals of image assessment for treatment response were inconsistent. Not all patients had brain images at disease progression. The intracranial PFS was not evaluated and analyzed. Therefore, these findings need to be validated in prospective large-scale studies in the future.

Conclusion

In conclusion, dose reduction may not affect the intracranial responses to afatinib, either alone or in combination with local treatments, in patients with advanced EGFR-mutated NSCLC and brain metastases. Further prospective studies for validation are warranted.

Clinical Practice Points

- Afatinib is commonly used as first-line treatment for advanced *EGFR*-mutated NSCLC, and dose adjustments are frequently required. However, the effectiveness of afatinib on brain metastasis after dose reduction has seldom been studied.
- Our results demonstrated that intracranial responses to afatinib were comparable in patients treated at different daily doses, either alone or combined with WBRT, SRS, or brain tumor resection.
- These findings will help the clinician in adjusting the doses of afatinib when treating patients with advanced *EGFR*-mutated NSCLC and brain metastases.

Disclosure

Dr Chen reports payments from AstraZeneca, Roche, Novartis, Pfizer, Eli Lilly, Merck Sharp and Dohme, ONO Pharmaceutical, and Boehringer Ingelheim for lectures including service on speakers' bureaus, as well as travel/accommodations/meeting expenses from Merck Sharp and Dohme, Chugai Pharmaceutical, Pfizer, and Boehringer Ingelheim. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.02.009.

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Supplemental Table 1 Clinical Characteristics of Patients With Initial Daily Dose of 30 mg and 40 mg

	30 mg (N = 19)	40 mg (N = 55)	*P* Value
Age ± SD, y (range)	64.4 ± 12.1 (35.7-79.9)	58.8 ± 9.7 (40.8-82.1)	.105
Gender			.927
Female	13 (68.4)	37 (67.3)	
Male	6 (31.6)	18 (32.7)	
Smoking			.817
Non-smoker	15 (78.9)	42 (76.4)	
Former/ex-smoker	4 (21.1)	13 (23.6)	
ECOG PS			.565
0-1	19 (100)	52 (94.5)	
2-4	0 (0)	3 (5.5)	
EGFR mutation			.499
Exon 19 deletion	12 (63.2)	34 (61.8)	
Exon 21 *L858R*	1 (5.3)	9 (16.4)	
Rare	4 (21.1)	6 (10.9)	
Complex	2 (10.5)	6 (10.9)	
Treatments for brain metastasis			.060
Afatinib alone	15 (78.9)	30 (54.5)	
Afatinib plus local treatments	4 (21.1)	25 (45.5)	

Data are presented as N (%).
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epithelial growth factor receptor; SD = standard deviation.

Supplemental Table 2 Clinical Characteristics of Patients Treated With Afatinib Alone and Afatinib Plus Local Treatments

	Afatinib Alone (N = 45)	Afatinib Plus Local Treatments (N = 29)	*P* Value
Age ± SD, y (range)	57.8 ± 10.7 (35.7-80.9)	64.1 ± 9.3 (49.8-82.1)	.031
Gender			.187
Female	33 (73.3)	17 (58.6)	
Male	12 (26.7)	12 (41.4)	
Smoking			.320
Non-smoker	36 (80.0)	21 (72.4)	
Former/ex-smoker	9 (20.0)	8 (27.6)	
ECOG PS			.557
0-1	44 (97.8)	27 (93.1)	
2-4	1 (2.2)	2 (6.9)	
EGFR mutation			.092
Exon 19 deletion	33 (73.3)	13 (44.8)	
Exon 21 *L858R*	4 (8.9)	6 (20.7)	
Rare	5 (11.1)	5 (17.2)	
Complex	3 (6.7)	5 (17.2)	
Initial daily dose			.060
30 mg	15 (33.3)	4 (13.8)	
40 mg	30 (66.7)	25 (86.2)	

Data are presented as N (%).
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epithelial growth factor receptor; SD = standard deviation.