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Original Article

Afatinib as First-Line Treatment in Elderly Patients with EGFR-Mutant Non-Small Cell Lung Cancer: Real-World Data Analysis

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SUMMARY

Background: Afatinib, a second-generation tyrosine kinase inhibitor (TKI), showed better overall survival (OS) in treatment-naïve advanced non-small cell lung cancer (NSCLC) patients with exon 19 deletion. However, treatment-related adverse events of afatinib are more common than those of first-generation TKIs. This study aimed to evaluate real-world data regarding the efficacy and treatment-related adverse events of afatinib in elderly patients with NSCLC.
Methods: In this retrospective study, we analyzed the real-world data of patients with NSCLC harboring epidermal growth factor receptor (EGFR) mutation who were treated with afatinib between January 2014 and December 2020 in Mackay Memorial Hospital. We analyzed and compared time to treatment failure (TTF), OS, treatment-related adverse events, and time to dose reduction between the young (age < 65 years) and elderly (age ≥ 65 years) groups.
Results: Treatment-related adverse events were comparable in the young and elderly groups. The median time to dose reduction was 1.04 months in the young group and 2.41 months in the elderly group (p = 0.78). The TTF (15.2 months vs. 12.2 months, p = 0.33) and OS (26.5 months vs. 23.8 months, p = 0.65) of afatinib were similar in the young and elderly groups.
Conclusions: Based on the results of this study, the efficacy and treatment-related adverse events of afatinib were similar in the young and elderly groups. Therefore, afatinib can be safely used in elderly patients with advanced NSCLC harboring EGFR mutation without an increase in side effects.

1. Introduction

Lung cancer remained the leading cause of cancer-related death worldwide, with approximately 1.8 million deaths in 2020.[1] Based on data from the Taiwan Cancer Registry, lung cancer is the second most commonly diagnosed cancer in Taiwan, and approximately 50% of patients with non-small cell lung cancer (NSCLC) are diagnosed after the age of 65 years and approximately 46% patients are in stage IV at initial diagnosis. Taiwan has officially become an aged society since 2018.[2] This implies that clinicians would encounter more number of elderly patients with lung cancer.

The epidermal growth factor receptor (EGFR) driver mutation accounts for non-squamous NSCLC in 50%–60% of Asian patients.[3] Tyrosine kinase inhibitors (TKIs) are the mainstream of treatment for patients with advanced NSCLC harboring EGFR mutations.[4] Based on LUX-Lung 3 and LUX-Lung 6, afatinib, a second-generation TKI, became the first-line treatment drug in patients with EGFR-mutant advanced NSCLC.[5,6] LUX-Lung 7 showed that in comparison with gefitinib, a first-generation TKI, afatinib achieved better progression-free survival (PFS) and time to treatment failure (TTF) in treatment-naïve EGFR-mutant advanced NSCLC patients.[7] Furthermore, a combined overall survival (OS) analysis showed that afatinib caused a higher increase in OS in the exon 19 deletion group than in the chemotherapy group.[8,9] This OS benefit was not seen in the first-generation TKI study. Afatinib provides better OS benefit; however, treatment-related adverse events, especially in the elderly, are still a concern for physicians.

Patients enrolled in clinical trials are different from those in clinical settings. In a clinical setting, older patients with poorer Eastern Cooperative Oncology Group (ECOG) performance status are enrolled. There are limited real-world studies that have evaluated the efficacy and side effects of afatinib in the elderly. Thus, we retrospectively analyzed and compared TTF, OS, treatment-related adverse events, and time to dose reduction in young (age < 65 years) and elderly (age ≥ 65 years) patients with advanced NSCLC harboring EGFR mutation who received afatinib in our hospital. This study aimed to evaluate real-world data regarding the efficacy and treatment-related adverse events of afatinib in elderly patients with advanced NSCLC.

2. Methods

2.1. Study design and patients

This retrospective analysis included treatment-naïve stage IV and recurrent NSCLC patients harboring sensitive EGFR mutations who received afatinib as first-line treatment in MacKay Memorial Hospital between January 2014 and December 2020. The inclusion

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criteria of patients were as follows: 1) patients aged ≥ 20 years, 2) those with histologically confirmed NSCLC, and 3) those who have never undergone any prior treatment for NSCLC. The exclusion criteria were as follows: 1) patients who died within 1 month or those who had < 1 month of follow-up after diagnosis, 2) those in whom NSCLC occurred concurrently with other malignancy, and 3) those with negative or unknown EGFR mutation result.

This study was approved by the ethics committee of our hospital, and we also received IRB approval (IRB number: 21MMHIS196e).

2.2. Statistical analysis

Patient characteristics, OS, TTF, and adverse events were compared between young and elderly patients. We used t-test and chi-square test to compare continuous data and categorical data. The Kaplan-Meier method was used for the survival analysis of OS, TTF, and time to dose modification. All tests were two-tailed and p-values < 0.05 were considered significant. We used a single variable Cox model to estimate hazard ratio and its confidence interval. Statistical analysis was performed using R version 4.0.2.

3. Results

3.1. Patient characteristics

A total of 120 patients with recurrent and advanced NSCLC were screened between January 2014 and December 2020. A total of 115 patients harboring EGFR mutation who received afatinib were enrolled in this study (Figure 1).

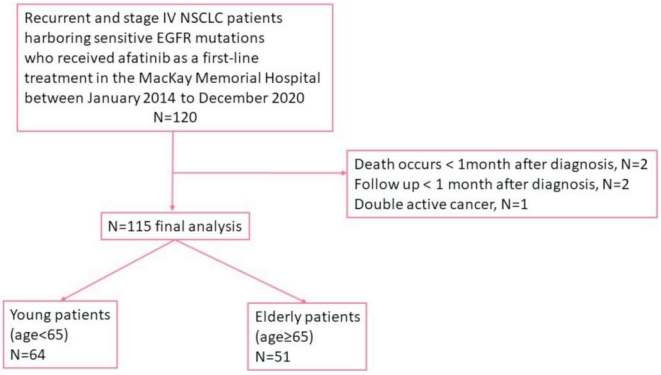

Figure 1. Enrollment flowchart.

The patient characteristics are summarized in Table 1. Of the 115 patients enrolled, 64 patients were aged < 65 years and 51 patients were aged ≥ 65 years. The mean age of patients in our study was 62.4 years (young group: 55.7 years; elderly group: 71 years; p < 0.01). Approximately one-third of our patients had brain metastases at initial diagnosis. In total, 43.8% and 45% patients in the young and elderly groups were men (p = 1.00). Smoker accounted for 37.5% and 29.4% in the young and elderly groups (p = 0.48). There were 14.2% and 23.5% patients with ECOG performance status ≥ 2 in the young and elderly groups, respectively (p = 0.29). The proportion of exon 19 deletion and L858R did not differ between the two groups (64.1% and 34.8% in the young group; 52.9% and 39.2% in the elderly group, respectively). The gender, ECOG status, initial brain metastases, smoking status, and the proportion of exon 19 deletion and L858R were not different between the young and elderly groups. Patient characteristics were similarly distributed.

3.2. Treatment-related adverse events

Toxicities of afatinib were evaluated and are summarized in Table 2. The most common adverse events were acneiform rash (79%) and diarrhea (75%), followed by paronychia (52%), stomatitis/mucositis (33%), interstitial pneumonitis (3%), and elevated liver function (1%). Acneiform rash was the most frequent adverse event in the young group, whereas diarrhea was more common in the elderly group. The incidence rate of any grade adverse events was similar in

Table 2
Frequent treatment-related adverse events of afatinib in young and elderly.

Adverse events, n (%)	Young (n = 64)	Elderly (n = 51)	p-value
Any grade			
Diarrhea	38 (59.3%)	37 (72.5%)	0.20
Acneiform rash	46 (71.9%)	33 (64.7%)	0.5
Stomatitis/mucositis	21 (32.8%)	12 (23.5%)	0.38
Paronychia	31 (48.4%)	21 (41.2%)	0.56
Pneumonitis	1 (1.6%)	2 (3.9%)	0.84
Elevated liver function	0 (0%)	1 (1.9%)	0.91
Grade 3–4			
Diarrhea	5 (7.8%)	3 (5.9%)	0.97
Acneiform rash	6 (9.4%)	1 (2.0%)	0.21
Stomatitis/mucositis	1 (1.6%)	1 (1.9%)	1
Paronychia	4 (6.3%)	0 (0%)	0.19
Pneumonitis	1 (1.6%)	2 (3.9%)	0.84
Elevated liver function	0 (0%)	1 (1.9%)	0.91

Table 1
Patient characteristics.

Patient characteristics	All (n = 115)	Young (n = 64)	Elderly (n = 51)	p-value
Age (mean)	62.4	55.7	71	< 0.01
Gender, n (%)				1
Male	51 (44.3%)	28 (43.8%)	23 (45%)	
Female	64 (55.7%)	36 (56.2%)	28 (55%)	
Smoking status, n (%)				0.48
Ever-smoker	39 (33.9%)	24 (37.5%)	15 (29.4%)	
Never-smoked	76 (66.1%)	40 (63.5%)	36 (70.6%)	
Baseline ECOG, n (%)				0.29
0–1	94 (81.7%)	55 (85.8%)	39 (76.5%)	
2–4	21 (18.2%)	9 (14.2%)	12 (23.5%)	
Extra-thoracic metastatic site, n (%)				
Brain	30 (26.1%)	16 (25.0%)	14 (27.5%)	0.93
Liver	17 (14.9%)	7 (10.9%)	10 (19.6%)	0.30
Bone	57 (49.6%)	30 (46.9%)	27 (52.9%)	0.65
Mutation status, n (%)				
Del 19	68 (59.1%)	41 (64.1%)	27 (52.9%)	0.31
L858R	41 (35.7%)	21 (32.8%)	20 (39.2%)	0.61

both the groups, without any statistical difference.

3.3. Initial treatment dose and time to dose reduction

The initial treatment dose and dose reduction data are summarized in Table 3. Approximately 38.2% (n = 21) and 41.2% (n = 21) patients in the young and elderly groups, respectively, were given 30 mg afatinib (p = 0.47). Forty-six patients underwent dose reduction. A total of 24 patients (37.5%) in the young group and 22 patients (43.1%) in the elderly group needed dose reductions (p = 0.67). The need for dose reduction was not higher in the elderly group.

The median time to dose reduction was 1.04 months in the young group and 2.41 months in the elderly group (p = 0.78) (Figure 2). The time to dose reduction showed no significant difference between the young and elderly groups.

3.4. TTF and OS

No significant difference was observed between the young and elderly groups in terms of TTF (young vs. elderly: 15.2 months vs. 12.2 months, p = 0.33) (Figure 3) and OS (young vs. elderly: 26.5 months vs. 23.8 months, p = 0.65) (Figure 4). In our study, 42 patients in the young group (n = 64) and 27 patients in the elderly group (n = 51) had disease progression during follow-up (Table 4). Approximately 26.2% and 18.5% patients young and elderly groups, respectively, received osimertinib after disease progression (p = 0.57).

4. Discussion

In the present study, approximately one-third of patients in the young and elderly groups were administered with afatinib at a dose of 30 mg. This proportion was similar to that of a previous real-world study, RealGiDo. In that study, 31% of patients were administered with < 30 mg afatinib.[10] This implies that clinicians would select patients with possible more adverse effects to initiate a low dose of afatinib based on their experience and better understanding of these risk factors.

In the present retrospective study, the incidence rate of dose modification was similar between the young and elderly groups (37.5% vs. 43.1%, p = 0.67). This was comparable to that in LUX-Lung 2; 37% of patients with a starting dose of 40 mg needed dose reduction to 30 mg.[11] In the present study, the need for dose modification was not higher in the elderly group.

Most dose reductions had been made during the first 6 months of clinical trials. In a real-world cohort, the dose of afatinib was adjusted during the first 6 months of treatment for approximately 65.8% of patients.[12] Our data showed similar results; the median time to dose reduction was 1.04 months in the young group and 2.41 months in the elderly group (p = 0.78). A short time to dose reduction indicated effective side effect management of afatinib.

Moreover, a previous post hoc analysis of LUX-3 and LUX-6 also showed that the plasma concentration of afatinib was 23.3 ng/mL in

Table 3
Initial treatment dose and dose reduction of afatinib.

	Young (n = 64)	Elderly (n = 51)	p-value
Initial dose, n (%)			0.47
30 mg	21 (32.8%)	21 (41.2%)	
40 mg	43 (67.2%)	30 (58.8%)	
Dose reduction, n (%)			0.67
Yes	24 (37.5%)	22 (43.1%)	
No	40 (62.5%)	29 (56.9%)	

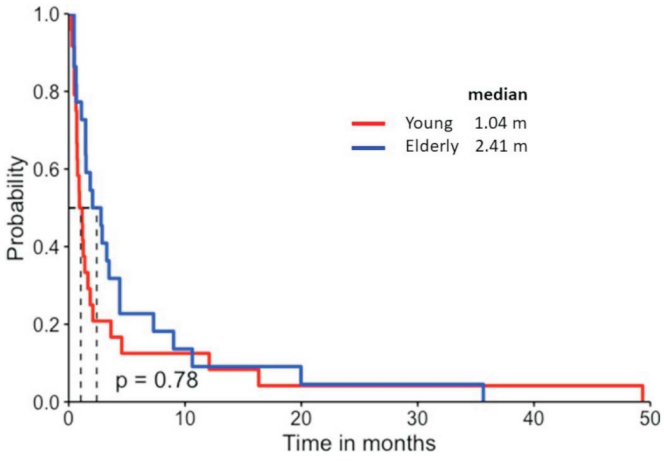

Figure 2. Time to dose reduction.

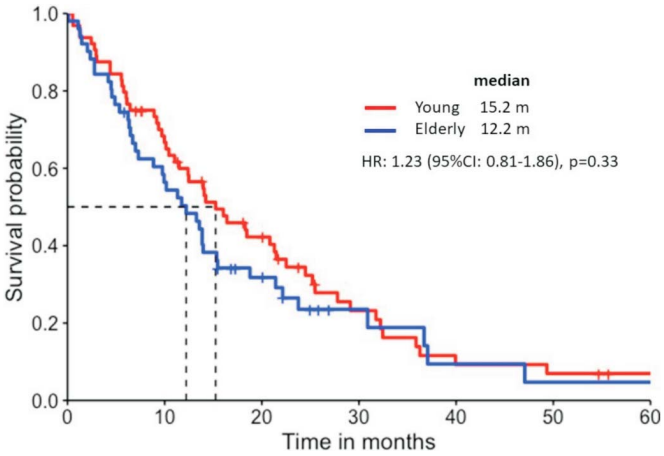

Figure 3. Time to treatment failure.

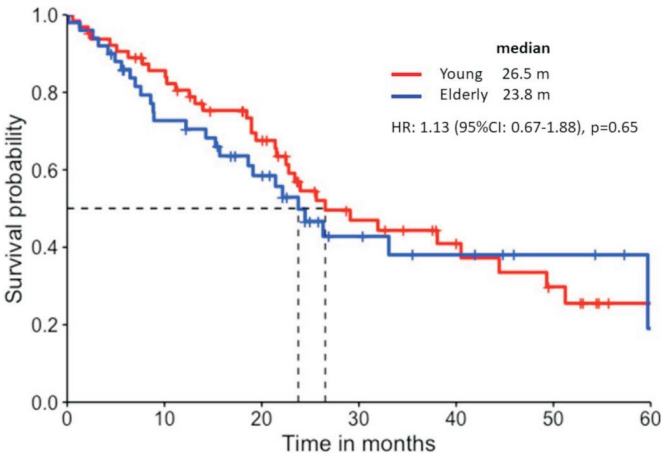

Figure 4. Overall survival.

Table 4
Second line treatment after disease progression.

Progression	Young (n = 64)	Elderly (n = 51)	p value
Yes	42 (65.6%)	27 (52.9%)	0.25
No	14 (21.9%)	12 (23.5%)	
Death	8 (12.5%)	12 (23.5%)	
Second line	**Young (n = 42)**	**Elderly (n = 27)**	**p value**
Osimertinib	11 (26.2%)	5 (18.5%)	0.57
Chemotherapy	21 (50.0%)	17 (63.0%)	
Nil	10 (23.8%)	5 (18.5%)	

the dose reduction group and 28.8 ng/mL in those without.[13] The plasma concentration of afatinib was similar in the two groups. In addition, the median PFS was similar in patients with dose reduction during the first 6 months versus those without dose reduction (LL3: 11.3 versus 11.0 months, hazard ratio [HR]: 1.25; LL6: 12.3 versus 11.0 months, [HR: 1.00]). The treatment effectiveness was consistent in all patients, with or without dose reduction. The RealGiDo study retrospectively reviewed 228 patients with EGFR mutated TKI-naïve NSCLC who were treated with afatinib to evaluate the impact of afatinib dose modification in a real-world setting.[10] Median TTF and time to progression were 18.7 and 20.8 months, respectively, and were not impacted by reduced starting dose or dose modifications. Therefore, we could safely adjust afatinib dose to minimize side effects without worrying about its efficacy.

Based on a previous real-world study in Japan, the mean age of patients with advanced NSCLC who were treated with first-generation TKIs was significantly higher than that of patients receiving second-generation TKIs (70.15 vs. 64.29, $p < 0.001$).[14] This was also observed in another real-word TKI study in Poland;[15] the mean age of patients receiving second-generation TKIs was lower. This implies that in a real-world setting, physicians preferred prescribing first-generation TKIs in elderly patients, although afatinib provided better PFS and OS. It was also observed in the database in our hospital, between January 2014 and December 2020, total number of patients who received 1st and 2nd generation TKI were showed in Table 5. Total 35.2% patients in the young group received afatinib and only 22.3% patients received afatinib in the elderly group ($p = 0.03$). The proportion of those received 2nd generation TKI was higher in the young group.

In the present study, TTF (15.2 months in the young group and 12.2 months in the elderly, $p = 0.33$) and OS (26.5 months in the young group and 23.8 months in the elderly group, $p = 0.65$) were similar between the young and elderly groups. The TTF in the present study is comparable with that of another retrospective study in Taiwan, in which the PFS of patients with EGFR-mutant NSCLC who were treated with afatinib was 14.1 months.[16]

In a pool analysis study of afatinib, the risk factors associated with severe diarrhea were age > 60 years, female sex, and low weight < 45 kg.[17] The risk of severe diarrhea for individuals administered with 40 mg afatinib was 6% for individuals with no risk factors, 7% for those with one risk factor, 15% for those with two risk factors, and 33% for those with all three risk factors. One risk factor alone did not increase the incidence of severe diarrhea. In the present retrospective study, there was no statistical difference in grade 1–2 or high grade (≥ 3) side effects between the young and elderly groups. Old age should not be the only reason to exclude the elderly from using afatinib.

Afatinib can be safely used in both young and elderly patients. The side effects were manageable in both the young and elderly groups and the treatment effectiveness were comparable.

4.1. Limitations

This study had several limitations. First, it was a single-center retrospective study; hence, the sample size was relatively small. Second, our study did not analyze patients who were treated with first-generation TKIs, so it is unclear whether the TTF and OS data of afatinib were better than those of first-generation TKIs in our hospital.

Table 5
Proportion of 2nd generation TKI in the young and elderly.

	< 65 years	≥ 65 years	p
1st generation TKI	118	178	
2nd generation TKI	64	51	
Afatinib/All TKI (%)	64/182 (35.2%)	51/229 (22.3%)	0.03

5. Conclusions

The treatment effectiveness of afatinib was comparable and the incidence rate of dose reduction was similar in the young and elderly groups. In addition, it was observed that there was no increase in side effects in the elderly group in our study. Therefore, these results suggest that afatinib can be safely prescribed in elderly patients. Age cannot be used to exclude the elderly from using afatinib. We can confidently adjust the dose while managing the side effects without compromising the treatment effectiveness. Afatinib can be safely used in elderly patients with advanced NSCLC harboring EGFR mutation without an increase in side effects.

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Conflict of interest

The authors declare that there is no conflict of interest. The material contained in the manuscript has not been previously published and is not being concurrently submitted elsewhere.

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