RESEARCH ARTICLE

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Efficacy and Tolerance of First-Line Afatinib in Elderly NSCLC Patients with *EGFR* Mutations in Vietnam: A Multicenter Real-World Study

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Abstract

Background: Afatinib, a second-generation epidermal growth factor receptor(EGFR) tyrosine kinase, has proven effective for non-small-cell lung cancer (NSCLC) patients with EGFR mutations through randomized controlled trials and real-world studies. Elderly patients exhibit unique characteristics in terms of physical condition and comorbidities, leading to differences in clinical practice for selecting the initial dosage and making dose adjustments compared to younger patients. This study aims to evaluate the effectiveness and adverse effects of first-line Afatinib treatment in elderly patients with NSCLC harboring EGFR mutations in Vietnam in a real-world context. **Methods:** We conducted a retrospective analysis of 135 patients, aged 65 years and older, across nine cancer centers in Vietnam. These patients, who harbored drug-sensitive EGFR mutations (excluding de novo T790M), received first-line Afatinib treatment between April 2018 and June 2022. The primary endpoints, time to treatment failure (TTF), and overall survival (OS) were assessed using the Kaplan-Meier method, and comparisons were conducted using the log-rank test. Secondary endpoints included the overall response rate (ORR) according to RECIST 1.1 and adverse effects as classified by CTCAE 4.0. **Results:** The median age was 71.2 years (SD ± 5.3). Comorbidities included cardiovascular disease (20.7%), diabetes (5.2%), chronic obstructive pulmonary disease (2.2%), and hepatitis B (0.7%). Common mutations constituted 71.9% of cases, with uncommon mutations representing 28.1%. Brain metastases were observed in 24.4% of patients. Initial treatment doses were 40 mg for 35.6% of patients and 30 mg for 62.2%. With a median follow-up of 34.3 months, the median TTF was 16.3 months (95% CI: 15.4-19.5), and the median OS was 32.9 months (95% CI: 28.9-37.5). Factors associated with decreased OS included poor performance status, current smoking, and the presence of uncommon mutations. The ORR was 77.8%, with a complete response of 11.1% and a disease control rate of 94.1%. The most common toxicities were dermatologic and mucosal, including diarrhea (55.6%), rash (48.9%), and stomatitis (40.7%), predominantly in grades 1 and 2. Initiating treatment at doses below 40 mg significantly reduced most toxicities compared to the 40 mg dose. The presence of brain metastases did not significantly affect ORR, TTF, or OS. Starting treatment at doses below 40 mg significantly lowered the response rate but did not impact TTF or OS. **Conclusion:** First-line treatment with Afatinib in elderly patients with NSCLC and EGFR mutations demonstrates significant efficacy and manageable toxicity in a Vietnamese multicenter real-life setting. The effectiveness of Afatinib was confirmed, with known and well-controlled adverse effects, supporting its use in this patient population.

Keywords: Advanced non-small cell lung cancer- EGFR mutations- afatinib- first-line- elderly patients

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Introduction

Lung cancer ranked second regarding prevalence and mortality among all cancer types in Vietnam, according to GLOBOCAN 2020 data [1]. Advancements in the past 20 years, including targeted therapy and immunotherapy,

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have significantly improved the prognosis for patients with advanced non-small cell lung cancer (NSCLC). With the high prevalence of EGFR mutations, ranging from 35.4% to 64.2%, Vietnamese NSCLC patients have benefited significantly from EGFR tyrosine kinase inhibitors (TKI) [2-5].

Since its approval in 2018, afatinib, a second-generation EGFR TKI, continues to be an important treatment option for advanced EGFR-mutant NSCLC patients in Vietnam, alongside first- and third-generation TKIs. The previous real-world study in Vietnam demonstrated the efficacy of afatinib in treating both common and uncommon EGFR mutations [6, 7]. Regarding tolerance, these studies revealed a toxicity profile in Vietnamese patients that is similar to the results observed in randomized controlled trials (RCTs) and other real-world studies in the region. In the previous multicenter study in Vietnam, the overall response rate for afatinib was 78.8%, the median time-to-treatment (TTF) failure was 16.7 months, and the most common toxicities (any grade/grade 3) were diarrhea (55.4%/3.5%), rash (51.9%/3.2%), paronychia (35.3%/5.0%), and stomatitis (22.2%/1.2%) [7].

In elderly patients, the treatment might be challenging due to frailty and comorbidities. Previous results have proven the effectiveness and managebele safety profile in elferly patients, however, patient characteristics may vary between RCTs and real world studies or according to clinical practice of cancer centers [8, 9]. On clinical setting in Vietnam, physicians frequently practice flexible starting doses selection and dose modification in the treatment of afatinib to improve tolerability. Addtionally, additional data on effectiveness of afatinib and risk-benefit ratio of dose adjustment in elderly patients remains important.

Materials and Methods

Study population

This retrospective study analyzed patients with stage IIIB-IV NSCLC (American Joint Committee on Cancer 8th edition) [10], specifically those harboring EGFR mutations identified through next-generation sequencing (NGS) or Real-time polymerase chain reaction (PCR) of tissue or circulating tumor DNA (ctDNA). We included patients from April 2018 to June 2022 who received first-line afatinib treatment at nine Vietnamese cancer centers, including Bach Mai Hospital, Vietnam National Cancer Hospital, Ho Chi Minh City Oncology Hospital, Cho Ray Hospital, Thong Nhat Hospital, National Lung Hospital, 108 Military Central Hospital, Hanoi Medical University Hospital, and Hanoi Oncology Hospital.

Inclusion criteria were patients aged 65 or older with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-3 and comprehensive medical records. Patients with concurrent malignancies or de novo T790M mutations were excluded.

Patients received Afatinib (Boehringer) until progression or intolerable toxicity. Afatinib dosage was individualized based on age, physical condition, and renal function, adhering to physician discretion. Monthly re-evaluations were conducted to monitor for disease progression or severe toxicity, with dosage adjustments made accordingly. If a patient tolerated an initial dose below 40 mg/day without adverse effects, escalation to the standard 40 mg/day dose was considered. The tolerated dose is defined as the highest dose that the patient can tolerate and maintain throughout the course of treatment.

Combination therapies included brain radiation—either whole-brain radiation or radiosurgery—selected by the physician based on the location, number, and size of brain metastases, as well as patient symptoms, in conjunction with bisphosphonate therapy for symptomatic bone metastases.

Treatment outcomes

The primary endpoint was the time-to-treatment failure (TTF), defined as the duration from the initiation of Afatinib treatment to discontinuation due to progression, death, or intolerable toxicity. Another primary endpoint was overall survival (OS), measured from the start of treatment to the patient's death from any cause or the end of the study in March 2024.

Secondary endpoints included the objective response rate (ORR), assessed according to RECIST 1.1 criteria [11], and treatment-related adverse events, evaluated using Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria [12]. Additionally, factors potentially influencing treatment outcomes were analyzed, both univariately and multivariately. These factors comprised age, ECOG performance status, comorbidities, smoking status, presence of initial brain metastasis, type of EGFR mutation, starting dose, and tolerated dose.

Data analyses

Data was analysed using R software for Windows version 4.3.3 (https://cran.r-project.org/bin/windows/base/). The presentation of continuous data as mean±standard deviation or median (interquartile range (IQR)), and categorical data as number (percentage). Comparison was done using the Fisher's exact test and Chi-squared tests as appropriated. TTF and OS were estimated by the Kaplan–Meier method and compared by the log-rank test. The median follow-up was calculated using the reverse Kaplan-Meier method. Multivariate Cox proportional hazard regression models was ultilized to evaluate factors associated with TTF and OS. A p-value of < 0.05 was considered statistically significant.

Results

Patients characteristics

Among 343 advanced-stage NSCLC patients with EGFR mutations who received first-line afatinib treatment from April 2018 to June 2022, 191 patients under 65 years old were excluded. Additionally, 17 patients who discontinued the drug due to reasons other than disease progression or side effects were also excluded. As a result, 135 patients were included in the study. The patient characteristics are presented in detail in Table 1.

The majority of the patients were men (57.0%). Most exhibited an ECOG performance status (PS) of 0-1, with only 9 patients (6.7%) classified as ECOG PS 2-3. The most prevalent comorbidity is cardiovascular disease,

affecting 20.7% of patients, followed by diabetes at 5.2%, chronic obstructive pulmonary disease (COPD) at 2.2%, and hepatitis B virus infection at 0.7%. Regarding EGFR mutations, 42.2% of patients harbor the Del 19 mutation, 29.6% have the L858R mutation, and 28.1% carry other less common mutations. Brain metastases are present in 33 patients, representing 24.4% of the study group. Regarding starting dose, 48 patients (35.6%) began with a dosage of 40 mg/day, whereas the majority, 62.5%, started with a 30 mg/day dosage.

Table 1. Demographic and Clinical Characteristics of Elderly Patients (≥65 Years) Treated with Afatinib

Characteristic	n (%)
Age (mean ± SD)	71.2 ± 5.3
Sex	
Male	77 (57.0%)
Female	58 (43.0%)
ECOG performance status at diagnosis	
PS 0-1	126 (93.3%)
PS 2-3	9 (6.7%)
Comorbidities (*)	
Chronic obstructive pulmonary disease	3 (2.2%)
Diabetes	7 (5.2%)
Cardiovascular diseases	28 (20.7%)
Hepatitis B	1 (0.7%)
Other	9 (6.7%)
No comorbidities	93 (68.9%)
Smoking status	
Current smoker	37 (27.4%)
Nonsmoker/former smoker	98 (72.6%)
Stage	
IIIB/IIIC	6 (4.4%)
Recurrence	5 (3.7%)
IV	124 (91.9%)
Brain metastasis at baseline	
Yes	33 (24.4%)
No	102 (75.6%)
EGFR mutations	
Del 19	57 (42.2%)
L858R	40 (29.6%)
Uncommon mutations	38 (28.1%)
Starting dose	
20 mg	3 (2.2%)
30 mg	84 (62.2%)
40 mg	48 (35.6%)
Tolerated dose	
20 mg	7 (5.2%)
30 mg	95 (70.4%)
40 mg	33 (24.4%)

ECOG, Eastern Cooperative Oncology Group; (*), A patient can have more than one comorbidity.

Time-to-Treatment Failure

With a median follow-up of 30.4 months (95%CI: 24.5-36.3), during which 112 events occurred (83.0% incidence), the mTTF was 16.3 months (95% CI: 15.4-19.5) (Figure 1).

Subgroup analyses (Table 2) revealed mTTF of 17.9 months for the Del19 mutation subgroup, 15.8 months for the L858R mutation subgroup, and 14.3 months for the uncommon mutation subgroup. The differences in mTTF between common and uncommon mutations were not statistically significant. Additionally, no significant differences in mTTF were observed between patients with and without brain metastases (p=0.424). Among patients initiating treatment at doses below 40 mg/day, a trend toward reduced mTTF was noted (16.1 months compared to 18.4 months); however, this difference did not reach statistical significance (p=0.341). Furthermore, there was no significant difference in mTTF between patients administered the tolerated dose of 40 mg/day or less (16.1 months vs. 17.5 months, p=0.461)

A total of 112 patients experienced failure of first-line afatinib treatment. Subsequent treatments for afatinib resistance included palliative care (34.8%), osimertinib (27.7%), and platinum-based doublet chemotherapy (23.2%) (Table 3).

Overall surrvival

During a median follow-up of 34.3 months (95% CI: 31.2-37.3), 74 patients (54.8%) died. The mOS was 32.9 months (95% CI: 28.9-37.5) (Figure 2).

Univariate subgroup analyses (Table 4) revealed that patients who smoked, exhibited poor performance status (ECOG PS 2-3), and harbored uncommon EGFR mutations experienced a statistically significant reduction in OS. Patients initiating treatment with a dose of less than 40 mg had an OS of 32.9 months, compared to 32.4 months for those starting at 40 mg/day; however, this difference was not statistically significant (p = 0.512). There was no statistically significant difference in OS between the groups with and without brain metastases, at 33.1 and 32.4 months, respectively. The group with uncommon mutations had a shorter OS compared to those with common mutations (p = 0.022) and the Del19 mutation (p = 0.036), but not when compared to the L858R mutation group (p = 0.207) (Figure 3).

Multivariate analysis identified current smoking status, poor performance status (PS 2-3), and uncommon gene mutations as independent predictors of poor prognosis in OS (Table 4).

Objective response rate

The overall response rate was 77.8%, with 11.1% achieving a complete response. The disease control rate was 94.1%.

Neither the location of mutations nor the presence of brain metastases influenced the objective response rate. Patients initiating treatment with a dose of less than 40 mg had a response rate of 71.3%, compared to 89.6% in those starting treatment at 40 mg, a difference that was statistically significant (p = 0.014) (Table 5).

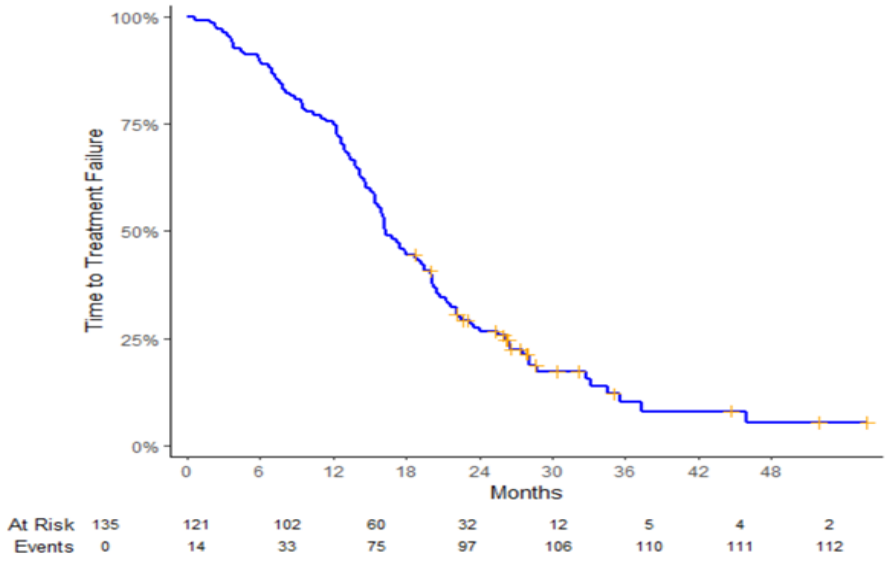

Figure 1. Kaplan–Meier Curve of the Time-to-Failure Treatment of the Study Population

Adverse events

Common adverse effects predominantly affect the skin and mucous membranes, with diarrhea (55.6%/5.2%), rash (48.9%/5.2%), and paronychia (40.7%/5.9%) being the most reported (Table 6). The majority of these effects are mild, classified as grade 1 or 2. However, the rate of grade 3 toxicity was below 10% across all adverse effects, except for paronychia in the group initiating treatment at 40 mg/day, which reached 12.5%. The incidence of unwanted effects was lower in patients starting treatment with a

Table 2. Time to Treatment Failure and Associated Factors in Elderly Patients (≥65 Years) Treated with Afatinib

Factors	mTTF	Univariate analysis (*)		Multivariate analysis (**)	
		p	HR (95% CI)	p	HR (95% CI)
Sex					
Male	15.4	0.67	1.00 (reference)	0.671	1.00 (reference)
Female	17.7		0.92 (0.64-1.34)		1.10 (0.72-1.68)
ECOG					
PS 0-1	16.3	0.695	1.00 (reference)	0.894	1.00 (reference)
PS 2-3	17.8		0.86 (0.40-1.85)		0.95 (0.43-2.10)
Smoking status					
Current smoker	14.7	0.134	1.00 (reference)	0.177	1.00 (reference)
Non/former smoker	18.1		0.73 (0.48-1.11)		0.72 (0.45-1.16)
EGFR mutations					
Del 19	17.9	0.349[a]	-	-	-
L858R	15.8	0.876[b]	-		
Common mutations	16.8	0.461[c]	1.00 (reference)	0.466	1.00 (reference)
Uncommon mutations	14.3	0.685[d]	1.09 (0.72-1.66)d		1.18 (0.76-1.83)d
Brain metastasis					
No	15.9	0.424	1.00 (reference)	0.623	1.00 (reference)
Yes	16.3		1.19 (0.78-1.81)		1.12 (0.72-1.73)
Starting dose					
40 mg	18.4	0.341	1.00 (reference)	0.169	1.00 (reference)
< 40 mg	16.1		1.21 (0.81-1.79)		1.40 (0.87-2.25)
Tolerated dose					
40 mg	17.5	0.461	1.00 (reference)	0.189	1.00 (reference)
< 40 mg	16.1		0.85 (0.55-1.31)		0.70 (0.41-1.19)

HR, Hazard ratio; CI, Confidence Interval; mTTF, median Time to Treatment Failure; (*), Log-rank test (**) Cox regression multivariate analysis; [a], Del 19 vs. L858R; [b], L858R vs. uncommon; [c], Del 19 vs. uncommon; [d], common mutations vs. uncommon mutations

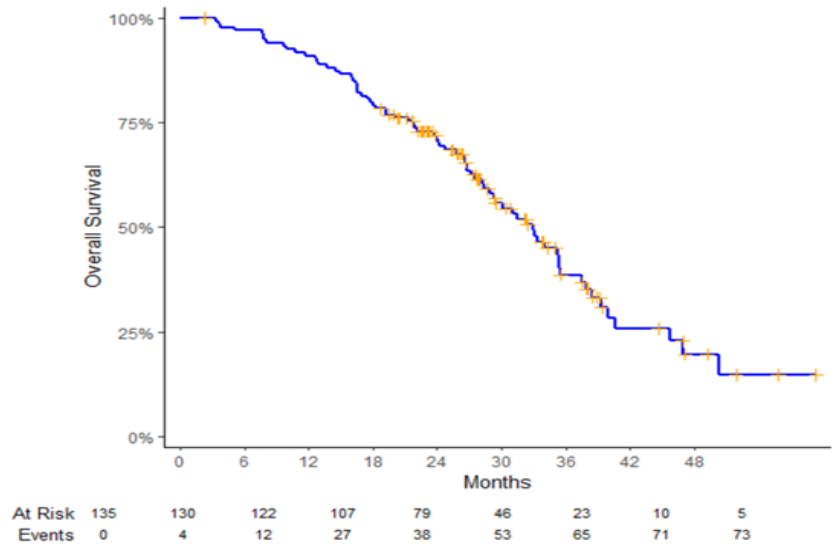

Figure 2. Kaplan–Meier Curve of the Overall Survival of the Study Population

Table 3. Subsequent Treatments in Elderly Patients Following Progression on Afatinib

Treatment Following Resistance to Afatinib	N= 112
Palliative care	39 (34.8%)
Osimertinib	31 (27.7%)
Doublet platinum chemotherapy	26 (23.2%)
Mono chemotherapy	6 (5.4%)
Unknown	10 (8.9%)

dose of less than 40 mg/day. There were no instances of interstitial pneumonia, grade 4 toxicity, or treatment-related mortality recorded.

Discussion

Compared to platinum-based doublet chemotherapy, Afatinib has significantly improved response rate and survival outcomes according to results of LUX Lung

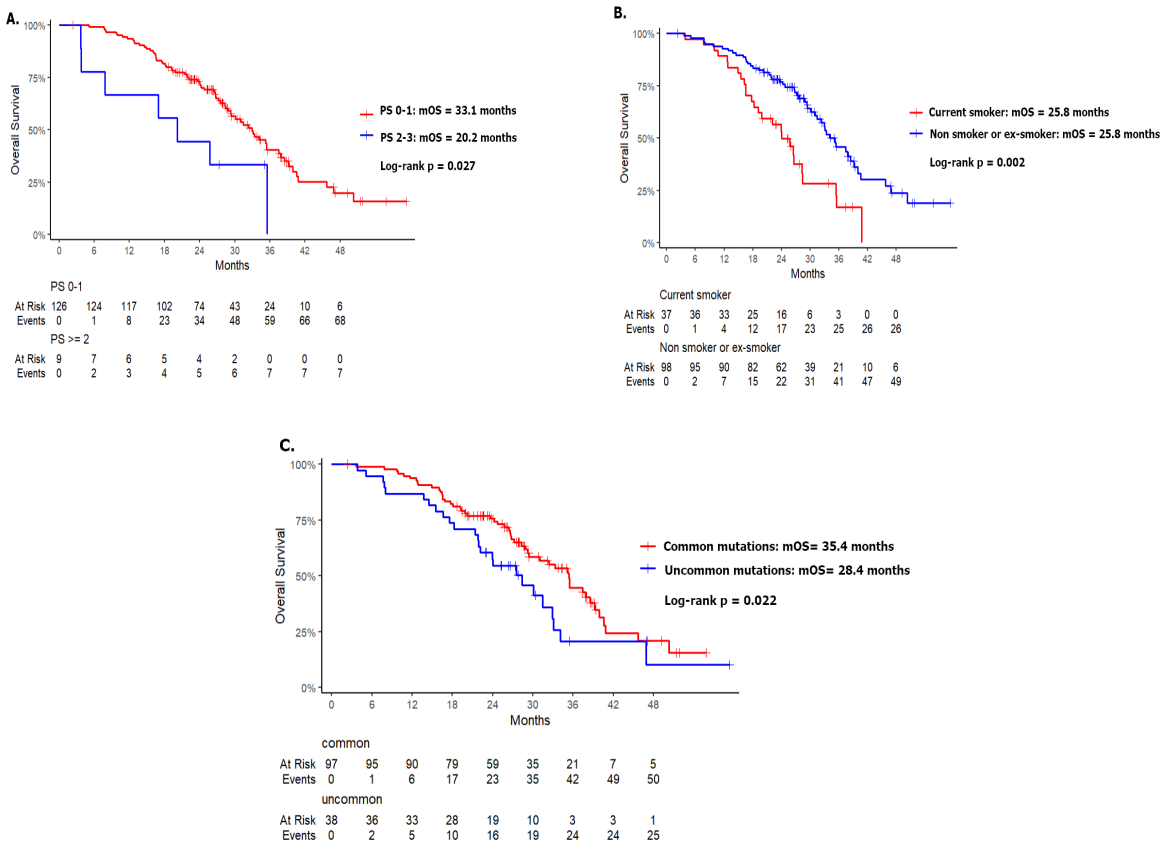

Figure 3: Kaplan–Meier Curve of the Overall Survival Stratified by Perfomance Status (A), smoking status (B) and EGFR mutations (C). Abbreviations: EGFR: Epidermal Growth Factor Receptor

Table 4. Factors Associated with Overall Survival in Elderly Patients (≥65 Years) Treated with Afatinib

Factors	mOS (95%CI)	Univariate analysis (*)		Multivariate analysis (**)	
		p	HR (95% CI)	p	HR (95% CI)
Sex					
Male	29.3	0.058	1.00 (reference)	0.548	1.00 (reference)
Female	35.2		0.63 (0.39-1.02)		0.85 (0.50-1.44)
ECOG					
PS 0-1	33.1	0.027	1.00 (reference)	0.046	1.00 (reference)
PS 2-3	20.2		2.37 (1.08-5.19)		2.38 (1.02-5.58)
Smoking status					
Current smoker	25.8	0.002	1.00 (reference)	0.027	1.00 (reference)
Non/former smoker	34.1		0.47 (0.28-0.77)		0.53 (0.31-0.93)
EGFR mutations					
Del 19	35.4	0.550[a]	-	-	-
L858R	37.9	0.207[b]	-		
Common mutations	35.4	0.036[c]	1.00 (reference)	0.022	1.00 (reference)
Uncommon mutations	28.4	0.022[d]	1.67 (1.03-2.72)d		1.84 (1.09-3.10)[d]
Brain metastasis					
No	32.4	0.565	1.00 (reference)	0.487	1.00 (reference)
Yes	33.1		1.17 (0.68-2.00)		1.22 (0.69-2.16)
Starting dose					
40 mg	32.4	0.512	1.00 (reference)	0.483	1.00 (reference)
< 40 mg	32.9		1.17 (0.73-1.89)		1.22 (0.70-2.13)
Tolerated dose					
40 mg	33.4	0.78	1.00 (reference)	0.692	1.00 (reference)
< 40 mg	32.9		1.08 (0.63-1.84)		0.88 (0.46-1.69)

HR, Hazard ratio; CI, Confidence Interval; mOS, median Overall Survival; (*), Log-rank test; (**), Cox regression multivariate analysis; [a], Del 19 vs. L858R; [b], L858R vs. uncommon; [c], Del 19 vs. uncommon; [d], common mutations vs. uncommon mutations

Table 5. Factors Associated with Overall Response Rate in Elderly Patients (≥65 Years) Treated with Afatinib

Characteristic	ORR[1]	p-value[2]
Sex		
Male	61 (79.2%)	0.642
Female	44 (75.9%)	
ECOG		
PS 0-1	100 (79.4%)	0.11
PS 2-3	5 (55.6%)	
Smoking status		
Current smoker	29 (78.4%)	0.918
Non/former smoker	76 (77.6%)	
Brain metastasis		
Yes	81 (79.4%)	0.422
No	24 (72.7%)	
EGFR mutations		
Del 19	49 (86.0%)	0.137
L858R	28 (70.0%)	
Uncommon mutations	28 (73.7%)	
Starting dose		
40 mg	43 (89.6%)	0.014
< 40 mg	62 (71.3%)	

ORR, Overall Response Rate; [1]n (%), [2]Pearson's Chi-squared test; Fisher's exact test

3 and 6 with ORR of 56% and 66,9%, respectively; mPFS of 11 and 11.1 months, respectively [4, 5]. In the analysis of OS, although there is no significant difference between afatinib and chemotherapy arms due to the cross-over [13], benefits on efficacy and tolerability established Afatinib as preferred treatment of choice in advance NSCLC harboring EGFR mutation. In clinical setting, real world evidence has revealed the treatment effectiveness of Afatinib with results of mPFS even higher than those in RCT. In a multi-center real world study in Malaysia, mPFS of 14.2 months was reported (95% CI, 11.85-16.55 months) [14]. Additionally, another study revealed outcome of mPFS was 14.1 months [15].

Our previous retrospective study with 343 EGFR mutant NSCLC patients across nine centers in Vietnam has showed encouraging efficacy and safety of Afatinib with ORR of 78.1% and mTTF 16.7 months. Majority of reported adverse events related to skin and mucous and was well managed [7].

In elderly patients, several RCTs revealed the treatment outcome and safety of those who received afatinib 40mg once daily. In LUX Lung 3 and 6, subgroup of older adults (age ≥ 65) had mPFS of 11.3 and 13.7 months, respectively. In LUX Lung 7, patients with age of 75 or older had improved treatment outcome with mPFS and mOS of 14.7 and 27.9 months, respectively. No new safety signal was identified [8]. Consequently, with starting

Table 6. Most Common Treatment-Related Adverse Events

(CTCAE grade)	All patients [a] n=135 (100%)	Starting dose 40 mg n=48(100%)	Starting dose ≤30 mg[b] n=87 (100%)	p value
Rash				
Any grade	66 (48.9%)	20 (41.7%)	46 (52.9%)	0.212[c]
≥ G 3	7 (5.2%)	3 (6.3%)	4 (4.6%)	0.699[d]
Dry skin				
Any grade	20 (14.8%)	8 (16.7%)	12 (13.8%)	0.653[c]
≥ G 3	0	0	0	-
Paronychia				
Any grade	55 (40.7%)	24 (50.0%)	31 (35.6%)	0.104[c]
≥ G 3	8 (5.9%)	6 (12.5%)	2 (2.3%)	0.024[d]
Diarrhea				
Any grade	75 (55.6%)	29 (60.4%)	46 (52.9%)	0.399[c]
≥ G 3	7 (5.2%)	4 (8.3%)	3 (3.4%)	0.246[d]
Stomatitis				
Any grade	35 (25.9%)	17 (35.4%)	18 (20.7%)	0.062[c]
≥ G 3	3 (2.2%)	2 (4.2%)	1 (1.1%)	0.288[d]
GOT/GPT increase				
Any grade	13 (9.6%)	6 (12.5%)	7 (8.0%)	0.543[c]
≥ G 3	0	0 (0.0%)	0	-

CTCAE, Common Terminology Criteria for Adverse Events; [a], There was no grade 4 adverse event (%); [b], only 3 patients with a starting dose of 20 mg; [c], Chi-square test; [d], Fisher's exact test

dose of 40mg once daily in RCTs, compared to mPFS of overall population, afatinib-treated elderly population generally has non-inferior treatment benefit [4, 8, 5]. However, with characteristics of performance status and comorbidities, older patients often experienced dose adjustment in clinical practice to improve tolerability. Furthermore, afatinib dose adjustment is quite common in both RCTs and real world clinical studies. In LUX Lung 3, dose reductions occurred in 53.3% of patients with 86.1% within the first six months. The dose reduction contributed to the alleviation of afatinib-related adverse event without compromising the treatment outcome with mPFS of 11.3 months, relative to mPFS of 11 months in subgroup who dose did not reduce [16]. In Realgido, patients who had initiated dose of ≥40 mg OD and dose reduce within the first 6 month, initiated dose of ≥40 mg and no dose reduce, initiated dose of ≤30mg had mTTF of 19.5 , 17.4, and 19.4 months, respectively, with no significant between-group difference. As a result, starting dose of ≤40mg, and tolerability-guided dose adjustment within the first six months did not negatively impact the clinical benefits of afatinib in the real world setting of 13 countries in the study whereases significantly improve safety profile with declined adverse events of grade 3 or 4 [17]. In this study, the data of 135 patients aging 65 or older was analyzed to investigate the effectiveness and tolerability of afatinib in the first-line treatment of EGFR mutant NSCLC. In detail, average age of the subgroup was 71.2 ± 5.3 years and 32.1% had comorbidities, including cardiovascular disease, diabetes, chronic obstructive pulmonary disease and hepatitis. Prevalance of brain metasteses was 24.4% while Del 19, L858R, and uncommon mutations accounted for 42.2%, 29.6%, and 28.1%, respectively. In our study, the dose of afatinib was flexibly selected to initiate the treatment and adjusted based on patient's tolerability. Majority of patients had starting dose of <40mg once daily (64.4%), and maintenance dose of 30mg once daily (74.4%). With the median follow-up of 30.4 month, mTTF and ORR were 16.3 months and 77.8%, respectively. The result was similar to the previously reported outcome of overall population, which were 16.7 months and 78.1%, respectively [7]. Upon progression with Afatinib, patients were subsequently treated with Osimertinib or chemotherapy (single-agent or doublet) with or without immunotherapy, and 34.8% of patient population received best supportive care because of frailty or patient's preference. In real-world situations, comparing the rate of osimertinib treatment after progression on afatinib across studies is challenging, especially in Vietnam, where both T790M testing and osimertinib are not reimbursed. This gap is a shared limitation in various real-world research contexts. For instance, studies from South Korea and Taiwan reveal that T790M testing rates are 68% and 62%, respectively, reflecting significant regional disparities in accessibility and support [18]. With the median follow-up of 34.3 months, mOS was 32.9 months (95%CI: 28.9-37.5). On the safety profile, adverse events were generally mild, grade 1 or 2, and associated with skin and mucosa. The result from our study again echoed the findings of LUX Lung 3, 6, and 7, on the efficacy and tolerability of afatinib in elderly patient [8]. Additionally, real world studies demonstrated encouraging clinical benefis of Afatinib in the patient subset. As in GIDEON study, mPFS, ORR, and mOS were 17.2 monhts, 72.0%, and 30.4 months, respectively in patients aging ≥ 70 years, which is comparable with our result [19]. Another study from

the Yen-Ting Chen et al. reported mTTF and OS of 12.2 và 23.8 months, respectively, in the subset of elderly who aged 65 or older, which were not significantly different from the outcome of younger patients [20]. Similar to our data, adverse events in the older subgroup primarily were related to skin or mucosa and in grade of 1 or 2 [20].

Subgroup analysis illustrated that clinical benefits of afatinib were consistent regardless of brain metastases status, with mTTF of 16.3 vs 15.9 months (p=0.42) and mOS of 33.1 vs 32.4 months (p=0.56) in patients with or without baseline brain involvement, respectively. In addition to the result of RCTs, real world data have provided evidence to support the role of afatinib as a treatment of choice for patients with brain metastases. A study from Hyun Ae Jung et al. in Korea reported intracranial response rate and CNS progression-free survival là 67.0% and 24.70 months (95% CI: 19.84–33.15 months), respectively [21]. In our study, there was a high proportion of uncommon mutations, accounting for 28.1% of study population, since afatinib is considered as preferred treatment option in this patient subset in Vietnam. In comparison with common mutations, patients harboring uncommon mutations had significantly inferior mOS in both univariate and multivariate analysis, but not ORR and mTTF. However, the outcomes of this patient subset were still considered encouraging with ORR, mTTF and mOS of 73.7%, 14.3 months and 28.4 months, respectively. Consequently, in elderly patients with uncommon mutations, Afatinib remained the preferred treatment of choice in the first-line setting.

As key issues of elderly patients, tolerability and risk-benefit ratio of starting dose selection and dose modification during treatment were topics of intensive research. In a real world study of Yen-Ting Chen et al, there is not staticially significant difference in incidence of grade 3 or higher adverse events between patients aging ≥65 and <65 years as treated with afatinib [20]. In elderly patients with age ≥70 years in GEDION study (Wolfgang M. Brueckl et al.), the rate of dose reduction was 57.6%. Additionally, 57.1% of subgroup with age ≥70 years and initial dose of afatinib 30mg/ngày had dose reduction to 20mg once daily. In spite of dose adjustment, grade 3 or higher adverse events still occured in 34.8% of patients with age ≥70 years [19]. In our study, 64.4% had starting dose of ≤40mg once daily and 75.6% were on the maintenance dose of ≤40mg once daily. On tolerability, majority of adverse events were grade 1 or 2 in severity. Less than 5% of study population experienced severe adverse evets, grade 3 or higher. Moreover, patients receiving starting doses of <40mg once daily had a declined rate of adverse events relative to those on the standard starting dose, with the significant difference in the incidence of grade 3 paronychia (p=0.024). On effectiveness, independent of starting dose or maintenace dose of 40mg or < 40mg once daily, there is no sigfinicant difference in mPFS and mOS while patients receiving the starting dose of 40mg once daily had superior objective response rate to those initiating the treatment with the lower dose (89.6% vs 71.3%, p=0.014). The result is similar to reported survival outcomes according to different starting dose levels or dose adjustment status in RCTs and real world studies. In detail, the finding generally revealed that starting dose selection and dose adjustment in treatment did not compromise the survival benefits of afatinib [16, 17, 22, 23]. Our univariate and multivariate analysis indicated that several factors associated with inferior survival outcome included poor performance status and smoking status in addition to uncommon mutations.

In conclusion, multicenter real-world data from Vietnamese patients reaffirm the effectiveness of first-line Afatinib treatment in elderly patients with advanced NSCLC harboring EGFR mutations. In this practical setting, the efficacy of Afatinib was evident across various patient subgroups, including those with or without brain metastases, those with both common and uncommon mutations, and patients receiving different initial doses. Adverse events, primarily of grade 1-2 affecting the skin and mucous membranes, were well-known and could be effectively managed. Furthermore, multivariate analyses identified uncommon mutations, a poor performance status (PS score ≥2), and current smoking as adverse prognostic factors for OS.

Author Contribution Statement

Anh Tu Do: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Project administration. Hoa Thai Thi Nguyen: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision. Phuong Cam Pham: Methodology, Investigation, Resources, Writing - Review & Editing. Tuan Khoi Nguyen: Investigation, Resources. Thi Anh Thu Hoang: Investigation, Resources. Tuan Anh Le: Investigation, Resources. Dinh Thy Hao Vuong: Investigation, Resources. Dac Nhan Tam Nguyen: Investigation, Resources. Van Khiem Dang: Investigation, Resources. Thi Oanh Nguyen: Investigation, Resources. Van Luan Pham: Investigation, Resources. Minh Hai Nguyen: Investigation, Resources. Thi Huyen Trang Vo: Investigation, Resources. Khoa Trong Mai: Investigation, Resources. Hung Kien Do: Investigation, Resources. Thanh Ha Vu: Investigation, Resources. Thi Thuy Hang Nguyen: Investigation, Resources. Thai Van Pham: Investigation, Resources. Le Huy Trinh: Investigation, Resources. Hoang Gia Nguyen: Investigation, Resources. Cong Minh Truong: Software, Formal analysis, Visualization, Writing - Review & Editing. Tran Minh Chau Pham: Investigation, Resources.

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Scientific Approval/Student Thesis

The Human Research Ethics Committee of Bach Mai Hospital in Hanoi, Vietnam, approved this study (Approval Number: 916/BM-HĐĐĐ). This research is not part of an approved student thesis.

Ethical Declaration

The Human Research Ethics Committee of the Bach Mai Hospital in Hanoi, Vietnam approved this study. The Human Research Ethics Committee of the Bach Mai Hospital has waived the informed consent for the

study due to its retrospective nature and the absence of patient safety concerns. In addition, patient records were anonymized and de-identified before undergoing analysis.

Data Availability

The de-linked and anonymized datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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