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Review Article

Comparing the Efficacy of Gefitinib, Erlotinib, and Afatinib in Non-Small Cell Lung Cancer with Activating Epidermal Growth Factor Receptor (*EGFR*) Mutations

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Abstract

Gefitinib and erlotinib are reversible Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs). Compared to standard chemotherapy, both of these agents have demonstrated significantly higher response rates and are associated with prolonged survival in patients with advanced Non-Small Cell Lung Cancer (NSCLC) harboring an activating *EGFR* mutation such as an axon 19 deletion or an L858R mutation. These agents are recommended as first-line treatments for NSCLCs with such mutations. Afatinib belongs to a class of irreversible inhibitors of the human epidermal receptor family. Two recent large-scale randomized trials demonstrated the high efficacy of afatinib as a first-line treatment for NSCLC with activating mutations of *EGFR* compared to standard chemotherapy.

Currently, various EGFR-TKIs including gefitinib, erlotinib, and afatinib are offered as first-line treatments in patients with advanced NSCLC harboring activating *EGFR* mutations. However, it is not clear if any of this EGFR-TKI should a first-line therapy advantage in these patients over the others. Herein, the latest data involving the use of these agents is reviewed.

Keywords: Afatinib; EGFR mutation; Erlotinib; Gefitinib; Non-small cell lung cancer

Abbreviations

EGFR-TKIs: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors; NSCLC: Non-Small Cell Lung Cancer; PFS: Progression-Free Survival; RR: Response Rate; ASCO: American Society of Clinical Oncology; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval

Introduction

First-generation reversible Epidermal Growth Factor Receptor–Tyrosine Kinase Inhibitors (EGFR-TKIs) such as gefitinib and erlotinib have proven to be highly effective in treating Non-Small Cell Lung Cancer (NSCLC) patients harboring activating *EGFR* mutations such as an exon 19 deletion or an L858R mutation [1,2]. Several randomized phase III trials of gefitinib and erlotinib as first-line treatments in patients with NSCLC with the aforementioned types of mutations demonstrated significantly longer Progression-Free Survival (PFS) times, higher degrees of tumor shrinkage, better tolerability, and an extended quality of life compared to platinum doublet chemotherapy [3-6]. Based on these studies, gefitinib and erlotinib are recommended as first-line treatment agents for these types of malignancies.

Afatinib is an irreversible pan Human Epidermal Receptor (pan-HER) inhibitor that down regulates ErbB signaling by covalently binding to the kinase domain of EGFR, HER2, or HER4. Large scale randomized phase III trials that compared afatinib to standard platinum-based chemotherapy as first-line therapy demonstrated significant improvement of PFS in selected patients harboring activating *EGFR* mutations [7,8]. Based on the results of these trials, the United States Food and Drug Administration approved afatinib as a first-line treatment for advanced NSCLC with activating *EGFR* mutations. Currently, gefitinib, erlotinib, and afatinib are recommended as standard first-line therapies for this category of NSCLC. In this review, the use of these therapeutic agents are explored and compared.

Efficacy of gefitinib, erlotinib, and afatinib as first-line therapy for *EGFR*-mutated NSCLC

Table 1 shows the results of previous clinical studies of gefitinib, erlotinib, and afatinib as first-line treatments in treatment-naïve patients with advanced NSCLC harboring an *EGFR* mutation. Response Rates (RRs) and PFSs of gefitinib, erlotinib, and afatinib are 55-74% and 9-10 months, 58-83% and 9-13 months, and 58-61% and 9-11 months, respectively [3-7, 9-11]. Based on the results of previous prospective studies, these *EGFR*-TKIs appear to show similar efficacy in terms of RR and PFS in patients with *EGFR*-mutated NSCLC.

Several subset analyses or retrospective studies that compared gefitinib to erlotinib in patients with activating *EGFR*-mutated NSCLC determined similar efficacies for both agents. Wu et al. showed that there was no significant difference between gefitinib and erlotinib in terms of RR and PFS in patients with NSCLC harboring activating *EGFR* mutations in their retrospective study [12]. Among the 224 patients with advanced NSCLC treated with gefitinib or erlotinib as first-line therapy who were reviewed, activating *EGFR*

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Table 1: Clinical trials of the EGFR-TKIs gefitinib, erlotinib, and afatinib as first-line treatments in patients with *EGFR*-mutated NSCLC.

Study	Phase	Treatment	Number of patients	Age (years)	RR (%)	Median PFS (months)	Median OS (months)
Sequist [9]	II	Gefitinib	31*	Median 62	55	9.2	17.5
Douillard [10]	IV Single-arm	Gefitinib	106†	Median 65	70	9.7	19.2
WJTOG3405 [3]	III	Gefitinib	86	<75	62	9.2	35.5
NEJ002 [4]	III	Gefitinib	114	<75	74	10.8	30.5
Koich [11]	II	Erlotinib	103‡	Median 65	78	11.8	NE
OPTIMAL [5]	III	Erlotinib	82	≥18	83	13.1	22.7
EURTAC [6]	III	Erlotinib	86	≥18	58	9.7	19.3
Lux-Lung 3 [7]	III	Afatinib	204	Median 62	61	11.1	NE
Lux-Lung6 [8]	III	Afatinib	242	Median 58	67	11.0	NE

Abbreviations: EGFR-TKIs: Epidermal Growth Factor Receptor-Tyrosine-Kinase Inhibitors; NSCLC: Non-Small Cell Lung Cancer; RR: Response Rate; OS: Overall Survival; NE; Not Evaluated

*Five patients had atypical *EGFR* mutation.

†Atypical *EGFR* mutations were detected in 4 patients (L861Q in two patients, G719X in the other two patients).

‡Two different types of *EGFR* mutation (L858R, T790M) were detected in 2 patients.

mutations were detected in 146. The median RR and PFS with gefitinib and erlotinib was 51% and 10.5 months (n = 94), and 58% and 10.4 months (n = 52), respectively. No statistically significant difference was noted in terms of RR and PFS between patients treated with gefitinib and those treated with erlotinib. Lim et al. reported similar efficacy in patients treated with either gefitinib or erlotinib in advanced NSCLC with activating *EGFR* mutations [13]. One hundred twenty one pairs of gefitinib-treated and erlotinib-treated patients were matched according to sex, smoking history, Eastern Cooperative Oncology Group performance status, and the type of *EGFR* mutation. Of the 242 patients, 63 (26%) received EGFR-TKIs as first-line therapy. The overall RRs in patients treated with gefitinib and those treated with erlotinib were 76.9% and 74.4%, respectively ($p = 0.575$). There was no statistically significant difference in terms of the median PFS (11.7 months vs. 9.6 months, $p = 0.056$, respectively). Additionally, no significant difference was observed between patients treated with gefitinib or erlotinib as a first-line treatment in terms of RR (76.7% vs. 90%, $p = 0.431$, respectively) or PFS (11.7 months vs. 14.5 months, $p = 0.507$, respectively).

Current randomized phase III studies comparing gefitinib and erlotinib for advanced NSCLC were presented at the 2014 annual meeting of American Society of Clinical Oncology (ASCO) [14]. Among the 561 patients enrolled in this study, 371 patients had an activating *EGFR* mutation (186 patients in the gefitinib group and 185 patients in the erlotinib group). The median PFS, time to treatment failure, and Overall Survival (OS) of gefitinib and erlotinib were 6.5, 5.6, and 22.8 months and 7.5, 5.3, and 24.5 months, respectively. No statistically significant difference was observed between patients treated with gefitinib and those treated with erlotinib in any category. However, patients with recurrence or previously treated NSCLC were enrolled in this study.

Considering the high efficacy of EGFR-TKIs in patients with advanced NSCLC harboring activating *EGFR* mutations, the use of these agents to treat other specific disease conditions, such as intracranial metastases that are associated with poor prognoses due to the lack of efficacious treatments other than radiotherapy, is worth considering. In previous retrospective studies and subset analyses of gefitinib and Erlotinib treatment against brain metastases in patients with NSCLC harboring *EGFR* mutations, investigators reported responses in these lesions that were comparable in significance to that of the primary tumor [15-18]. In their retrospective study, Lee et al. documented that erlotinib had a better control rate than gefitinib for leptomeningeal metastases in NSCLC patients [19]. Among 25 patients (14 treated with erlotinib, 11 with gefitinib) with NSCLC reviewed in their study, 17 patients had tumors with activating *EGFR* mutations. There was a significantly better cytological negative conversion rate of leptomeningeal cancer in patients treated with erlotinib than those treated with gefitinib (64.3% vs. 9.1%, $p = 0.012$). Cytological negative conversion rate of leptomeningeal cancer was defined as a rate of the absence of malignant cells in the cerebrospinal fluid three times in succession in this study. However, 9 patients had already been treated at the time the brain metastases were detected, and all patients received intra the cal chemotherapy. Thus, this study is unable to confirm the superiority of erlotinib as a first-line therapy against *EGFR*-mutated NSCLC with intracranial metastases compared with gefitinib. Radiation therapy has been considered a standard treatment in patients with intracranial metastases in NSCLC. A recent prospective study showed that the efficacy of erlotinib was similar to that of whole brain radiotherapy in terms of OS in patients with NSCLCs harboring *EGFR* mutations [20]. To the best of our knowledge, the efficacies of gefitinib or afatinib as first-line EGFR-TKI therapies for brain metastases in NSCLCs harboring *EGFR* mutations have not been studied.

Both the exon 19 deletion and L858 Rare activating *EGFR* mutations that predict active response to EGFR-TKIs and survival. However, activity of EGFR-TKIs may vary among these types of *EGFR* mutations. Several clinical studies reported that patients harboring an exon 19 deletion treated with EGFR-TKIs showed longer survival compared to similarly treated patients harboring an L858Rmutation [21-24]. Results of a pooled analysis of the LUX-Lung 3 and 6 trials with afatinib were presented at the ASCO annual meeting in 2014. The survival benefit of afatinib as first-line treatment was strongly apparent in patients with an exon 19 deletion mutation. In these patients, the median OS of afatinib (236 patients)

and chemotherapy (119 patients) was 31.7 months and 20.7 months (HR = 0.59, 95% CI: 0.45-0.77, p = 0.0001), respectively. In patients with the L858R mutation, the median OS with afatinib (183 patients) and chemotherapy (93 patients) was 22.1 months and 26.9 months (HR = 1.26, 95% CI: 0.92-1.71, p = 0.16), respectively. Recent meta-analysis noted that the exon 19 deletion was associated with longer PFS compared to the L858R mutation in patients with NSCLC treated with EGFR-TKIs [25]. Based on the results of 6phase III trials [3-8] of EGFR-TKIs including gefitinib, erlotinib, and afatinib as first-line treatments, indirect comparison revealed longer PFS in patients with an exon 19 deletion than in those with an L858R mutation (HR= 0.59, 95% CI:0.38-0.92, p= 0.019). Additionally, direct meta-analysis based on the results of 7 prospective or retrospective studies [4,23,26-30] involving 549 patients treated with gefitinib or Erlotinib as first-line treatment showed similar results (HR = 0.75, 95% CI: 0.65-0.85, $p < 0.001$). On the other hand, Maemondo et al. directly compared PFS according to these two mutation types in subset analysis of the NEJ002 study [4]. The number of patients with exon 19 deletions or L858R mutations was 58 and 49, respectively, and the median PFS for each group was 11.5 vs. 10.8 months, respectively. No significant difference was noted in terms of PFS between those groups of patients (Hazard Ratio [HR] = 0.939, 95%, Confidence Interval [CI]: 0.3518-2.5061, p = 0.9).

EGFR-TKIs treatment for NSCLC with activating *EGFR* mutations in patients who are elderly or have poor performance statuses

In the 6 aforementioned phase III trials comparing gefitinib, erlotinib, and afatinib with standard chemotherapy as first-line treatments for *EGFR*-mutated NSCLC, patients with Performance Status (PS) scores of 2-4 were excluded [3-8]. Additionally, elderly patients (70 years or older) were excluded in the WJOG 3405 study and the NEJ 002 study. However, previous small phase II studies showed that gefitinib as a first-line treatment in elderly patients and/or patients with poor PS in *EGFR*-mutated NSCLCs showed efficacy and tolerability on par with the results of the WJOG 3405 and the NEJ 002 studies [31-33].

Although no assessment of efficacy or tolerability of erlotinib in the elderly population was conducted in either the OPTIMAL or EUROTAC studies, no negative effects such as lower response rates, shorter survivals, or the development of sever toxicities were documented. Jackman et al. reported efficacy and relatively good tolerability of erlotinib in their small phase II study for chemotherapy-naïve elderly patients (70years or older) with advanced NSCLC. Among 43 patients enrolled in their study, activating *EGFR* mutations were detected in 9 patients, all of whom exhibited partial response or stable disease with erlotinib treatment. The TRUST study was an open-label phase IV trial of erlotinib in advanced non-selected NSCLC patients who had previously failed or were ineligible for chemotherapy or radiotherapy [34]. Among the TRUST population, 485 elderly patients (70 years or older) receiving first-line erlotinib were examined. Erlotinib-related toxicities and serious toxicities occurred in 18% and 7% of subpopulation patients, respectively. Furthermore, 27% of this subpopulation of patients required dose reductions. To the best of our knowledge, no prospective study of erlotinib in elderly patients harboring activating *EGFR* mutations has been conducted. Based on the results of previous phase III trials including the LUX-Lung 3 and 6, a similar efficacy for afatinib in elderly patients (65 years or older) was reported [7,8]. Meanwhile, severe treatment-related toxicities (grade 3 to 5) due to afatinib treatment were reported more commonly in patients 65 years or older.

Table 2: Severe toxicity (grade ≥3) of gefitinib, erlotinib, and afatinib in NSCLCs harboring *EGFR* mutations.

Study	EGFR-TKI	Toxicity				
		Rash	Diarrhea	Fatigue	ILD	Elevated transaminase
WJOG 3405 [3]	Gefitinib	2%	1%	2%	2.3%	14%
NEJ002 [4]	Gefitinib	5.3%	0.9%	2.6%	2.6%	26.3%
OPTIMAL [5]	Erlotinib	2%	1%	0%	0%	4%
EURTAC [6]	Erlotinib	13%	5%	0%	1%	2%
LUX-Lung 3 [7]	Afatinib	16.2%	14.4%	1.3%	1%	-
LUX-Lung 6 [8]	Afatinib	14.2%	5.4%	0.4%	0.4%	1.7%

Abbreviations: NSCLC: Non-Small Cell Lung Cancer; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine-Kinase Inhibitor; ILD: Interstitial Lung Disease

Toxicity profile of gefitinib, erlotinib, and afatinib in patients with *EGFR*-mutated NSCLC

Table 2 shows severe toxicity (grade ≥3) related to treatment with gefitinib, erlotinib, and afatinib based on the results of prospective phase III trials comparing these EGFR-TKIs with standard chemotherapy as first-line treatments in patients with NSCLC harboring an activating *EGFR* mutation. In the recent randomized phase III study comparing gefitinib with erlotinib in previously treated NSCLC patients as described above [14], severe toxicity symptoms of rash and elevated transaminase occurred in 2.2% and 13% of patients treated with gefitinib and 18.1% and 3.3% of those treated with erlotinib, respectively. Rash and diarrhea are the most common toxicities related to EGFR-TKI treatment. These symptoms of severe toxicity were observed more in patients treated with afatinib than those treated with gefitinib or erlotinib.

Discussion

Results from previous clinical studies show that EGFR-TKIs used in first-line treatments, including gefitinib, erlotinib, and afatinib, have shown similar efficacy as determined by RR and PFS in patients with NSCLC harboring an activating *EGFR* mutation. As for treatment-related toxicities, severe toxicities, especially rash and diarrhea, occurred more often in patients treated with afatinib than in those treated with gefitinib or erlotinib. Although the LUX-Lung 7, which is a prospective phase II study comparing afatinib with gefitinib as first-line treatments in patients with activating *EGFR*-mutated NSCLC, is ongoing (NCT01466660), no prospective trials comparing afatinib with erlotinib or comparing erlotinib with gefitinib as first-line treatments for these NSCLC subtypes have been conducted. Clinical data that provide direct comparisons between these EGFR-TKIs are sorely lacking.

Recently, results of an indirect and integrated study comparing several EGFR-TKIs in patients with advanced NSCLCs harboring activating *EGFR* mutations were published [35]. Researchers assessed and compared efficacy of gefitinib, erlotinib, afatinib, and icotinib (BPI-2009) in terms of RR, PFS, and OS. Icotinib is an oral EGFR-TKI and showed similar efficacy to, and less toxicity than, gefitinib

in a randomized double-blind phase III non-inferiority study [36]. The outcome of the integrated study was indirectly based on the results of 12 previous randomized phase III trials [3-8,36-41] that investigated these EGFR-TKIs in 182 cases of NSCLC harboring an *EGFR* mutation. The results showed that gefitinib, erlotinib, afatinib, and icotinib had equivalent efficacy in all measured outcomes with no statistically significant differences except for toxicity. The toxicity was more severe in patients treated with erlotinib or afatinib. Severe diarrhea was particularly more frequent in patients treated with afatinib compared with those treated with the other three EGFR-TKIs. Additionally, this meta-analysis showed significantly more severe treatment-related toxicity involving rashes in patients treated with afatinib than in those treated with gefitinib. No other significant differences were noted with the remaining EGFR-TKIs. Treatment-related toxicities, especially rash and diarrhea, seem to be slightly more prevalent in patients treated with afatinib compared to gefitinib or erlotinib. Among those EGFR-TKIs, afatinib is the most recently approved agent for use in patients with advanced *EGFR*-mutated NSCLC. Thus, few physicians may be accustomed to managing toxicities such as rash and diarrhea in the early phases. At this time, afatinib should not be excluded from consideration as an initial treatment based solely on the slightly higher probability of developing severe toxicities compared to gefitinib or erlotinib.

Based on the aforementioned investigation, most available EGFR-TKI may be equally suitable for certain NSCLC patients such as those within tracranial metastases, those harboring specific *EGFR* mutations, and elderly patients. Erlotinib may be a reasonable option for first-line therapy in patients harboring *EGFR* mutations with asymptomatic brain metastases. However, previous preliminarily studies were not sufficient to conclude whether erlotinib would be more effective than gefitinib, afatinib, or radiation therapy in such patients. Thus far, no prospective study has been conducted to assess whether EGFR-TKIs are differentially efficacious in NSCLCs with exon 19 deletions compared to L858Rmutations. Previous meta-analysis showed that gefitinib or erlotinib caused longer PFS in patients with an exon 19 deletion than in those with L858R mutations. However, it remains unclear whether gefitinib or erlotinib is more effective against each type of *EGFR* mutation in NSCLC. On the other hand, afatinib may bring an OS benefit in the subset of patients harboring an exon 19 deletion, according to the LUX-Lung 3 and Lux-Lung 6 studies. Although these data were derived by combined analysis, they were the first to report that an EGFR-TKI had a significant OS benefit over chemotherapy when administered as a first-line treatment for *EGFR*-mutated NSCLC. As for NSCLC harboring an exon 19 deletion mutation, afatinib might be the more appropriate first-line agent based on its OS benefit. However, further research is needed to confirm whether patients with an exon 19 deletion and those with an L858R mutation belong to different patient populations. Additionally, more efforts are needed to investigate the mechanism of action of each EGFR-TKI agent on different types of *EGFR* mutations. While several previous prospective small phase II studies showed efficacy and tolerability of gefitinib and erlotinib in elderly patients (70 years or older or 75 years or older, respectively) with activating *EGFR* mutations, no data from prospective trials of afatinib in elderly *EGFR*-mutated NSCLC patients have been available. While lung and bronchus cancer is most frequently diagnosed in people aged 65 to 74 years with the median age at diagnosis being 70 years based on the Surveillance, Epidemiology, and End Results (SEER) Program (http://seer.cancer.gov/), only a low percentage of elderly patients 70 years or older were enrolled in large-scale phase III trials for NSCLC. Therefore, those treated with new protocol therapies may not be represented in the whole elderly patient population. Seventy years or older may be considered the boundary age of cell senescence after which the rate of age-related changes increase [42]. Moreover, many elderly patients with NSCLC have comorbidity with other diseases such as obstructive pulmonary disease, decreased heart function, impaired renal function, etc. Thus, elderly NSCLC patients ought not to be considered in the same population as younger patients. Clinical studies to assess tolerability for EGFR-TKI therapy (other than performance status) are needed in elderly patients with advanced NSCLC who are disqualified from chemotherapy. Two prospective phase II studies of afatinib in elderly patients with NSCLC harboring *EGFR* mutations are ongoing (UMIN000015834, UMIN000014820).

Conclusion

There are no data providing direct comparisons between afatinib, gefitinib, and erlotinib as first-line therapies. It has not been demonstrated which EGFR-TKI is optimal as a first-line therapy for activating *EGFR*-mutated advanced NSCLC. Basedon previous investigations, gefitinib, erlotinib, and afatinib appear to provide similar efficacy in patients with NSCLC harboring activating *EGFR* mutations, as determined by response and survival. Some preliminary data suggested that some of these agents might be more suitable than others depending on the type of *EGFR* mutation, disease stage, and patient age. However, no definite evidence has been documented to confirm these observations. Future investigations may further assist physicians in choosing the appropriate EGFR-TKIs as initial-line therapies based on the disease condition, specific *EGFR* mutation status, and age of the patient. Until such a time, patients with *EGFR*-mutated NSCLCs are better off being treated with whatever EGFR-TKIs are readily available to their physicians.

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