Which Is Better EGFR-TKI Followed by Osimertinib: Afatinib or Gefitinib/Erlotinib?

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Abstract. *Background/Aim:* Treatment with EGFR-tyrosine kinase inhibitor (TKI) shows a durable response against NSCLC harboring EGFR mutation; however, treatment resistance occurs within 1-1.5 years following first-line EGFR-TKIs [first- and second-generation (G) TKIs]. When resistant NSCLC exhibits T790M mutations, osimertinib is the standard therapy. However, intratumoral heterogeneity and clonal evolution may occur in NSCLC. Afatinib may overcome tumor heterogeneity, leading to T790M clonal purity. We aimed to determine whether NSCLC treatment with afatinib followed by osimertinib (afatinib group) provides higher therapeutic efficacy than other 1st-G EGFR-TKIs followed by osimertinib (1st-G group). *Materials and Methods:* This multicenter retrospective study evaluated outcomes between afatinib group and 1st-G group. We analyzed clinical data from NSCLC patients receiving osimertinib after progression following 1st- or 2nd-G EGFR-TKIs between March 28, 2016 and March 31, 2018. Patients with performance status (PS) 0-2 were enrolled to reduce bias of patients' conditions. *Results:* We enrolled 111 patients treated with osimertinib. The median age was 69 (range: 39-88) years. Out of 111 patients, 33 (29.7%) were men, 100 (90%) had PS 0-1, and 35 (31.5%) were in the afatinib group. The objective RR and DCR were significantly higher in the afatinib group than in the 1st-G group [82.9% vs. 53.9% ($p=0.0065$); 91.4% vs. 71.1% ($p=0.032$)]. The

median PFS tended higher in the afatinib group than in the 1st-G group (15.6 vs. 8.9 months, $p=0.195$). Conclusion: Afatinib followed by osimertinib may provide better outcomes for T790M-positive NSCLC than 1st-G EGFR-TKIs. Afatinib followed by osimertinib may be a therapeutic option for NSCLC harboring EGFR mutation.

Approximately 75% of all lung cancer cases, the most common cause of cancer-related death worldwide, are non-small cell lung cancer (NSCLC) (1). Although the efficacy of platinum-based doublet chemotherapy, the standard treatment for advanced NSCLC for decades, seems to have plateaued (2), molecular-targeted chemotherapeutics have the potential to increase efficacy in some patients (3). EGFR tyrosine kinase inhibitors (TKIs), such as first-generation (1st-G) EGFR-TKIs (gefitinib and erlotinib), treatment exhibit higher response rates (RRs), longer progression-free survival (PFS), and better tolerability in NSCLC patients harboring epidermal growth factor receptor (EGFR) mutations compared to treatment with standard platinum-based chemotherapy (4-7). Moreover, afatinib, a second generation (2nd-G) EGFR-TKI, shows longer overall survival (OS), higher RR, and longer PFS than standard cytotoxic chemotherapy (8). Furthermore, afatinib exhibits significant improvements in PFS [hazard ratio (HR): 0.73, 95% confidence interval (CI): 0.57-0.95; $p=0.017$] compared with gefitinib in patients with common EGFR mutations (Del 19 and L858R), as seen in the LUX-Lung 7 trial (9).

Although EGFR-TKI treatment showed durable response against NSCLC harboring EGFR mutations, most cases experience cancer relapse within 1-1.5 years following treatment initiation with first-line 1st- and 2nd-G EGFR-TKIs (4-8). In many of these cases, acquired resistance is observed when a subsequent biopsy is obtained. Therefore, a key consideration when assessing therapeutic choice is the

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evaluation of mechanism following disease progression. The most common mechanism of resistance to 1st- and 2nd-G EGFR-TKI treatment is a T790M mutation where threonine is substituted with methionine at the 790th amino-acid codon on exon 20 of the EGFR gene, this mutation is present in approximately 50% of tumors at time of acquired resistance (10-13).

Osimertinib, an oral irreversible EGFR-TKI, was shown to specifically block EGFR-T790M with minimal inhibition of wild-type EGFR (14). These results lead to initiation of clinical trials that demonstrated excellent outcomes in NSCLC patients with T790M mutation yielding a response rate of 61% and PFS of 9.6 months (15). A phase III trial (AURA III) was undertaken to compare platinum combination chemotherapy and osimertinib in patients with EGFR-TKI-sensitive mutation harboring lung cancers that showed exacerbation during or after EGFR-TKI treatment (16). In that study, osimertinib exceeded pemetrexed plus platinum therapy with statistical significance in PFS (10.1 vs. 4.4 months; HR=0.30, $p<0.001$).

Although osimertinib exhibits enhanced efficacy on RR (for 80% vs. 76%; $p=0.24$) and PFS (for 18.9 vs. 10.2 months; HR=0.46, $p<0.001$) compared to 1st-G EGFR-TKIs (17), there are no molecular targets of therapy due to the heterogeneity of resistance mechanisms that are not well understood or currently undruggable (18, 19). As a result, in the course of clinical practice for most patients following cancer progression after osimertinib treatment, chemotherapy is the only remaining option for second-line treatment.

Therefore, in treating patients with sequential EGFR-TKIs, it may prove efficacious to reserve osimertinib use as a second-line option to maximize treatment time on targeted drugs. However, there is little data assessing the cumulative benefit of sequential EGFR-TKIs in NSCLC patients harboring *EGFR* mutations (20, 21). One multicenter observational study assessed total treatment duration of sequential afatinib and osimertinib in NSCLC patients harboring the *EGFR* mutation with T790M-acquired resistance and showed good time on treatment (median: 27.6 months), afatinib (median PFS: 11.9 months) followed by osimertinib (median PFS: 14.3 months) (20). However, no study has attempted to assess if a given EGFR-TKI (gefitinib, erlotinib, afatinib) proves better in sequential therapy followed by osimertinib. Therefore, we analyzed the efficacy of these drugs in patients sequentially treated with osimertinib to evaluate an optimal sequential therapy in real-world clinical practice.

Materials and Methods

We conducted a multicenter retrospective study across three medical centers in Japan. The study design and methodology was approved by the Institutional Review Board of each participating institution.

Table I. Patient characteristics.

Characteristics	1st-G group N=76	Afatinib group N=35
Age		
Median (range)	70 (41-88)	64 (39-84)
Gender		
Male/Female	22/54	11/24
Smoking history		
Never/Ever	50/26	18/17
Performance Status		
0/1/2	19/50/7	9/22/4
Histology		
Adenocarcinoma/Others	76/0	35/0
Sensitive <i>EGFR</i> mutation		
Exon 19 (deletion)/L858R	37/39	23/12
Substance to be measured		
Plasma/Cytology/Tissue	19/12/45	8/6/21
The last EGFR-TKI		
Gefitinib/Erlotinib/Afatinib	31/45/0	0/0/35
Number of prior regimens		
1/2/3/4/5/6 or more	30/19/7/5/6/9	2/4/5/10/3/11
Response of the last EGFR-TKI		
CR/PR/SD/PD/NE	1/43/15/13/4	0/10/13/11/1
Response rate/Disease control rate	57.9%/77.6%	28.6%/65.7%
Brain metastasis before osimertinib		
none/meta +	38/38	15/20

1st-G group: the patients treated with afatinib followed by osimertinib. Afatinib group: the patients treated with 1st-generation EGFR-TKIs followed by osimertinib. CR: Complete response, PR: partial response, SD: stable diseases, PD: progression diseases, NE: not evaluated.

Research was conducted in accordance with the Declaration of Helsinki and the World Health Organization's Guidelines for Good Clinical Practice.

Patient selection. Cases with patients treated with osimertinib at the Osaka International Cancer Institute, the Osaka Habikino Medical Center and the National Hospital Organization Kinki-chuo Chest Medical Center were reviewed between March 28, 2016 (the date osimertinib was approved in Japan) and March 31, 2018. Study participants were consecutively enrolled among patients in routine practice according to the following criteria: patients with T790M mutation who were treated with osimertinib after acquired resistance to EGFR-TKIs at any time for advanced NSCLC and who had good Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0-2, and major *EGFR* mutation (Exon19: deletion19 or Exon21: L858R) before initial EGFR-TKI treatment to reduce biasing toward patient conditions. Patients were excluded from our analysis if they had received osimertinib treatment as part of a clinical trial.

Data collection. Clinical data, including age, sex, smoking status, ECOG PS, *EGFR* mutation status, the place of re-biopsy and the content of all treatments, were collected from electronic medical records and pharmacy databases. *EGFR* mutation and T790M status were determined per local methodology and practices. Clinical responses were defined according to the Response Evaluation

Table II. The efficacy of osimertinib following between afatinib and 1st-G group.

	N	RR (%)	DCR (%)	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)
All patients	111	63.1%	78.4%	2 1.8%	68 61.3%	17 15.3%	17 15.3%	7 6.3%
Afatinib group	35	82.9%	91.4%	2 5.7%	27 77.1%	3 8.6%	3 8.6%	0 0%
1st-G group	76	53.9%	72.4%	0 0%	41 53.9%	14 18.4%	14 18.4%	7 9.2%

1st-G group: the patients treated with afatinib followed by osimertinib. Afatinib group: the patients treated with 1st-generation EGFR-TKIs followed by osimertinib. RR: Response rate, DCR: diseases control rate, CR: complete response, PR: partial response, SD: stable diseases, PD: progression diseases, NE: not evaluated.

Criteria in Solid Tumors, version 1.1 (22). PFS was determined from the first administration date of osimertinib to the date of disease progression or death from any cause. Patients were followed-up until the March 31, 2018.

Statistical analyses. Kaplan-Meier curves were used to evaluate PFS, which was compared using the log-rank test. Median values and 95.0% CIs were also reported. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. Only variables with a $p < 0.05$ in the univariate analysis were included in the multivariate analysis. All statistical analyses were conducted using R software, version 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered a statistically significant difference and $p < 0.15$ was considered to be moderately trending difference.

We classified patients treated with afatinib followed by osimertinib (afatinib group) or the patients treated with 1st-G EGFR-TKI followed by osimertinib (1st-G group) by last administration of EGFR-TKI before osimertinib, evaluated the outcomes between the afatinib and 1st-G groups.

Results

A total of one hundred eleven patients were assessed for eligibility. The median follow-up time was 14.3 (range=1.0-25.2) months. The median age was 69 (range=39-88) years. Out of the 111 patients, 33 (29.7%) were men, 68 (61.3%) never smoked, 100 (90%) had PS 0-1, 58 (52.3%) had brain metastasis before treatment with osimertinib, all had adenocarcinoma, 60 (54.1%) had exon19 deletion and 28 (25.2%) were measured in T790M status by liquid biopsy of plasma. Furthermore, 35 (31.5%) were in the afatinib group and 76 (68.5%) were in the 1st-G group. Characteristics were generally consistent between groups, although the afatinib group had a higher median treatment line (5 vs. 4) than 1st-G group. All patients received starting doses of 80 mg/day osimertinib (Table I).

The objective RR and DCR of osimertinib across all study participants were 63.1% and 77.5% respectively, with the objective RR and DCR significantly higher in the afatinib group than in the 1st-G group (82.9% vs. 53.9%, $p=0.0065$,

Table III. Survival measures comparing patients with brain metastases.

	N	RR (%)	DCR (%)	CNS PD rate (%)
All patients	111	63.1%	78.4%	16 (14.4%)
Brain metastasis+	58	53.4%	74.1%	16 (27.6%)
Brain metastasis-	53	73.6%	83.0%	0 (0%)

RR: Response rate, DCR: disease control rate, CNS PD rate: central nervous system disease progression rate.

and 91.4% vs. 71.1%, $p=0.032$, respectively; Table II). Comparing patients with or without brain metastasis, the objective RR and DCR were 53.4% vs. 73.6% ($p=0.046$) and 74.1% vs. 83.0% ($p=0.366$), respectively. The central nervous system PD rates of osimertinib were significantly higher in patients with brain metastasis than those without (27.6% vs. 0%, $p < 0.001$; Table III).

The median PFS across all patients was 12.0 (95%CI: 8.4-16.0) months, and OS was not achieved (Figure 1a and b). The median PFS was moderately higher in the afatinib group than in the 1st-G group [17.0 (95%CI=8.5-infinity) vs. 9.7 (95%CI=7.8-15.7) months; $p=0.164$; Figure 2a], and the median OS values were not significantly different between the groups ($p=0.322$; Figure 2b).

Discussion

In the present study, we demonstrated that RR and DCR in the afatinib treated group is superior to those in 1st G EGFR-TKI treated groups prior to osimertinib therapy. Furthermore, the sequential therapy using afatinib showed a trend for longer PFS than the sequential therapy using other 1st-G TKIs. In a post-hoc analysis of the Lux-Lung7 trial, the median OS with afatinib vs. gefitinib in patients who received a 3rd-G EGFR-TKI following discontinuation of study treatment was not evaluable vs. 46.0 months (HR=0.51, 95%CI=0.17-1.52, $p=0.22$) (23). This post-hoc

Figure 1. Kaplan–Meier plots for (a) progression-free survival and (b) overall survival of osimertinib in eligible patients.

Figure 2. Kaplan–Meier plots for (a) progression-free survival and (b) overall survival of osimertinib following between afatinib and 1st generation EGFR-TKIs (gefitinib or erlotinib).

analysis showed similar results to the analyses we conducted in this study. Our results showed that treatment with osimertinib following afatinib showed significantly better responses than osimertinib following 1st-G EGFR-TKI.

These differences of effects may result from an induction of tumor heterogeneity during afatinib or 1st-G EGFR-TKI treatment. It is generally accepted that tumors undergo complex evolution over the course of their development and during cancer treatment, thus resulting in a further increase

in tumor heterogeneity (24, 25). Recent studies have implemented the construction of divergence-based phylogenetic trees to illustrate tumor development including in cases of NSCLC (26, 27). Truncal mutations are clonal mutations that are present in all tumor cells and regions, and branch mutation are later subclonal events that are present in only a small proportion of tumor cells, resulting in intratumoral clonal diversity (27, 28). A recent study showed a high prevalence of other common genetic mutations

besides EGFR mutations in advanced-stage *EGFR* mutation-positive NSCLC (29). These additional aberrations included known oncogenic drivers in intracellular signaling and cell cycle pathway genes (25). Furthermore, this analysis also indicated that co-occurring mutations are very common in T790M-positive tumors. Therefore, the heterogeneity of *EGFR* mutations in *EGFR* mutation-positive NSCLC has potential clinical implications since different EGFR TKIs have varying effectiveness dependent on the specific mutation. Preclinical studies indicate that 2nd-G EGFR-TKIs may have a broader inhibitory profile against various types of *EGFR* mutations compared to 1st- or 3rd-G EGFR-TKIs (30-32). Furthermore, afatinib showed more potency than gefitinib, erlotinib, and osimertinib against compound mutations (32). Conversely, the clinical benefits of osimertinib are superior if co-occurring genetic alternations are present in advanced T790M-positive NSCLC (29). Our results may be explained by the possibility that afatinib may exhibit increased efficacy by targeting co-occurring genetic diversity in *EGFR* mutations leading to enrichment of T790M cells than 1st-G EGFR-TKIs.

There are certain limitations to our study. Due to its retrospective nature, information bias cannot be excluded. Additionally, there are some differences in patient characteristics between two groups that may have skewed the results. Some factors in the afatinib group were inferior, compared to 1st-G EGFR-TKI group; however, the overall outcome was better in the afatinib group. This result may further strengthen our hypothesis. Second, the follow-up time was not sufficient to calculate the full long-term survival outcome measure. Finally, we could not analyze the overall survival from the first-line chemotherapy because of difference in the number of prior chemotherapies prior to osimertinib treatment. We classified the afatinib group or 1st-G group by last administration of EGFR-TKI before osimertinib therapy initiation. Therefore, there were some patients treated with afatinib and 1st-G EGFR-TKI in both groups. However, a study by Imamura *et al.* showed plasma mutation scores of EGFR circulating tumor DNA with activating mutations decreased rapidly in response to EGFR-TKI within at least 14 days (33). Therefore, we think that the effect of osimertinib is potentiated mainly by the last EGFR-TKI prior to osimertinib initiation even if this exposure is for a very short duration, and we found that results of our study is in-line with that of a recent observational study (20).

Conclusion

Afatinib followed by osimertinib may provide better benefit for NSCLC harboring T790M-positive mutations than the use of other first-generation EGFR-TKIs. We believe that afatinib followed by osimertinib is one of the best therapeutic options for NSCLC harboring *EGFR* mutations.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

All Authors report no conflicts of interest.

Authors' Contributions

M. Tamiya and A. Tamiya designed the study, and wrote the initial draft of the manuscript. M. Tamiya, A. Tamiya, and H. Suzuki contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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