SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 20: 43, 2024

Comparison of the efficacy of first-/second-generation EGFR-tyrosine kinase inhibitors and osimertinib for EGFR-mutant lung cancer with negative or low PD-L1 expression

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Received January 13, 2024; Accepted March 28, 2024

DOI: 10.3892/mco.2024.2741

Abstract. In epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) with negative or low programmed death ligand-1 (PD-L1) expression, the acquisition rate of the T790M mutation is higher after treatment with first-/second-generation EGFR-tyrosine kinase inhibitors (TKIs) and the progression-free survival (PFS) is longer in patients treated with osimertinib. The present study compared the clinical course after the initiation of each EGFR-TKI monotherapy in patients with EGFR-mutant NSCLC with negative or low PD-L1 expression. Data of patients with EGFR-mutant NSCLC with negative or low PD-L1 expression who were treated with EGFR-TKI monotherapy were retrieved and retrospectively analyzed. Between June 2013 and November 2023, 26 and 29 patients were treated with first-/second-generation EGFR-TKIs and osimertinib, respectively. The PFS time was longer in patients treated with osimertinib (median, 22.5 months) than in those treated with first-/second-generation EGFR-TKIs (median, 12.9 months). However, the EGFR-TKI treatment duration, defined as the PFS for osimertinib, or the sum of the PFS for first-/second-generation EGFR-TKIs and sequential osimertinib therapy after the acquisition of the T790M mutation, was similar between patients treated with first-/second-generation EGFR-TKIs (median, 23.0 months) and osimertinib (median, 22.5 months). The Cox proportional hazard model suggested that there was no significant difference in the EGFR-TKI treatment duration between patients treated with first-/second-generation EGFR-TKIs and patients treated with osimertinib (hazard ratio, 1.31, 95% CI, 0.55-3.13). In conclusion, first-/second-generation EGFR-TKIs and osimertinib were associated with a similar EGFR-TKI treatment duration in patients with EGFR-mutant NSCLC with negative or low PD-L1 expression. The findings suggested that both treatments are promising for this population.

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Key words: EGFR, lung cancer, programmed death ligand-1, prognosis

Introduction

Although systemic chemotherapy has been the standard therapy for advanced non-small cell lung cancer (NSCLC), its effectiveness is limited. Recently, the identification of driver mutations and the development of targeted therapies have improved the prognosis of NSCLC patients with driver mutations. Among them, in patients with NSCLC harboring the epidermal growth factor receptor (EGFR) mutation, first-generation EGFR-TKIs showed an improved progression-free survival (PFS) compared with chemotherapy including carboplatin plus paclitaxel [median PFS, 10.8 months with gefitinib versus 5.4 months with chemotherapy; hazard ratio (HR), 0.30, P<0.001] (1) and cisplatin plus docetaxel (median PFS, 9.2 months versus 6.3 months; HR 0.489, P<0.0001) (2). Second-generation EGFR-TKIs, including afatinib and dacomitinib, have also shown prolonged PFS (median PFS, 11.0 months with afatinib versus 10.9 months with gefitinib; HR, 0.73, P=0.017) (3) or overall survival (OS) (median OS, 34.1 months with dacomitinib versus 26.8 months with gefitinib; HR, 0.760, P=0.0438) (4) compared to first-generation EGFR-TKIs. Furthermore, although exon 20 T790M mutation is one of the major resistance mechanisms for first-/second-generation EGFR-TKIs, osimertinib, a third-generation EGFR-TKI, can overcome the resistance resulting from exon 20 T790M mutation. Osimertinib showed an improved PFS (median PFS, 18.9 months versus 10.2 months; HR, 0.46, P<0.001) and OS (median OS, 38.6 months with osimertinib versus 31.8 months with the first-generation EGFR-TKIs; HR, 0.80, P=0.046) compared with first-generation EGFR-TKIs (5,6). Therefore, osimertinib has become one of the major therapeutic options for EGFR mutant NSCLC.

However, the response of EGFR mutant NSCLC to EGFR-TKIs is not consistent for all cases. In patients with EGFR mutant NSCLC with positive programmed death ligand-1 (PD-L1) expression, first-/second-generation EGFR-TKIs (7-9) and osimertinib monotherapy (10-13) is reported to be less effective, and combined therapy with EGFR-TKIs plus vascular endothelial growth factor inhibitors or cytotoxic agents may be more effective (14). On the other hand, PFS after the treatment with osimertinib is longer in patients with EGFR mutant NSCLC with negative or lower PD-L1 expression (10-13). In addition, PD-L1 expression is also associated with the acquisition rate of the T790M mutation after treatment with first-/second-generation EGFR-TKIs (7-9). For patients who acquired resistance through the T790M mutation, the effectiveness of sequential therapy with osimertinib has been demonstrated in the AURA study (15).

Thus, for EGFR mutant NSCLC with negative or lower PD-L1 expression, both sequential therapy with first-/second-generation EGFR-TKI plus osimertinib and first-line osimertinib therapy are considered promising. However, there is little information about the efficacy of these EGFR-TKI monotherapies for this population. We conducted this observational study to compare them.

Materials and methods

Patient selection. Data of patients who met the criteria were retrieved from medical charts. The following inclusion criteria were used: i) patients with NSCLC harboring the common EGFR mutation, ii) patients with NSCLC in which the tumor proportion score (TPS) of PD-L1 was confirmed to be less than 50% using the 22C3 antibody in clinical practice, and iii) patients with NSCLC who were treated with first-line EGFR-TKI monotherapy. The testing for T790M mutations after the treatment with first-/second-generation EGFR-TKIs was started in clinical practice in 2016. Thus, the following exclusion criterion was established: i) patients in whom the entire treatment for NSCLC was discontinued before 2016.

The present study was conducted following the Declaration of Helsinki and Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan) and approved by the Ethics Committee, University of Toyama (approval number: R2023018). Owing to the retrospective nature of the study, the need to obtain written informed consent was waived, and we disclosed the study information to the subjects prior to their participation.

Driver mutation and PD-L1 expression. EGFR mutation status and PD-L1 expression were evaluated using data retrieved from medical charts. EGFR mutation was evaluated by polymerase chain reaction or next-generation sequencing, and PD-L1 expression was evaluated based on TPSs determined using the 22C3 antibody.

Statistical analysis. Patient characteristics were compared using Fisher's exact test. To compare the efficacy of EGFR-TKI monotherapies for EGFR mutant NSCLC with negative or lower PD-L1 expression, the PFS, EGFR-TKI treatment duration, and OS were evaluated in the present study. PFS was calculated from the initiation date of the treatment with EGFR-TKIs until the date of disease progression defined by the Response Evaluation Criteria in Solid Tumors version 1.1 or clinically judged disease progression, whichever occurred first. EGFR-TKI treatment duration was defined as the sum of the PFS of first-line EGFR-TKI treatment and subsequential osimertinib therapy after the acquisition of the T790M mutation. If the treatment was changed because of an adverse event without disease progression, PFS and EGFR-TKI treatment duration was censored on the day on which the next treatment was started. OS was calculated from the initiation date of the EGFR-TKI therapy until death and censored at the last visit without death.

Kaplan-Meier curves were constructed, and survival was compared by log-rank test in patients subdivided according to treatment option. The Cox proportional hazard model was used to assess the association between the treatment option and EGFR-TKI treatment duration while adjusting for sex, ECOG performance status (PS), EGFR mutation status, and brain metastases. These independent variables were selected because they were considered to influence the survival in patients with EGFR mutant NSCLC.

All statistical analysis was performed using the JMP statistical software package, version 17.0.0 (SAS, Cary, NC, USA).

Results

Patient selection. Between 2007 and 2023, 150 patients with EGFR mutant NSCLC received first-line EGFR-TKI treatment, and PD-L1 expression was evaluated in 74 patients. Of these 74 patients, 17 patients were excluded for a PD-L1 TPS of ≥50%, and 2 patients were excluded because the entire treatment for NSCLC was discontinued before 2016. Finally, 55 patients who were treated with first-line EGFR-TKIs between 2013 and 2023 were included in the analysis.

Table I shows the patient characteristics. Female patients with a PS of 0-1 were more prevalent. First-/second-generation EGFR-TKIs and osimertinib were administered in 26 and 29 patients, respectively. The first-/second-generation EGFR-TKIs were gefitinib, erlotinib, and afatinib. Patients aged ≥75 years were more prevalent in the osimertinib group. First-line treatment with EGFR-TKIs were started between 2013 and 2021 in first-/second-generation EGFR-TKI group, while it was started between 2018 and 2023 in osimertinib group. The median observation period was 38.3 months and 17.9 months in the first-/second-generation EGFR-TKI group and the osimertinib group, respectively.

Survival. The median (95% CI) PFS was 12.9 (9.7-22.9) months and 22.5 (7.6-28.8) months in patients who were treated with first-/second-generation EGFR-TKIs and osimertinib, respectively (P=0.232, log-rank test). After first-/second-generation EGFR-TKI therapy, 18 of the 26 patients showed disease progression during the treatment. Among them, the T790M mutation was evaluated in 16/18 (88.9%) patients, and 10/16 patients (62.5%) showed the T790M mutation, who were

Table I. Patient characteristics.

Characteristics	First-/second-generation, n (%) (n=26)	Third-generation, n (%) (n=29)	P-value
Age, years			
<75	18 (69.2)	10 (34.5)	0.015
≥75	8 (30.8)	19 (65.5)	
Sex			
Male	10 (38.5)	9 (31.0)	0.584
Female	16 (61.5)	20 (69.0)	
PS			
0-1	20 (76.9)	25 (86.2)	0.490
≥2	6 (23.1)	4 (13.8)	
Histology			
Adenocarcinoma	26 (100.0)	27 (93.1)	>0.999
Squamous	0 (0.0)	1 (3.4)	
NOS	0 (0.0)	1 (3.4)	
EGFR			
EGFR del 19	13 (50.0)	14 (48.3)	>0.999
EGFR L858R	13 (50.0)	15 (51.7)	
PD-L1, %			
<1	16 (61.5)	14 (48.3)	0.419
1-49	10 (38.5)	15 (51.7)	
Brain metastases			
Yes	7 (26.9)	4 (13.8)	0.315
No	19 (73.1)	25 (86.2)	
Stage			
IIIB	1 (3.8)	0 (0.0)	0.746
IVA	4 (15.4)	3 (10.3)	
IVB	9 (34.6)	13 (44.8)	
Recurrence	12 (46.2)	13 (44.8)	

First-/second-generation and third-generation refer to first-/second-generation and third-generation EGFR-tyrosine kinase inhibitors. del, deletion; EGFR, epidermal growth factor receptor; NOS, not otherwise specified; PD-L1, programmed death ligand-1; PS, performance status.

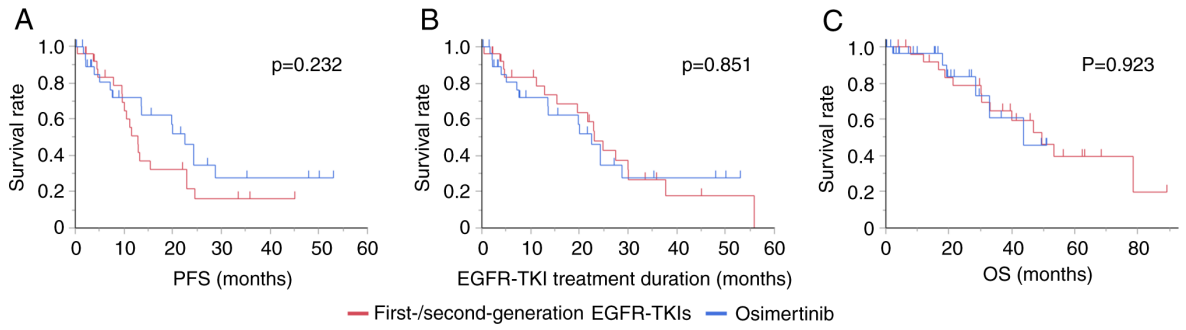

Figure 1. Kaplan-Meier curves for (A) PFS, (B) EGFR-TKI treatment duration and (C) OS in patients who were treated with first-/second-generation EGFR-TKIs or osimertinib. EGFR-TKI treatment duration was defined as the PFS for osimertinib, or the sum of the PFS for first-/second-generation EGFR-TKIs and sequential osimertinib therapy after the acquisition of the T790M mutation. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival.

subsequently treated with osimertinib. The median (95% CI) EGFR-TKI treatment duration was 23.0 (12.9-30.0) months and 22.5 (7.6-28.8) months in patients who were treated with first-/second-generation EGFR-TKIs and osimertinib, respectively (P=0.851, log-rank test). EGFR-TKI therapy was terminated in 22 patients (progression: 18, adverse

Table II. Multivariate analysis (Cox proportional hazard model) for the EGFR-TKI treatment duration.

Characteristics	HR	95% CI	P-value
Age, years			
<75	1.79	0.75-4.25	0.191
≥75	1.00		
Sex			
Male	2.31	1.05-5.09	0.038
Female	1.00		
PS			
0-1	0.71	0.25-1.99	0.509
≥2	1.00		
EGFR			
EGFR L858R	2.54	1.08-5.94	0.032
EGFR del 19	1.00		
Brain metastases			
No	1.25	0.46-3.38	0.657
Yes	1.00		
First-line treatment			
Third-generation	1.31	0.55-3.13	0.542
First-/second-generation	1.00		

First-/second-generation and third-generation refer to first-/second-generation and third-generation EGFR-TKIs. del, deletion; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; PS, performance status.

event: 4) in first-/second-generation EGFR-TKI group. Of these, 13/22 patients (59.1%) and 8/22 patients (36.4%) were treated with platinum doublet therapy and immune checkpoint inhibitor therapy, respectively. On the other hand, osimertinib therapy was terminated in 15 patients due to disease progression. Of these, 3/15 patients (20.0%) and 2/15 patients (13.3%) were treated with platinum doublet therapy or immune checkpoint inhibitor therapy, respectively. The median (95% CI) OS was 49.5 (30.4-not estimated) and 43.7 (28.5-not estimated) in patients who were treated with first-/second-generation EGFR-TKIs and osimertinib, respectively (P=0.923, log-rank test) (Fig. 1).

Table II shows the results of the Cox proportional hazard model for EGFR-TKI treatment duration. The independent variables were sex, PS, EGFR mutation status, brain metastases, and EGFR-TKI therapy. The hazard ratio (95% CI) of osimertinib for first-/second-generation EGFR-TKIs was 1.31 (0.55-3.13), which suggested that the EGFR-TKI treatment duration was not statistically different between the two monotherapies.

Discussion

Both sequential treatment with first-/second-generation EGFR-TKIs plus osimertinib and first-line treatment with osimertinib are considered promising for patients with EGFR mutant NSCLC with negative or lower PD-L1 expression. The present study was conducted based on this concept and confirmed that the prognosis is equally favorable in patients with EGFR mutant NSCLC with negative or lower PD-L1 expression who were treated with first-/second-generation EGFR-TKIs or osimertinib.

There are several mechanisms for increasing the PD-L1 expression (16). One is derived by interferon-gamma produced by CD8 T lymphocytes. In other words, increased PD-L1 expression corresponds with tumor-infiltrating CD8 T lymphocytes, which may result in the association between PD-L1 expression and the efficacy of immune checkpoint inhibitors. Consistent with this, Shirasawa *et al* (17) reported that NSCLC with high PD-L1 expression and a high density of infiltrating CD8 T lymphocytes had significantly better PFS than that with high PD-L1 expression and a low density of tumor-infiltrating CD8 T lymphocytes after the treatment with immune checkpoint inhibitors.

The other mechanism is based on oncogene signals. It has been demonstrated that EGFR (18) and ALK signals (19) increase PD-L1 expression, and depression of the ERK2 signal by siRNA decreases PD-L1 expression (20). Furthermore, the Axl gene mutation associated with resistance to osimertinib (21,22) is reported to increase PD-L1 expression (23). The hypothesis was proposed that low PD-L1 expression is associated with more homogeneous and less immunogenic tumor cells in EGFR mutant NSCLC, resulting in a slow-growing disease that responds well to EGFR-TKIs. In this type of tumor, acquired resistance is more likely to occur in EGFR pathways. Conversely, high PD-L1 expression may result from activated oncogenes not related to the EGFR mutation, which leads to EGFR-TKI resistance and acquired resistance outside the EGFR pathways (7).

Therefore, in EGFR mutant NSCLC with negative or lower PD-L1 expression, both sequential therapy with first-/second-generation plus osimertinib and first-line osimertinib therapy can be promising treatment strategies. In this study, first-/second-generation EGFR-TKIs and osimertinib were equally effective. The T790M mutation was highly detectable, consistent with previous reports (7-9), and the median PFS of 22.5 months in the osimertinib first-line treatment group was longer than that shown in the FLAURA trial (5). First-line treatment with osimertinib may be preferable because the sequential therapy requires re-biopsy.

The present study has several limitations. First, a small sample size may provide insufficient statistical power for the detection of differences in survival. In addition, it was difficult to evaluate the survival in patients treated with second-generation EGFR-TKI because we addressed patients treated with first-generation EGFR-TKIs and second-generation EGFR-TKI as one group. Finally, although we performed multivariate analysis using the Cox proportional hazard model to adjust for patient characteristics, some biases and confounding factors may affect the analysis, considering the retrospective nature of the study. For example, differences in the timing of treatment may have introduced biases that affected the outcome. In addition, it cannot be excluded that differences in observation duration and late-line treatment after the EGFR-TKI therapy between the two groups might have influenced the analysis.

In summary, the present study showed that the median (95% CI) EGFR-TKI treatment duration was 23.0 (12.0-30.0) and 22.5 (7.6-28.8) months in patients treated

with first-/second-generation EGFR-TKIs and osimertinib, respectively. This suggests that the sequential therapy with first-/second-generation EGFR-TKIs plus osimertinib and first-line treatment with osimertinib are equally effective for patients with EGFR mutant NSCLC with negative or lower PD-L1 expression.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MI designed the study and wrote the original draft of the manuscript. SMi, NT, KH, TH, ZS, KoT, CT, SO, KK, SI, TM, RH and SMa contributed to the acquisition of data. KaT contributed to the interpretation of data and supervised the study. MI and SO confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted according to the Declaration of Helsinki and Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan) and approved by the Ethics Committee, University of Toyama (approval no. R2023018; Toyama, Japan). The need to obtain informed consent from the study subjects was waived under the approval of the Ethics Committee, University of Toyama, and information about the study was disclosed to the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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