Impact of Sequential Therapy With Osimertinib on the Overall Survival in Patients With EGFR-mutant Non-small Cell Lung Cancer

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Research Article

Keywords: epidermal growth factor receptor, tyrosine kinase inhibitor, lung cancer, osimertinib, survival, prognosis

Posted Date: July 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-747775/v1

Version of Record: A version of this preprint was published at The Egyptian Journal of Bronchology on March 20th, 2022. See the published version at https://doi.org/10.1186/s43168-022-00121-1.

Abstract

Purpose. We conducted a retrospective analysis of the data of patients with epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) to investigate the associations between the available treatment options and the overall survival.

Methods. We retrieved the patient data from the medical charts. Patients who were diagnosed as having EGFR-mutant NSCLC and treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) between 2007 and 2020 at our institution were included in the analysis.

Results. A total of 130 patients were included in the analysis. A log-rank test identified EGFR exon 19 deletion in the tumor, an Eastern Cooperative Oncology Group performance status of 0-1, serum lactate dehydrogenase level, local therapy for brain metastasis, and sequential osimertinib therapy for patients with the T790M mutation acquired after primary EGFR-TKI therapy as being significantly associated with a better overall survival. Analysis using a Cox proportional hazards model identified EGFR exon 19 deletion in the tumor, an Eastern Cooperative Oncology Group performance status of 0-1, serum lactate dehydrogenase level, local therapy for brain metastasis, and sequential therapy with osimertinib as being independently associated with a prolonged overall survival.

Conclusion. Our analysis suggested that sequential therapy with osimertinib in patients with acquired drug resistance associated with the appearance of the T790M mutation after the primary EGFR-TKI therapy was associated with prolongation of the overall survival in patients with EGFR-mutant NSCLC in clinical practice settings.

Introduction

Treatment with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors has been shown to improve the prognosis in patients with EGFR-mutant non-small cell lung cancer (NSCLC). At first, first-generation EGFR-TKIs were shown to prolong the progression-free survival (PFS) as compared to cytotoxic agents [1, 2]. Thereafter, afatinib, a second-generation EGFR-TKI, was shown to prolong the PFS than the first-generation EGFR-TKIs [3], and this drug yielded a longer overall survival (OS), although the difference did not reach statistical significance [4]. In a more recent trial, the PFS and OS were significantly prolonged in the osimertinib treatment arm (a third-generation EGFR-TKI) as compared to the control arm treated with a first-generation EGFR-TKI [5]. In addition to these therapeutic advances, reports have shown that about a half of the patients who are treated with a first- or second-generation EGFR-TKI develop acquired resistance to the primary EGFR-TKI therapy, associated with the emergence of the EGFR exon 20 T790M mutation [6], but that the PFS in these patients can still be prolonged by sequential therapy with osimertinib [7]. Other studies have reported that patients who developed resistance associated with the emergence of the T790M mutation after treatment with afatinib who received sequential osimertinib therapy showed an extremely prolonged OS [8, 9].

Based on the above, it is evident that therapeutic advances have yielded improvement of the prognosis of patients with EGFR-mutant NSCLC in clinical practice. We conducted a retrospective study to investigate the associations of the available therapeutic options with the OS in patients with EGFR-mutant NSCLC.

Methods

Patient selection

Clinical information was retrieved from the medical charts. The inclusion criteria were as follows: 1) patients with cytologically or histologically diagnosed EGFR-mutant NSCLC; 2) patients who had received EGFR-TKI therapy as the first-line treatment between 2007 and 2020 at our institution. The exclusion criteria were as follows: 1) patients in whom the exon 20 T790M mutation was detected in the tumor even prior to the start of the first-line treatment.

This retrospective study was conducted in accordance with the principles outlined in the Declaration of Helsinki and Ethics Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan). We disclosed information about the study to the patients under the approval of the Ethics Committee, University of Toyama (approval number: R2019103).

Clinical information

The tumor EGFR mutations were classified as exon 19 deletion, exon 21 L858R, or uncommon mutations. Compound mutations with common (exon 19 deletion or exon 21 L858R) and uncommon mutations were classified as uncommon mutations.

Tumor PD-L1 expression was evaluated by immunohistochemistry in formalin-fixed and paraffin-embedded tumor tissue specimens, using the 22C3 antibody (BML, Tokyo, Japan). The proportion of PD-L1-positive cells in the tumor was evaluated as the tumor proportion score (TPS) for PD-L1 expression.

Local therapy for brain metastasis was defined as local therapy administered at the start of first-line treatment, and included stereotactic radiotherapy, whole-brain irradiation, and surgery.

Sequential therapy with osimertinib was defined as treatment with osimertinib for patients who developed acquired resistance to the primary EGFR-TKI therapy associated with appearance of the T790M mutation in the tumor. Re-administration of first- or second-generation EGFR-TKIs was defined as re-administration of other first- or second-generation EGFR-TKIs for patients with acquired resistance to the primary EGFR-TKIs. Changes of the EGFR-TKIs administered for other reasons such as development of adverse events associated with the initial EGFR-TKIs were not included in the above definition.

Statistical analysis

Survival curves were drawn by the Kaplan-Meier method. OS was calculated from the date of initiation of treatment with an EGFR-TKI until death, and censored at the last visit of the patient. Patient data were

dichotomized according to categorical variables or median values of numerical variables, and the OS was compared by the log-rank test. Variables that were determined as showing an association with P values of < 0.2 were selected as independent variables to be entered into the Cox proportional hazards model. All the statistical analyses were performed using JMP ver. 15.0.0 (SAS, Cary, NC).

Results

A total of 158 patients with EGFR-mutant NSCLC were treated at our institution between 2007 and 2020. Of the 158 patients, 25 patients were excluded from this analysis because they did not receive first-line EGFR-TKI treatment, and 3 patients were excluded because the T790M mutation was detected in the tumor even at initial diagnosis. Data of the remaining 130 patients with EGFR-mutant NSCLC who had been treated with EGFR-TKIs as the first-line treatment were included in this analysis. The date of death could be confirmed for 52 (40%) patients, but not for 48 patients (36.9%), because the latter were transferred to some other hospital prior to their death. Anticancer therapy was ongoing at the time of the analysis in this study in 30 (23.1%) patients.

Table 1 shows the patient characteristics. Of the 130 patients, 84 (64.6%), 25 (19.2%), and 21 (16.2%) patients received first-line treatment with a first-generation (including gefitinib and erlotinib), second-generation (afatinib), and third-generation (osimertinib) EGFR-TKI, respectively. Five (3.8%) patients received combined EGFR-TKI plus vascular endothelial growth factor (VEGF) inhibitor therapy, and 36 (27.7%) patients received platinum-doublet therapy at some point during the clinical course. Twenty-one (16.2%) patients received sequential therapy with osimertinib, and 16 (12.3%) patients received re-administration of another first- or second-generation EGFR-TKI. Out of the total of 109/130 patients who did not receive sequential therapy with osimertinib, the anticancer therapy had been discontinued in 43 patients even prior to 2016, when osimertinib therapy first became available. Brain metastasis was detected at the initial diagnosis in 37 (28.5%) patients, and was treated by stereotactic radiotherapy in 14 patients, stereotactic radiotherapy and surgery in 1 patient, and whole-brain irradiation in 9 patients.

Table 1
Patient characteristics

		n (%)
Age (yr)	< 75	70 (53.8%)
	≥ 75	60 (46.2%)
Sex	Male	48 (36.9%)
	Female	82 (63.1%)
Histology	Adenocarcinoma	125 (96.2%)
	Others	5 (3.8%)
EGFR mutation	Exon 19 del	56 (43.1%)
	Exon 21 L858R	62 (47.7%)
	Uncommon mutation	12 (9.2%)
PS	0–1	93 (71.5%)
	≥ 2	37 (28.5%)
LDH (U/L)	< 200	58 (44.6%)
	≥ 200	72 (55.4%)
Tumor PD-L1 TPS	≥ 1%	36 (27.7%)
	< 1%	24 (18.5%)
	Unknown	70 (53.8%)
History of surgery	Yes	22 (16.8%)
	No	109 (83.2%)
Brain metastasis	Yes	37 (28.5%)
	No	93 (71.5%)
First-line EGFR-TKI used	1st generation TKIs	84 (64.6%)
	Afatinib	25 (19.2%)
	Osimertinib	21 (16.2%)
History of platinum-doublet therapy	Yes	36 (27.7%)

EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; LDH, serum lactate dehydrogenase; PD-L1, programmed death ligand 1; PS, performance status; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

		n (%)
	No	94 (72.3%)
History of VEGF inhibitor therapy	Yes	5 (3.8%)
	No	125 (96.2%)
Sequential therapy with TKIs	Osimertinib	21 (16.2%)
	1st/2nd generation TKIs	16 (12.3%)
	None	93 (71.5%)
History of ICI therapy	Yes	13 (10.0%)
	No	117 (90.0%)

EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; LDH, serum lactate dehydrogenase; PD-L1, programmed death ligand 1; PS, performance status; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

Table 2 shows the association between the patient characteristics and the OS as determined by the log-rank test; comparison by the log-rank test identified exon 19 deletion in the tumor, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, a serum lactate dehydrogenase (LDH) level of < 200 U/L, and sequential therapy with osimertinib as being associated with a prolonged OS. Figure 1 shows the Kaplan-Meier curves for OS in patients who did and did not receive sequential therapy with osimertinib. The OS duration was longer (median, 78.5 months) in patients who had received sequential therapy with osimertinib as compared to those who had received re-administration of first- or second-generation EGFR-TKIs (median, 31.5 months) and patients who had received neither of the above (median, 33.0 months) (P = 0.019, log-rank test).

Table 2
Associations of the patient characteristics with the OS (log-rank test)

		OS (median)	95% CI	P
Age (yr)	< 75	40.0	31.5-NE	0.523
	≥ 75	34.0	25.5–52.7	
Sex	Male	33.1	20.5–46.8	0.254
	Female	52.7	30.4-NE	
Histology	Adenocarcinoma	40.0	31.5–54.7	0.931
	Others	32.3	22.6–32.3	
EGFR mutation	Exon 19 del	NR	33.1-NE	0.011
	Exon 21 L858R	40.0	22.6–52.7	
	Uncommon mutation	32.3	5.3-NE	
PS	0–1	52.7	34.0-87.6	0.002
	≥ 2	30.4	10.3–40.0	
LDH (U/L)	< 200	51.3	34.0-78.5	0.046
	≥ 200	28.6	17.2-NE	
PD-L1 TPS	≥ 1%	51.3	32.3–87.6	0.394
	< 1%	46.8	30.4–78.5	
	Unknown	31.5	19.4-NE	
History of surgery	Yes	NR	28.3-NE	0.184
	No	38.8	28.6–52.7	
Brain metastasis	Yes (with local therapy)	NR	36.1-NE	0.033

CI, confidence interval; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; LDH, serum lactate dehydrogenase; NE, not estimated; PD-L1, programmed death ligand 1; PS, performance status; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

		OS (median)	95% CI	P
	Yes (without local therapy)	17.2	5.3-NE	
	No	34.0	28.6–52.7	
First-line TKI used	1st generation TKIs	36.1	28.0-51.3	0.157
	Afatinib	NR	19.2-NE	
	Osimertinib	NR	20.5-NE	
History of platinum-doublet therapy	Yes	40.3	28.6-NE	0.470
	No	34.0	28.3–87.6	
History of VEGF inhibitor therapy	Yes	54.7	11.0-54.7	0.895
	No	38.8	30.4–78.5	
Sequential therapy with TKIs	Osimertinib	78.5	46.8-NE	0.019
	1st/2nd generation TKIs	31.5	13.0-NE	
	None	33.0	22.6–38.8	
History of ICI therapy	Yes	54.7	18.7-NE	0.389
	No	36.1	28.6–78.5	

CI, confidence interval; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; LDH, serum lactate dehydrogenase; NE, not estimated; PD-L1, programmed death ligand 1; PS, performance status; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

Table 3 shows the results of the analysis conducted using a Cox proportional hazards model conducted to identify the factors influencing the OS. The analysis identified the type of EGFR mutation in the tumor, the ECOG PS, the serum LDH level, treatment status for brain metastasis, and sequential therapy with osimertinib as factors that significantly influenced the OS. First-line treatment with afatinib or osimertinib showed a risk reduction versus treatment with a first-generation TKI, although the difference did not reach statistical significance.

Table 3
Associations of the patient characteristics with the OS (Cox proportional hazard model)

		HR	P
EGFR mutation	Exon 19 del	0.40 (0.21–0.78)	0.007
	Exon 21 L858R	1.00	
	Uncommon mutation	0.83 (0.32–2.13)	0.699
PS	0–1	035 (0.18–0.67)	0.002
	≥ 2	1.00	
LDH (U/L)	< 200	0.43 (0.23–0.82)	0.011
	≥ 200	1.00	
History of surgery	Yes	0.77 (0.33–1.83)	0.557
	No	1.00	
Brain metastasis	Yes (with local therapy)	0.18 (0.05–0.65)	0.008
	Yes (without local therapy)	1.00	
	No	0.68 (0.28–1.62)	0.384
First-line TKI used	1st generation TKIs	1.00	
	Afatinib	0.50 (0.21–1.20)	0.120
	Osimertinib	0.37 (0.10–1.29)	0.119
Sequential therapy with TKIs	Osimertinib	0.25 (0.11–0.60)	0.002
	1st/2nd generation TKIs	1.01 (0.44–2.33)	0.973
	None	1.00	

EGFR, epidermal growth factor receptor; HR, hazard ratio; LDH, serum lactate dehydrogenase; PS, performance status; TKI, tyrosine kinase inhibitor.

Discussion

In the present study, we showed that sequential therapy with osimertinib in EGFR-mutant NSCLC patients with acquired T790M mutation was associated with a longer OS. Furthermore, the hazard ratio for death was lower in patients who received afatinib or osimertinib as first-line treatment than in patients who received first-generation EGFR-TKIs as the first-line treatment, although the difference did not reach statistical significance.

The AURA study demonstrated that osimertinib yielded a longer PFS as compared to platinum-doublet therapy in patients with acquired resistance to primary EGFR-TKI therapy associated with emergence of the T790M mutation [7]. Therefore, the effectiveness of osimertinib for patients with acquired T790M mutation might be reflected in the results of the present study, with improvement of the prognosis of EGFR-mutant NSCLC with clinical application of sequential osimertinib therapy. However, it has also been reported that patients with acquired resistance to primary EGFR-TKI therapy associated with the emergence of the T790M mutation showed a longer PFS of first-line EGFR-TKI treatment [10–13], and a lower incidence of brain metastasis under the treatment not including osimertinib [14]. Therefore, in addition to the effectiveness of osimertinib, the selection of T790M-positive patients after first-line EGFR-TKI treatment might have resulted in the selection of patients with a favorable prognosis, resulting in a longer survival.

In the FLAURA trial, patients with untreated EGFR-mutant NSCLC who received first-line osimertinib treatment showed a significantly longer OS as compared to patients who received first-generation EGFR-TKIs as the first-line treatment [5]. However, a subset analysis revealed that there was no clear evidence of prolongation of the OS in the osimertinib arm in the Asian as compared to the non-Asian subset of patients. The effectiveness of first-line treatment with osimertinib in Asians may be an issue that warrants further investigation in the future. In the present study, multivariate analysis revealed no significant association between the type of EGFR-TKI used for first-line treatment and the OS. This could be because some patients in whom the first-/second-generation EGFR-TKIs were changed to osimertinib due to the appearance of side effects rather than due to acquired resistance to the EGFR-TKIs have been included in the first- or second-generation EGFR-TKI group. In addition, the number of patients who were treated with osimertinib as first-line treatment was very small (n = 21), which could have led to a lack of statistical power.

Analysis of the OS data from the LUX-Lung 3, LUX-Lung 6 [15], and FLAURA [5] trials showed that the study treatment was more beneficial in patients with tumors carrying the exon 19 deletion as compared to exon 21 L858R as the EGFR mutation. The results of the present study showed that the hazard ratio for death was lower in patients with tumors carrying the exon 19 deletion. It is considered that the higher efficacy of EGFR-TKIs in patients with tumors carrying the exon 19 deletion might have contributed to the results of the present study.

Two previous studies have reported that combined therapy with erlotinib, a first-generation EGFR-TKI, plus a VEGF inhibitor yielded a longer PFS as compared to erlotinib monotherapy [16, 17]. However, in both of these clinical trials, the PFS, but not the OS, was compared as the primary endpoint. Furthermore, a meta-analysis demonstrated that combined erlotinib plus VEGF inhibitor therapy was associated with a longer PFS, but no prolongation of the OS in patients with EGFR-mutant NSCLC [18]. In the present study, comparison by the log-rank test showed no association between combined first-generation EGFR-TKI plus VEGF inhibitor therapy and the OS, although no definitive conclusions can be drawn because of the retrospective nature of the study and the small number of patients who received the combination therapy.

Numerous studies have reported serum LDH as a prognostic factor, and indicated an association of the serum LDH with the OS in patients with NSCLC, whether treated by EGFR-TKI therapy [19], cytotoxic chemotherapy, or best supportive care [20]. As the mechanisms underlying this association, it is considered that tumor hypoxia is linked to glycolytic enzymes and angiogenetic factors, including LDH and VEGF, and that the invasive ability and angiogenic capability of tumors is promoted by acidification of the extracellular space induced by lactic acid [21, 22].

Development of brain metastasis has been reported to influence to clinical course of patients with EGFR-mutant NSCLC [14] [23]. In the present study, out of 37 patients with brain metastasis, 24 had received local therapy for brain metastasis. According to one previous report, the OS was longer in patients with brain metastasis who were treated with upfront radiotherapy as compared to systemic chemotherapy [24]. Because of the retrospective nature of our study, it would be difficult to exclude selection bias to definitively establish the superiority of the treatment option used in the present study. However, the present study findings do suggest that local therapy for brain metastasis might indeed prolong the survival in patients with EGFR-mutant NSCLC who develop brain metastasis.

There were several limitations of the present study. First, because of the retrospective nature of the study design, selection bias could have affected the results. Second, the survival rate might have been overestimated because of censoring of the patients when they were transferred to another hospital due to worsening of the general status. Third, none of the patients in this study had received combined therapy with gefitinib and cytotoxic agents, even though combined gefitinib plus chemotherapy has also been reported to yield a longer survival as compared to EGFR-TKI monotherapy [25]. Thus, we could not evaluate the association between this therapy and the patient survival.

In conclusion, the present study showed that patients developing acquired resistance to EGFR-TKI therapy associated with the emergence of the T790M mutation who received sequential therapy with osimertinib showed a longer OS than patients who did not receive sequential therapy with osimertinib. Our findings indicate that the development of new therapeutic strategies has led to improved prognosis of patients with EGFR-mutant NSCLC in the clinical setting.

Declarations

Funding: None

Competing interests: None

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' contributions: MI contributed to the conception and design of the work, and data analysis. Data collection was performed by MI, MM, IM, KH, ZS, KT (Kotaro Tokui), CT, SO, KK, SI, TM, RH, and SM. The

interpretation of the data and revision of the manuscript were performed by MI, MM, IM, KH, ZS, KT (Kotaro Tokui), CT, SO, KK, SI, TM, RH, SM, and KT (Kazuyuki Tobe).

Ethics approval

The study was conducted under the approval of the Ethics Committee, University of Toyama (approval number: R2019103).

Consent to participate/Consent for publication: The informed consent was waived and we disclosed the study information, under the approval of the Ethics Committee, University of Toyama (approval number: R2019103).

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Figures

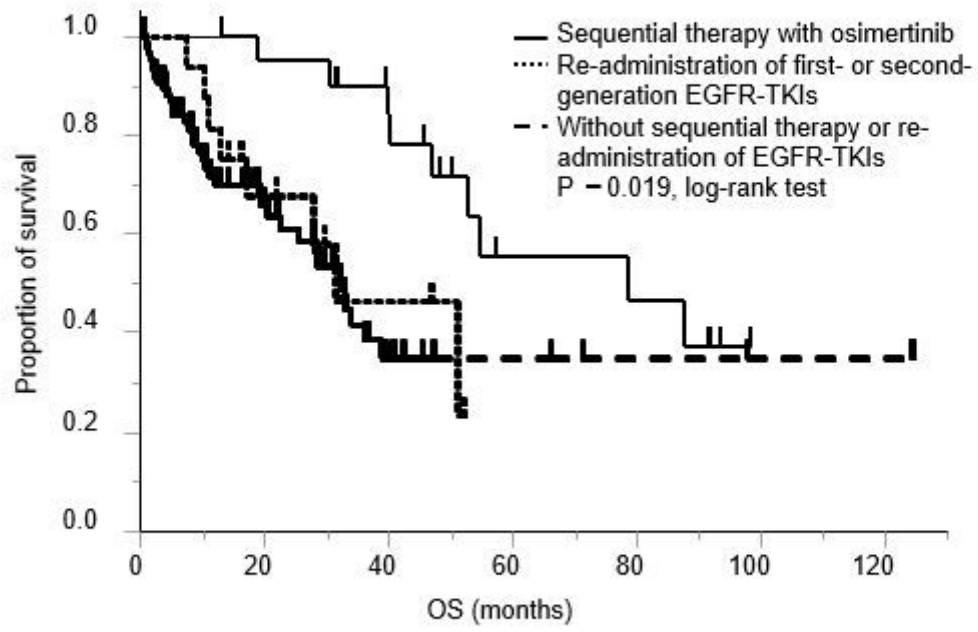

Figure 1

Kaplan-Meier curve for OS in patients who received sequential therapy with osimertinib, who received re-administration of the first-/second-generation EGFR-TKIs, and who received neither of the above. Solid line: patient group that received sequential therapy with osimertinib; dotted line: patient group that received re-administration of first-/second-generation EGFR-TKIs; dashed line: patients who neither received neither sequential therapy with osimertinib, nor re-administration of first-/second-generation EGFR-TKIs.