RESEARCH ARTICLE

Osimertinib as a Potential Targeted Therapy for Non-Small Cell Lung Carcinoma (NSCLC) Patients with EGFR Exon 20 T790M

Nur Zam Zam[1], Harun Iskandar[2], Nur Ahmad Tabri[3], Arif Santoso[2], Nurjannah Lihawa[4], Harry Akza Putrawan[5], Ferry Sandra[6,*]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, Indonesia
[2]Thoracal Oncology Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, Indonesia
[3]Asthma and COPD Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, Indonesia
[4]Infection and Tuberculosis Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, Indonesia
[5]Interventional Pulmonology Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Hasanuddin, Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, Indonesia
[6]Department of Biochemistry and Molecular Biology, Division of Oral Biology, Faculty of Dentistry, Universitas Trisakti, Jl. Kyai Tapa No. 260, Jakarta 11440, Indonesia

*Corresponding author. Email: ferry@trisakti.ac.id

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Abstract

BACKGROUND: Emergence of drug resistance due to epidermal growth factor receptor (EGFR) Exon 20 T790M poses a challenge in the effective management of non-small cell lung carcinoma (NSCLC). Significant breakthrough in the management of NSCLC with a specific genetic alteration causes substantial condition improvement in patients whose cancer progressed after first-generation tyrosine kinase inhibitor treatment and who developed tumors with EGFR Exon 20 T790M mutation. The present study analyzed a cohort of NSCLC patients and investigated the incidence of the EGFR Exon 20 T790M status with Osimertinib therapy, along with its impact on survival rates.

METHODS: This was a retrospective cohort study on 22 NSCLC subjects who were genetically examined for EGFR status from plasmic cell free total nucleic acid. Subjects with EGFR Exon 20 T790M mutation were treated with/without Osimertinib. Demographic and clinical data were descriptively summarized, and the differences of each variable and correlation between survival rate and EGFR Exon 20 T790M were analyzed.

RESULTS: Subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had survival rates of 10.77±2.45 and 4.78±1.48, respectively (p=0.000). Based on 1-year survival status of subjects with EGFR Exon 20 T790M, there were 3 Osimertinib-treated survivors and 2 Osimertinib-treated non-survivors. Eight subjects with EGFR Exon 20 T790M and without Osimertinib treatment did not survive (p=0.001).

CONCLUSION: Since the treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

KEYWORDS: non-small cell lung carcinoma, EGFR, Exon 20, T790M, osimertinib

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Introduction

The epidermal growth factor receptor (EGFR) mutation is an emerging and promising treatment target for non-small cell lung carcinoma (NSCLC).(1) This mutation is particularly prevalent in South-East Asian NSCLC patients, which is found in more than half of all NSCLC patients. Meanwhile it is also found in 10-20% of Caucasian patients.(2) NSCLC-associated EGFR mutation exhibits a higher incidence in women, non-smokers, and those with adenocarcinoma histology.(3) Fortunately, clinical outcomes for NSCLC patients have significantly improved since the introduction of tyrosine kinase inhibitors (TKIs) targeting EGFR.(4)

The initial generation of TKIs has shown remarkable results in prolonging patients' progression-free survival (PFS).(5,6) However, impact on overall survival (OS) may be limited due to disease progression. Recent findings have shed light on the differences in treatment response between the two most common types of EGFR mutations. Patients with Exon 19 deletion tend to have longer PFS on TKI treatment and show more extended OS compared to those with Exon 21 L858R point mutation.(7,8) Although there is an evidence suggesting that particular EGFR mutation had higher affinity with TKI (9), the true mechanism is still debated.

Despite the initial benefits observed with TKI therapy, a majority of NSCLC patients with active EGFR mutations develop resistance during treatment.(1) Since there has been a significant breakthrough in the management of NSCLC with a specific genetic alteration (10-12), there was substantial condition improvement in patients whose cancer progressed after first-generation TKI treatment and who developed tumors with EGFR Exon 20 T790M mutation.(13) The T790M mutation in NSCLC play role in reducing adenosine triphosphate (ATP)-competitive-kinase-inhibitor, so that the mutation can prevent the effect of inhibitor, thus EGFR-mediated signalling will not be defected.(14)

Based on above reasons, the present study was conducted to analyze a cohort of NSCLC patients and to investigate the incidence of the EGFR Exon 20 T790M status with Osimertinib therapy, along with its impact on survival rates. Understanding these factors will provide valuable insights in aiding the development of effective treatment strategies for NSCLC patients with EGFR mutations.

Methods

Subject and Data Collection

A retrospective cohort study was conducted on 22 NSCLC subjects within October 2019 and July 2022 in Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, and its network centers. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Universitas Hasanuddin (Approval No.: 270/UN4.6.4.5.31/PP36/2022). Demographic and clinical data including age, gender, body mass index, smoking status, Brinkman Index and family history were collected from subjects. Brinkman Index was calculated by multiplying average-cigarette-consumed-everyday with years-of-smoking, mild <200, moderate 200-600, severe >600.

EGFR Genetical Examination

All NSCLC subjects were genetically examined for EGFR status. From each NSCLC subject, 10 mL blood was collected. Blood sample was processed to collect plasmic cell free total nucleic acid (cfTNA) using MagMAX cell free total nucleic acid isolation kit (ThermoFisher, Waltham, MA, USA). DNA library was prepared Oncomine Lung cfDNA Assay (ThermoFisher). Then the sequencing was performed with Ion Torrent next-generation sequencing (NGS) (ThermoFisher). The NGS data was analyzed and interpreted with Ion Reporter and Oncomine Reporter.

Osimertinib Treatment and Survival Status

All NSCLC subjects were treated with Carboplatin and Paclitaxel in a cycle of 6-treatments and 21-days-interval. In the 6th month, EGFR genetical examinations were performed. Among the subjects with EGFR Exon 20 T790M, some received 80 mg Osimertinib for 1 dosage/daily (Tagrrisso, AstraZeneca, Cambridge, UK), while others continued with the second cycle of Carboplatin and Paclitaxel treatment. The subjects were observed until they deceased. The subject survival status was recorded for further analysis.

Statistical Analysis

Demographic and clinical data were descriptively summarized and statistically analyzed using Chi-Square test. Correlation between survival rate and EGFR Exon 20 T790M was analyzed with Log Rank (Mantel-Cox) test. One-year survival status and EGFR mutation in different exons were statistically analyzed using Chi-Square test as well. Significant values were determined at $p<0.05$. All

statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) version 24.0 (IBM Corporation, Armonk, NY, USA).

Results

Based on the subjects' characteristic, there were 12 male and 10 female subjects with majority age of 45-65 years, non-smoking (Brinkman Index), and no family history of lung cancer (Table 1). Meanwhile, based on the EGFR mutation status, there were subjects with mutation of EGFR Exon 20 T790M and mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R (n=8) (Table 2). There were also subjects without mutation of EGFR Exon 20 T790M but having mutation of EGFR Exon 19 deletion (n=5) or EGFR Exon 21 L858R (n=4).

Study subjects with (n=13) and without (n=9) EGFR Exon 20 T790M had a significnat mean difference of 7.77 months with *p*-value of 0.000 (Table 3). As shown in Kaplan-Meier survival curve (Figure 1), subjects without EGFR Exon 20 T790M (blue line) had survival time <10 months, while subjects with EGFR Exon 20 T790M (red line) had survival time >10 months with 3 positive censored tick marks. Based on subjetcs' 1-year survival status, there were more non-survivor with EGFR Exon 20 T790M (n=10) compared with the survivor (n=3), while all subjects without EGFR Exon 20 T790M did not survive (Table 4).

Among the subjects with EGFR Exon 20 T790M, there were subjects treated with (n=5) and without (n=8) Osimertinib. Based on 1-year survival status of subjects with EGFR Exon 20 T790M, there were 3 Osimertinib-treated survivors and 2 Osimertinib-treated non-survivors (Table 5). However, without any Osimertinib treatment, NSCLC subjects with EGFR Exon 20 T790M did not survive.

Table 1. The subject's characteristic based on EGFR Exon 20 T790M.

Variable	EGFR Exon 20 T790M [n (%)]		*p*- value[#]
	(+) (n=13)	(-) (n=9)	
Age			
<45 years old	-	2 (9.1)	0.204
45-65 years old	11 (50.0)	6 (27.3)	
>65 years old	2 (9.1)	1 (4.5)	
Gender			
Male	5 (22.7)	7 (31.8)	0.069
Female	8 (36.4)	2 (9.1)	
Body mass index			
Underweight	7 (31.8)	6 (27.3)	0.548
Normal	6 (27.3)	3 (13.6)	
Overweight	-	-	
Brinkman Index			
Non-smokers	7 (31.8)	2 (9.1)	0.003*
Mild	-	-	
Moderate	5 (22.7)	-	
Severe	1 (4.5)	7 (31.8)	
Family history			
Yes	4 (18.2)	2 (9.1)	0.658
No	9 (40.9)	7 (31.8)	

[#]Chi-Square test, *p<0.05.

Discussion

Lung cancer is a complex disease that often involves genetic alterations affecting the EGFR tyrosine kinase

Table 2. Correlation of EGFR Exon 20 T790M with other EGFR mutations.

Other EGFR Mutation	EGFR Exon 20 T790M [n (%)]		*p*- value[#]
	(+) (n=13)	(-) (n=9)	
EGFR Exon 19 deletion	5 (22.7)	5 (22.7)	0.429
EGFR Exon 21 L858R	8 (36.4)	4 (18.2)	

[#]Chi-Square test.

Table 3. Survival rate related to EGFR Exon 20 T790M.

Group	Survival Rate (Month) [Mean±SD]	Mean Difference	*p*- value[#]
EGFR Exon 20 T790M (+) (n=13)	10.77±2.45	7.77	0.000*
EGFR Exon 20 T790M (-) (n=9)	4.78±1.48		

[#]Log Rank (Mantel-Cox), *p<0.05.

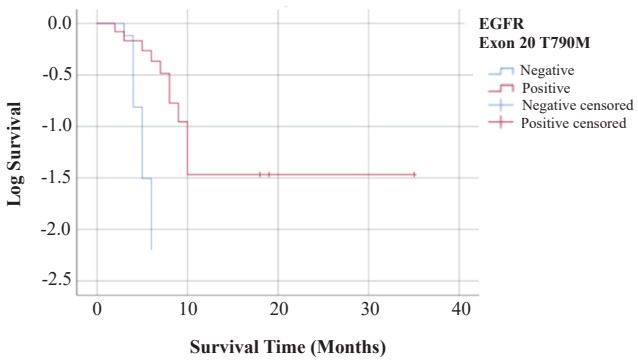

Figure 1. Kaplan-Meier survival curve of subjects with/without EGFR Exon 20 T790M.

signaling pathways, with approximately 75% of examined cases showing such changes.(15) Among these pathways, EGFR pathway is of particular interest with the most common mutations are in-frame deletions (85%–90%) of exon 19 deletion (45%–50%) and Exon 21 L858R mutation (40%–45%).(16) While targeted therapies like TKIs have shown promise in inhibiting tumor growth, the emergence of the EGFR Exon 20 T790M mutation has been identified as a common mechanism of resistance to these therapies. (17,18) The EGFR Exon 20 T790M competes with the TKI, reducing its efficacy and leading to treatment resistance.(14) Among the various post-TKI mutations, the EGFR Exon 20 T790M has the highest incidence.(1,17)

The EGFR Exon 20 T790M mutation is frequently observed in lung cancer patients who have previously undergone TKI therapy and developed resistance.(19) Interestingly, it tends to occur more often in individuals over the age of 40 and women.(20,21) In accordance, in this study, most subjects with EGFR Exon 20 T790M were in the age of 45-65 years old. Advanced age may be associated with a reduced function of tumor-suppressor genes (22), potentially contributing to the occurrence of the EGFR Exon 20 T790M.

In this study, smoking status, as assessed using the Brinkman index, non-smoker was correlated with the presence of the EGFR Exon 20 T790M. This result is in accordance with previous report, showing that the never smokers with EGFR Exon 20 T790M develop lung cancer more frequently than ever smokers. In addition, EGFR Exon 20 T790M was found more in female gender. (23) Similar data were also found in this study, most subjects with EGFR Exon 20 T790M were not smoking, and more female subjects (n=8) than male subjects (n=5) were detected with EGFR Exon 20 T790M. However, the underlying mechanism behind the higher occurrence of the EGFR Exon 20 T790M in non-smokers is not yet understood.

In this study, family history did not appear to have a significant association with the EGFR Exon 20 T790M, although there is a possibility of the mutation being inherited. (24) Additionally, the specific location of the mutation within the exon did not seem to be correlated. Although the EGFR Exon 20 T790M often coexists with other EGFR mutations, such as Exon 19 deletion and Exon 21 L858R mutation, the pathogenetic mechanism underlying this coexistence is still not fully understood.(25,26)

In this study, there was a significant difference in the survival rate of subjects with the EGFR Exon 20 T790M (10.77 months) than the one of subject without the mutation (4.78 months). These results were influenced by the Osimertinib treatment, since data of 1-year survival status showed that among 5 subjects treated with Osimertinib, 3 of them were survive (Table 5) with long survival time (Figure 1). These findings are consistent with similar studies which reported longer overall survival in subjects with EGFR Exon 20 T790M mutations who received EGFR-TKI treatment compared to those without the mutation and without EGFR-TKI treatment.(27)

There are some limitations of the current study. To overcome these limitations and gain a deeper understanding of the clinical outcomes and prognosis associated with the EGFR Exon 20 T790M, a multi-center study with a larger sample size is recommended. Such a study should also consider the type and duration of treatment provided, enabling a more robust analysis of the impact of the EGFR Exon 20 T790M on patient outcomes.

Table 4. One-year survival status related to EGFR Exon 20 T790M.

One-year Survival Status	EGFR Exon 20 T790M [n (%)]		*p*-value[#]
	(+) (n=13)	(-) (n=9)	
Survivor	3 (13.6)	-	0.121
Non-survivor	10 (45.5)	9 (40.9)	

[#]Chi-Square test.

Table 5. One-year survival status related to EGFR Exon 20 T790M with Osimertinib treatment.

One-year Survival Status	Osimertinib Therapy [n (%)]		*p*-value[#]
	(+) (n=5)	(-) (n=8)	
Survivor	3 (23.1)	-	0.001*
Non-survivor	2 (15.4)	8 (61.5)	

[#]Chi-Square test, *$p<0.05$.

Conclusion

Since treatment of Osimertinib demonstrated a noteworthy survival rate among NSCLC subjects with EGFR Exon 20 T790M, thus Osimertinib could be suggested as a potential targeted therapy for NSCLC subjects with EGFR Exon 20 T790M.

Authors Contribution

NZZ involved in concepting and planning the research. NZZ, HI, NAT, AS, NL, and HAP performed the data acquisition data analysis. FS aided in interpreting the results. NZZ and FS drafted and revised the final the manuscript. All authors took parts in giving critical revision of the manuscript.

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