Response Evaluation on Single Common and Uncommon EGFR Mutation on First-Generation EGFR-TKI Therapy in NSCLC Patients

Rena Arusita Maranatha[1], Laksmi Wulandari[2], Gatot Soegiarto[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Academic Hospital, Surabaya 60286, Indonesia, [2]Thoracic Oncology Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Academic Hospital, Surabaya 60286, Indonesia, [3]Clinical Immunology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Academic Hospital, Surabaya 60286, Indonesia

Abstract

Objective: To compare the response of first-generation EGFR-TKI (epidermal growth factor receptor-tyrosine kinase inhibitors) in non-small cell lung cancer (NSCLC) patients with single common and uncommon EGFR mutation.

Methods: Patients were divided into two groups, the uncommon (exon 21 L861Q, exon 18 G719X, exon 18 delE709) and common EGFR mutation group (exon 19 deletion, exon 21 L858R). Health-related quality of life (HRQOL) using EuroQol EQ-5D® questionnaire, body weight, performance status (PS), Response Evaluation Criteria in Solid Tumors (RECIST) on chest CT, progression-free survival (PFS) and overall survival (OS) was recorded during TKI therapy.

Results: The value of HRQOL was stable and PS was constant in both groups, body weight was constant in uncommon group (42.1%) and increased in common group (44.1%; p=0.165). The uncommon group showed mostly progressive disease in RECIST (47.4%) while the common group showed mostly partial response (42.2%; p=0.007). PFS in the uncommon group was 4 (2.0-6.0) months and 7.0 (2.0-21.0) months in the common group (p=0.001). OS in the uncommon and common group were 4.00±1.71 months and 10.00±6.94 months (p<0.001), respectively.

Conclusion: NSCLC patients with common EGFR mutations showed a better response and survival rate compared to uncommon EGFR mutations on first-generation TKI therapy.

Keywords: *NSCLC, EGFR mutation, tyrosine kinase inhibitor, uncommon, common.*

Corresponding author:
Laksmi Wulandari
Thoracic Oncology Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Academic Hospital, Jalan Mayjen Prof. Dr. Moestopo no. 6-8, Airlangga, Gubeng, Surabaya, East Java 60286, Indonesia
Phone numbers: +6231-5501656 / +628123019591
E-mail address: laksmi.wulandari@fk.unair.ac.id
Orcid ID: 0000-0002-5000-0151

Introduction

Lung cancer is a leading cause of cancer-related death worldwide. In 2018, more than 1.6 million individuals were diagnosed with lung cancer and five-year survival is roughly 17% for all stage[1, 2]. There are substantial evolutions in the management of non-small cell lung cancer (NSCLC) in the most recent decade. Analysis of immunology and genomic tumor biomarker have now become a regular examination in NSCLC, notably adenocarcinoma. One of the gene alteration examinations that has been generally applied is the

epidermal growth factor receptor (EGFR) mutation. About 90% of all EGFR mutations are deletion of exon 19 deletion and point mutation L858R in exon 21. Meanwhile, less-common EGFR mutations, likewise called "uncommon", "rare", "nonclassical", or "minor" are about 10% of all EGFR mutations. They might comprise of insertion at exon 20, point mutation at exon 18 or compound mutations[2].

EGFR tyrosine kinase inhibitors (TKI) is one of the significant discoveries in the treatment of lung cancer. Longer progression-free survival (PFS), a better quality of life and lighter drug side effects were seen in patients given first-generation EGFR-TKI compared to patients receiving standard chemotherapy. Most patients with EGFR mutations respond well to EGFR-TKI, yet a few patients don`t show the expected response[3]. These uncommon mutations are sensitive to first-generation EGFR-TKI in a lesser degree than common mutations.

A comprehension of the therapeutic response of various EGFR mutation to TKI is important in deciding a patient's treatment. This encouraged the authors to observe the therapeutic response of patients with a single uncommon EGFR mutation after first-generation EGFR-TKI compared to common mutations in Indonesia.

Methods

Participant of this study were lung cancer patients who were treated at a tertiary hospital. Patients with stage III and IV NSCLC[4], bearing EGFR mutation, had at least one measurable lesion (>10 mm on CT scan) were included. Patients who had incomplete initial and follow-up datas, had previously received cytotoxic chemotherapy for NSCLC, had complex or TKI-resistant exon 20 T790M mutation were excluded.

This retrospective study was run from January 2016 to May 2019. The total sampling approach was done to obtain the number of participant in this study. Participants were divided into the common and uncommon mutations group. The common mutation group consisted of exon 19 deletion or exon 21 L858R and the uncommon group consisted of either exon 18 G719X, exon 18 delE790, or exon 21 L861Q.

The study procedure included collecting data from medical records of patients who received first-generation EGFR-TKI as first-line therapy. First-generation EGFR-TKIs available for use in Indonesia were Gefitinib 250 mg (Astra Zeneca Ltd, Surabaya, Indonesia) and Erlotinib 150 mg (Astellas Pharma Inc., Jakarta, Indonesia). Gefitinib or Erlotinib was taken orally, once daily. Information taken from medical records were the health-related quality of life (HRQOL), body weight, performance status (PS), and Response Evaluation Criteria in Solid Tumors (RECIST) of Chest CT. HRQOL was measured utilizing the EuroQol EQ-5D® questionnaire in Indonesian version. The questionnaire comprised of 5 simple questions, covering physical symptoms and other functional domains[5]. The EuroQol EQ-5D questionnaire in Indonesian version was declared valid and reliable to measure the HRQOL of lung cancer patients with α=80.84[6]. PS was measured by the World Health Organization (WHO) scale. Chest CT was interpreted with RECIST[7] and the CT scan utilized was Hitachi type RH-6G-E31 series number 12G173J (Hitachi-Aloka Medical, Mitaka, Tokyo, Japan). PFS and overall survival (OS) were also observed.

The results of the study were presented in the form of mean±standard deviation (SD) or median (minimum-maximum) and percentage (%). The statistical analysis used was independent t-test or Mann Whitney test ($p<0.05$). Statistics analysis used IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of Participant

There were more male and smoking patients in the uncommon group (Table 1). Better initial performance status was seen in in the common group. Most of the EGFR mutations in the uncommon group and common group were exon 21 L861Q (52.6%) and exon 19 deletions (64.7%; $p<0.001$), respectively. Most participant received Gefitinib EGFR-TKI therapy (76.9%).

Response Evaluation in the Common and Uncommon Group

Most patient in both groups had a constant score of HRQOL value and constant body weight after receiving EGFR-TKI therapy. Results of the CT Scan demonstrated that RECIST of most patient in the uncommon group

(47.4%) was progressive disease, while partial response was seen in most participant in the common group (42.2%; p=0.007; Table 2).

Progression-Free Survival

PFS could be observed in 11 and 82 participants of the uncommon and common group, respectively. The average PFS of participant common groups was longer in the uncommon group (Table 3).

Overall Survival

OS could be observed in 19 participant in the uncommon group and 82 out of 121 participant in the common group. The average OS of participant common groups was longer in the uncommon group (Table 3).

Table 1. Characteristics of Participants

Variables	Uncommon (n=19)	Common (n=102)	p
Gender (%) Male Female	 15 (77.8) 4 (22.2)	 41 (40.2) 61 (59.8)	0.007*
Smoking status (%) Non-smoker Smoker	 7 (36.8) 12 (63.2)	 62 (60.8) 40 (39.2)	0.092
Initial PS (%) 0-1 ≥2	 11 (57.9) 8 (42.1)	 94 (92.2) 8 (7.8)	0.001
Lung cancer stage (%) IIIA IIIB IV	 1 (5.3) 3 (15.8) 15 (78.9)	 5 (4.9) 16 (15.7) 81 (79.4)	0.951
Types of anatomic pathology (%) Adenocarcinoma Adenosquamous Squamous cell carcinoma	 18 (94.7) 1 (5.3) 0 (0.0)	 100 (98.0) 1 (1.0) 1 (1.0)	0.674
Samples of anatomic pathology (%) Lung parenchym Pleural effusion Cervical lymph nodes	 15 (78.9) 3 (15.8) 1 (5.3)	 81 (79.4) 17 (16.7) 4 (3.9)	0.890
Sampling technique (%) Bronchoscopy FNAB Core biopsy Surgical specimen Pleural cytology	 0 (0.0) 15 (78.9) 1 (5.3) 0 (0.0) 3 (15.8)	 11 (10.8) 72 (70.6) 1 (1.0) 1 (1.0) 17 (16.7)	0.728

Cont... **Table 1. Characteristics of Participants**

EGFR mutation (%) Exon 19 deletion Exon 21 L858R Exon 21 L861Q Exon 18 G719X Exon 18 deletion (delE709_T710insD)	 0 (0.0) 0 (0.0) 10 (52.6) 7 (36.8) 2 (10.5)	 66 (64.7) 36 (35.3) 0 (0.0) 0 (0.0) 0 (0.0)	0.000**
EGFR-TKI (%) Gefitinib Erlotinib	 14 (73.7) 5 (26.3)	 79 (77.5) 23 (22.5)	0.769

Abbreviations: PS=performance status; FNAB=fine-needle aspiration biopsy; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; *significant $p<0.05$; **significant $p<0.001$.

Table 2. Comparison of RECIST EuroQol EQ-5D, Body weight, and PS in the Common and Uncommon Mutation Groups

Varibles	**Uncommon (n=19)**	**Common (n=102)**	**p**
EuroQol EQ-5D (%) Decrease Constant Increase	 5 (26.3) 9 (47.4) 5 (26.3)	 23 (22.5) 57 (55.9) 22 (21.6)	0.956
PS (%) Worsen Constant Improved	 2 (10.5) 14 (73.7) 3 (15.8)	 10 (9.8) 64 (62.7) 28 (27.5)	0.367
Body weight (%) Decrease Constant Increase	 7 (36.8) 8 (42.1) 4 (21.1)	 32 (31.4) 25 (24.5) 45 (44.1)	0.165
RECIST (%) Progressive disease Stable disease Partial response Complete response	 9 (47.4) 8 (42.1) 2 (10.5) 0 (0.0)	 26 (25.5) 32 (31.4) 43 (42.2) 1 (1.0)	0.007*

Abbreviations: PS=performance status; RECIST=response evaluation criteria in solid tumors; *significant $p<0.05$

Table 3. Comparison of Age, PFS, and OS in the Common and Uncommon Groups

Variables	Uncommon	Common	p
Age	56.0 (39.0-73.0)	55.5 (22.0-85.0)	0.392
PFS	4.0 (2.0-6.0)	7.0 (2.0-21.0)	0.001*
OS	4.00 ± 1.71	10.00 ± 6.94	0.000*

Abbreviations: PFS=progression-free survival; OS=overall survival; *significant p<0.05

Table 4. Comparison of PFS and OS in each EGFR Mutation

Variables	n	Median (range)	p
PFS			
Exon 21 L861Q	5	4.0 (3.0-5.0)	
Exon 18 G719X	4	4.0 (3.0-6.0)	
Exon 18 delE709	2	3.0 (2.0-4.0)	0.029*
Exon 19 deletion	53	6.0 (2.0-21.0)	
Exon 21 L858R	29	8.0 (2.0-16.0)	
OS			
Exon 21 L861Q	10	4.00 ± 1.76	
Exon 18 G719X	7	4.00 ± 1.98	
Exon 18 delE709	2	4.50 ± 0.70	0.000**
Exon 19 deletion	47	11.00 ± 7.73	
Exon 21 L858R	26	9.50 ± 5.13	

Abbreviations: PFS=progression-free survival; OS=overall survival; *significant p<0.05; **significant p<0.001.

Discussions

Previous studies have revealed lesser responses in uncommon mutations compared to common mutations[3]. In this study, most participants in the common group experienced partial response (PR), while most participant in the uncommon group experienced progressive disease (PD). The discovery that affinity of the first generation TKI to the uncommon EGFR mutation protein was lower than the affinity to common EGFR mutation of protein might play a role in this response. Up to 6-14 times higher concentrations of gefitinib are needed to inhibit the growth of cells expressing mutations G719X and L861Q, respectively when compared to cells expressing L858R[8]. Another comparable study found that a higher concentration of first-generation TKI was needed to cause a 50% inhibition in uncommon mutations compared to common mutations[9].

In the common group, a superior response rate was seen in exon 19 deletion compared to exon 21 L858R. This finding is consistent with the results of a meta-analysis of earlier studies[10]. Evidence that exon 19 deletion has higher autophosphorylation rates and higher sensitivity to first-generation TKI compared to exon 21 L858R mutations[11] might clarify the distinction in response rate between the two common mutations. RECIST of other uncommon mutation subtypes are dominated by progressive disease (PD), akin to the findings of previous studies where the response rate of

the uncommon mutation subtype is remarkably low[10,12]. However, on the other hand, a subtype of uncommon mutation that showed a better response rate than other mutation subtypes in this study were L861Q.

Participants in the uncommon group had a shorter PFS and OS median compared to the common group. PS and smoking status are independent predictors of OS in lung cancer. In the uncommon group, the proportion of patients with good PS was less and the extent of patients with smoking history was greater than the uncommon group. This characteristics explain the shorter survival rate seen in patients with uncommon mutations[13].

HRQOL, a patient-reported outcome (PRO), was also a significant endpoint in numerous NSCLC-related studies[5,14] besides response rate and survival. A large portion of the patients in both groups showed the constant EQ-5D score, indicating no HRQOL difference was found between the two groups. These conditions may be influenced by several factors, for example, employment, education, marital status, and other comorbid diseases[15,16].

In contrast to cytotoxic chemotherapy, EGFR-TKI can be given to patients with any PS with fairly good therapeutic outcomes[17]. In this study, the extent of patients with initial poor PS was more noteworthy in the uncommon group than the common group. However, the evaluation of the PS of the two groups did not show significant improvement after TKI therapy. The presence of confounding variables, for example, other comorbid diseases and presence of TKI adverse effects, may likewise influence the subsequent PS. Weight loss is said to be a prognostic factor of diminished survival, decreased quality of life and more symptoms in lung cancer patients[18,19].

The limitations of this study were the small number of patients in the uncommon mutation group and the retrospective character of the study. Some baseline characteristics, such as current smoking status, duration of smoking, body mass index, presence of comorbid diseases and adverse effects of TKI, could not be fully obtained from the medical records. Further research for uncommon mutations is expected to analyze good therapeutic modalities for each subtype.

Conclusions

Advanced NSCLC patients with common and uncommon EGFR mutations demonstrated no significant difference in HRQOL value after receiving first-generation TKI, as observed from the EQ-5D score, PS and body weight in the two groups. However, the response rate and survival of common mutations were significantly better compared to uncommon EGFR mutations on first-generation TKI therapy.

Ethical Approval: Ethical approval for the research was attained at the ethics committee of hospital (1007/KEPK/III/2019).

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: None.

References

1. Han B., Tjulandin S., Hagiwara K., Normanno N., Wulandari L., Laktionov K., Hudoyo A., He Y., Zhang Y-P., Wang M-Z., Liu CY., Ratcliffe M., McCormack R., Reck M. EGFR mutation prevalence in Asia-Pacific and Russian patients with advanced NSCLC of adenocarcinoma and non-adenocarcinoma histology: The IGNITE study. Lung Cancer. 2017; 113:37-44.
2. O'Kane GM., Bradbury PA., Feld R., Leighl NB., Liu G., Pisters K-M., Kamel-Reid S., Tsao MS., Shepherd FA. Uncommon EGFR mutations in advanced non-small cell lung cancer. Lung Cancer. 2017; 109:137-144.
3. Chen Z-Y., Zhong W-Z., Zhang X-C., Su J., Yang X-N., Chen Z-H., Yang J-J., Zhou Q., Yan H-H., An S-J., Chen H-J., Jiang B-Y., Mok TS., Wu Y-L. EGFR mutation heterogeneity and the mixed response to EGFR tyrosine kinase inhibitors of lung adenocarcinomas. Oncologist. 2012; 17(7):978-985.
4. Wulandari L., Soegiarto G., Febriani A., Fatmawati F., Sahrun. Comparison of Detection of Epidermal Growth Factor Receptor (EFGR) Gene Mutation in Peripheral Blood Plasma (Liquid Biopsy) with Cytological Specimens in Lung Adenocarcinoma Patients. Indian Journal of Surgical Oncology. 2020;
5. Trippoli S., Vaiani M., Lucioni C., Messori A., Pharmacoeconomics Q-o-lSGotMPi. Quality of

Life and Utility in Patients with Non-Small Cell Lung Cancer. PharmacoEconomics. 2001; 19 (8):855-863.

6. Setiawan D., Dusafitri A., Galistiani GF., van Asselt ADI., Postma MJ. Health-Related Quality of Life of Patients with HPV-Related Cancers in Indonesia. Value in Health Regional Issues. 2018; 15:63-69.
7. Schwartz LH., Litière S., de Vries E., Ford R., Gwyther S., Mandrekar S., Shankar L., Bogaerts J., Chen A., Dancey J., Hayes W., Hodi FS., Hoekstra OS., Huang EP., Lin N., Liu Y., Therasse P., Wolchok JD., Seymour L. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer. 2016; 62:132-137.
8. Watanabe S., Minegishi Y., Yoshizawa H., Maemondo M., Inoue A., Sugawara S., Isobe H., Harada M., Ishii Y., Gemma A., Hagiwara K., Kobayashi K. Effectiveness of gefitinib against non-small-cell lung cancer with the uncommon EGFR mutations G719X and L861Q. J Thorac Oncol. 2014; 9(2):189-194.
9. Kancha RK., Peschel C., Duyster J. The Epidermal Growth Factor Receptor-L861Q Mutation Increases Kinase Activity without Leading to Enhanced Sensitivity Toward Epidermal Growth Factor Receptor Kinase Inhibitors. Journal of Thoracic Oncology. 2011; 6(2):387-392.
10. Kobayashi Y., Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Sci. 2016; 107(9):1179-1186.
11. Mitsudomi T., Yatabe Y, Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. The FEBS Journal. 2010; 277(2):301-308.
12. Kuiper JL., Hashemi SMS., Thunnissen E., Snijders PJF., Grünberg K., Bloemena E., Sie D., Postmus PE., Heideman DAM., Smit EF. Non-classic EGFR mutations in a cohort of Dutch EGFR-mutated NSCLC patients and outcomes following EGFR-TKI treatment. Br J Cancer. 2016; 115(12):1504-1512.
13. Kawaguchi T., Takada M., Kubo A., Matsumura A., Fukai S., Tamura A., Saito R., Maruyama Y., Kawahara M., Ignatius Ou S-H. Performance Status and Smoking Status Are Independent Favorable Prognostic Factors for Survival in Non-small Cell Lung Cancer: A Comprehensive Analysis of 26,957 Patients with NSCLC. Journal of Thoracic Oncology. 2010; 5(5):620-630.
14. Claassens L., van Meerbeeck J., Coens C., Quinten C., Ghislain I., Sloan EK., Wang XS., Velikova G., Bottomley A. Health-related quality of life in non-small-cell lung cancer: an update of a systematic review on methodologic issues in randomized controlled trials. J Clin Oncol. 2011; 29(15):2104-2120.
15. Yang S-C., Lin C-C., Lai W-W., Chang S-M., Hwang J-S., Su W-C., Wang J-D. Dynamic changes in quality of life after three first-line therapies for EGFR mutation-positive advanced non-small-cell lung cancer. Ther Adv Med Oncol. 2018; 10:1758834018755072-1758834018755072.
16. Tan Z., Liang Y., Liu S., Cao W., Tu H., Guo L., Xu Y. (2013) Health-Related Quality of Life as Measured with EQ-5D among Populations with and without Specific Chronic Conditions: A Population-Based Survey in Shaanxi Province, China. PLOS ONE 2013; 8(7):e65958.
17. Corre R., Gervais R., Guisier F., Tassy L., Vinas F., Lamy R., Fraboulet G., Greillier L., Doubre H., Descourt R., Chouaid C., Auliac J-B. Octogenarians with EGFR-mutated non-small cell lung cancer treated by tyrosine-kinase inhibitor: a multicentric real-world study assessing tolerance and efficacy (OCTOMUT study). Oncotarget. 2018; 9(9):8253-8262.
18. Yang R., Cheung MC., Pedroso FE., Byrne MM., Koniaris LG., Zimmers TA. Obesity and weight loss at presentation of lung cancer are associated with opposite effects on survival. J Surg Res. 2011; 170(1):e75-e83.
19. Rodriguez AM., Braverman J., Aggarwal D., Friend J., Duus E. The experience of weight loss and its associated burden in patients with non-small cell lung cancer: results of an online survey. JCSM Clinical Reports. 2017; 2(2):1-12.