Original Article

Characteristics of EGFR Gene Mutation in Lung Adenocarcinoma at Adam Malik General Hospital

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Abstract

Background: Epidermal growth factor (EGFR) is a transmembrane receptor that plays an important role in the development of cancer phenotypes. Some patients with lung cancer have genetic mutations. Several studies have found a close correlation of EGFR gene mutation with 15-20% of lung adenocarcinoma cases. This study aimed to determine the EGFR profile in adenocarcinoma lung cancer patients at Haji Adam Malik General Hospital.

Methods: This was a prospective cohort study conducted at Haji Adam Malik General Hospital, Medan. This study used patients data for 3 years, starting from January 1, 2014 to D[1]ecember 31, 2016. The sample size in this study was 34 patients. The data were then analyzed using SPSS.

Results: All patients were adenocarcinoma lung cancer patients with positive EGFR mutation. There were 9 subjects with EGFR mutation in exon 19; 11 subjects with exon 21 L858R mutation; and 3 subjects with exon 21 L861Q mutation. Meanwhile, there were 3 subjects with uncommon EGFR mutations, namely exon 18 mutation. Majority of subjects with exon 19 mutation were male, aged >60 years, smokers with mixed types of cigarettes and severe brinkmann index. In subjects with exon 21 L858R mutation, most of the patients were male, aged 50-60 years, smokers with mixed cigarette types and severe brinkmann index. The same characteristics were also observed in subjects with exon 18 mutation. However, for exon 21 L861Q mutation, the majority of subjects were female with varying ages, and were not smokers.

Conclusion: Most of the study subjects profiles were male, aged over 60 years, smokers, with mixed types of cigarettes, and with severe Brinkman Index. The EGFR mutations most commonly occured in exon 21, followed by exon 19 (ins/del exon 19), exon 18, and a combination of 2 exons.

Keywords: Adenocarcinoma, EGFR, Lung cancer

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INTRODUCTION

Lung cancer is the leading cause of malignancy globally, accounting for up to 11.4% of all cancer diagnoses in both sex. Lung cancer is also the second most common cancer worldwide with total cases around 2.21 million cases and highest mortality among all type of cancers (1.8 million deaths per year). The incidence and mortality are higher in male compare with female with ratio 2:1 and varies across region.[1] According to GLOCOBAN 2020, lung cancer is the third rank of highest incidence of lung cancer with the highest mortality in both sex. Every year, 34.783 new cases of lung cancer with 30.843 deaths detected in Indonesian population.[2] This is why lung cancer must be considered as in Indonesia's health issue that need special attention and research concentration in the treatment and outcome aspect.

Lung cancer is generally classified into two histologic types: non-small cell carcinoma (NSCLC) and small cell carcinoma (SCLC). NSCLC is the most common type of lung cancer, accounting for about 85% of all lung cancer cases, and consists of several subtypes, including squamous carcinoma (epidermoid carcinoma), adenocarcinoma, and large cell carcinoma.[3,4] Further, these types of lung cancer has the their own molecular characteristics of which adenocarcinoma is known as the histology type of lung cancer that has the most oncogenes and tumor supressor genes related lung carcinogenesis.[5–7]

Some people with lung cancer have genetic mutations. Several studies have found a close correlation between mutations in the Epidermal Growth Factor (EGFR) gene with 15–20% of lung adenocarcinoma cases. In East Asia, the percentage of EGFR gene mutations in lung adenocarcinoma cases was higher at 38%[8] while Asia-Pasific showed the highest prevalence of EGFR mutations.[9] Meanwhile, EGFR gene mutations were expressed in 89% of lung adenocarcinoma cases in India.[10] EGFR is a transmembrane receptor of the ErbB family, consisting of four closely related members: HER1/ErbB1, HER2/neu/erbB2, HER3/ErbB3, and HER4/ErbB4.[11] EGFR activation can trigger signal transduction and subsequent intracellular cancer cells proliferation, inhibition of apoptosis, neoangiogenesis, and distant metastasis, all of which are important for the development of cancer phenotypes.[12]

Based on the description above, the researcher conducted a study to determine the EGFR profile in patients with adenocarcinoma lung cancer at Haji Adam Malik General Hospital.

METHODS

This was a prospective cohort study conducted at the Department of Pulmonology and Respiratory Medicine at Haji Adam Malik General Hospital, Medan. This study used patient data for 3 years, starting from January 1, 2014, to December 31, 2016.

The sample size in this study was 34 patients. The inclusion criteria in this study were: all patients diagnosed with mutation-positive adenocarcinoma, were examined for EGFR mutations using PCR method with specific alleles targeting specific EGFR mutations at exons 19 and 21 in subjects who had an established cytological or histopathological diagnosis, and had consumed tyrosine kinase inhibitor (TKI) drugs for at least 3 months. The exclusion criteria were incomplete patient data.

The molecular examination process is broadly divided into two parts, namely the preparation of manual examination materials to obtain deoxyribonucleic acid (DNA) from cytological slide scrapings or deparaffinization of paraffin blocks through FFPE and amplification of detection from DNA using the principle of allele-specific detection with Cobas z 480 (Roche, Switzerland). The minimum tumor percentage is 5% of the total examination material. The kit used for material preparation was the Cobas® DNA Sample Preparation Kit (P/N: 05985536190). The kit used for amplification and mutation detection was the Cobas® EGFR Mutation Test Kit (P/N: 06471463190).

Data on medical record (MR) numbers and patient names were obtained using the International Classification of Diseases and Related Health Problems 10 (ICD – 10). The data were then copied into data collection sheet. The data collected were demographic data, which included: MR number, name, gender, age, smoker, type of cigarette, Brinkman Index (BI), and exon data. The data were then analyzed using SPSS.

RESULTS

The characteristics of adenocarcinoma lung cancer patients can be seen in Table 1. Adenocarcinoma lung cancer patients with favorable gene mutations were mostly male with as many as 24 patients (70.6%) while the female were 10 patients (30.6%). Subjects aged 60 years were 14 patients (41.2%), followed by those aged 51–60 years with as many as 13 patients (38.2%), and the least was aged 41–50 years with 7 patients (20.6%). There were no patients under 41 years of age.

Based on smoking status, the number of smokers was higher than the non-smokers, namely 24 patients (70.6%) vs 10 patients (30.4%).

Table 1. Characteristics of the subjects

Profile	N	Percentage (%)
Gender		
Male	24	70.6
Female	10	30.4
Age		
<30 years	-	-
31–40 years	-	-
41–50 years	7	20.6
51–60 years	13	38.2
>60 years	14	41.2
Smoking Status		
Smokers	24	70.6
Non-smokers	10	30.4
Type of cigarettes		
Filtered	8	33.3
Non-filtered	-	-
Mixed	16	66.7
Brinkman Index (BI)		
Mild	-	-
Moderate	-	-
Severe	24	100

Most of the smokers smoked mixed type of cigarettes (66.7%) while the rest smoked only filtered cigarettes (33.3%). None of the subjects consumed non-filtered cigarettes. All patients had severe BI.

Table 2. Profile of EGFR mutations by exons

EGFR	N	Percentage (%)
Exon 18		
G719A	2	5.9
G719C	-	-
G719D	-	-
G719S	2	5.9
G719V	-	-
Exon 19		
Ins/del exon 19	13	38.2
Exon 21		
L858R	11	32.4
L816Q	5	14.7
2 Exons		
Ins/del exon 19 and exon 21 L858R	1	2.9
Total	34	100

The profile of EGFR mutations based on exons in Table 2 shows that the percentage of Exon 18 with G719A and G719S types was 5.9%. The percentage of Exon 19 with type insertion/deletion 19 was 38.2%. Exon 21 with L858R type was 32.4%, while the L86Q type was 14.7%. Meanwhile, the percentage of 2 Exons with ins/del exon 19 and exon 21 L858R types was 2.9%.

Based on Table 3, the percentage of pattern combinations of Exon 18 or Exon 19 or Exon 21 were 11.8%, 38.2%, and 47.1%, respectively. Meanwhile, the percentage of the combination of 2 Exons (Exon 18 and Exon 21) was 2.9%.

Table 3. EGFR combination patterns

Combination pattern	N	Percentage (%)
Exon 18 or exon 19, or exon 21		
Exon 18	4	11.8
Exon 19	13	38.2
Exon 21	16	47.1
2 exons combination		
Exon 18 and exon 21	1	2.9
3 exons combination	-	-
Total	34	100

The characteristics of patients with EGFR mutations based on the type of exon that experienced mutations were not much different. There were 9 subjects with exon 19 EGFR mutations, 11 subjects with exon 21 L58R mutation, and 3 subjects with exon 21 L861Q mutation. Nevertheless, there were 3 subjects with uncommon EGFR mutations, namely exon 18 mutations.

Table 4. Clinical characteristics by type of exon

Characteristic	Exon 19	Exon 18	Exon 21 L858R	Exon L861Q
Gender				
Female	3	0	2	2
Male	6	3	9	1
Age (years)				
40–50	3	0	2	1
51–60	2	0	5	1
>60	4	3	4	1
Smoking Status				
Smokers	6	0	2	1
Non-Smokers	3	3	9	2
Types of cigarettes				
Filter	2	0	4	1
Non-filter	-	0	0	0
Mixed	4	3	5	0
Brinkmann Index				
Mild	-	0	0	0
Moderate	-	0	0	0
Severe	6	3	9	1

The majority of subjects with exon 19 mutations were male, aged >60 years, smokers with mixed types of cigarettes and severe BI.

In subjects with mutations in exon 21 L858 R, most patients were male, aged 50-60 years, smokers with mixed cigarette types and severe BI. The same characteristics were also found in subjects with exon 18 mutations. However, for exon 21 L861Q mutations, most subjects were females of various ages and were non-smokers. More detailed information regarding the characteristics of subjects based on the type of exon that undergoes mutations can be seen in Table 4.

DISCUSSION

The development of lung cancer studies towards biomolecular aspects makes targeted therapy a promising therapeutic option. EGFR is an oncogene mutation that has been discussed in numerous clinical studies and meta-analyses. Overall, the presence of EGFR mutations suggests a good prognosis in patients with lung cancer. Various meta-analyses have shown that EGFR mutations were more common in the type of adenocarcinoma, the elderly, and non-smokers.[13] This study obtained that most patients with lung adenocarcinoma who received targeted therapy were men (70.6%) compared to women. A similar result was pointed out in a study conducted in Indonesia (61% of male subjects with EGFR mutations).[14]

Data at Haji Adam Malik Hospital Medan from January 2010 to May 2012 revealed that around 143 (85.62%) lung cancer patients were male, while 24 patients (14.37%) were female. This study observed that female had the most EGFR mutations in exon 19 and exon 21 of 35.7% and 38.1%, respectively.[15] It was thought that this was due to differences in the epidemiological distribution of lung cancer. According to Tseng, et al. in 2017, lung adenocarcinoma patients with EGFR mutations were predominantly female, non-smokers, and already terminally ill.[16] However, Jang, et al. stated that there were no significant differences in clinical characteristics of age, sex, smoking status, and body surface area in lung cancer patients with exon 19 and exon 21 L858R mutations.[13] To date, there have been no studies which describe the pathobiology of a gender-specific predisposition to the presence of EGFR mutations in lung cancer, so the available data were only epidemiological from various countries.[8,16,17]

Based on smoking habits in this study, it was asserted that 70.6% of the patients were active smokers with heavy BI. A study on 199 patients in China expressed an opposite result that patients with EGFR mutations were more commonly non-smokers compared to those who smoked.[17] EGFR mutations appeared to be more common in subjects who were women, with adenocarcinoma histology, Japanese, and have never smoked.[18]

Similarly, meta-analyses and other global epidemiological studies explained that this EGFR mutation was more dominant in the non-smoking population. Furthermore, current smokers or ex-smokers with a high number of cigarettes/year in patients with EGFR mutations suggested a poor prognosis.[17] The differences in clinical characteristics of EGFR mutations for the North Sumatra population are still debatable. Further studies are expected to explain it in more detail. Common oncogene mutations in lung cancer and their association with smoking status were significant risk factors for lung cancer.

EGFR mutations are currently divided into 2 types, namely common mutations such as mutations in exon 19 as well as exon 21 L858R; and uncommon mutations such as mutations in exon 18 and exon 20.[17] This study only described the prevalence of common mutations such as exon 19 and exon 21 due to limited facilities. This study discovered that exon 19 was the exon that experienced the most mutation among the other 2 exons, namely 38.2% (ins/deletion 19), while exon 21 experienced the second most mutation (14.7%). Another study conducted in 2018

also indicated that exon 19 deletion was the most common mutation, followed by mutations of exon 21.[19]

Another study with a wider population also explained that 51% of EGFR mutations were exon 19, followed by exon 21 of 28%, exon 20 of 6%, and exon 18 of 5%.[8] Globally, differences in the clinical characteristics of lung cancer patients with EGFR mutations were also differentiated based on the type of mutation, in which patients with an exon 19 dominant mutation were more frequently associated with the non-smoker population and higher levels of life expectancy when compared to exon 21 L858R and exon 20.[17,18,20]

LIMITATIONS

The limitation of the research in this study is this study only described the prevalence of common mutations such as exon 19 and exon 21 due to limited facilities.

CONCLUSION

Most of study subjects were male, aged over 60 years, smokers with mixed types of cigarettes, and with heavy BI. The most common EGFR mutation were exon 21 mutation.

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CONFLICT OF INTEREST

None.

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