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Adverse Event Profiles of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Adenocarcinoma Lung Patients in North Sumatera Population

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Abstract

BACKGROUND: In early 2000, a new targeted therapy was introduced and appeared to be a medical revolution due to the great emergence of procedural treatments in lung cancers. This new target therapy has been developed recently, which is also accompanied by the development of molecular markers as medical guidance.

AIM: This study aims to assess the side effect of the usage of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) on lung adenocarcinoma patients in North Sumatera.

METHODS: This study was a descriptive analysis study with consecutive sampling. Data was collected from the medical records of 50 pulmonary adenocarcinoma patients who have been treated by EGFR-TKI erlotinib and gefitinib. The statistical analysis was performed through SPSS software.

RESULTS: From this study, the majority of subjects were in the age range of 50–60 years old (24%), had no smoking history (52%), and were in Stage IVA (62%) at the time of diagnosis. Allele-specific polymerase chain reaction was performed and showed that exon 19 was found as the commonest mutations (62%). After using the first generation of EGFR-TKI including erlotinib and gefitinib, the majority of subjects experienced Grade I toxicities (46%) involved skin (acneiform).

CONCLUSION: The most common adverse event that is occurred in the cases was in skin disorders (72% of cases), which is particularly indicated by acne rash (46% of cases). The degree of toxicity during the medications was populously on degree 1 (46% of cases).

Introduction

Recent advances in medications related to pulmonary oncology (adjuvant chemotherapy, targeting therapies, and individual therapies) have been achieved in the recent 10 years [1]. As one of the highest mortalities among all solid cancer, there was a surge of the medical approach, including pharmacology and intervention pulmonology in the comprehensive management of lung cancer [2]. The selection of therapy must be performed, considering the rapid growth of the disease which worsens the cancer growth on the assumption of no medical treatments. Furthermore, several cases of cancer require immediate treatments although the diagnosis has not been determined yet [3].

Local modality therapies are surgery and radiotherapy treatments. For systemic therapies, conventional chemotherapies and any other targeted therapies such as intervention that disturbs the specific tumorous structures at the molecular level can be utilized. Lung cancer treatment is often multimodal, whereas radiotherapy and chemotherapy may have been administered altogether as radio-chemotherapy. Chemotherapy, radiotherapy, and radio-chemotherapy may initially be performed before the surgery (neoadjuvant therapies) which is also followed by adjuvant therapies [4].

New targeted therapies have been introduced since early 2000, which are more popularly known as target therapies. The discovery of these medical treatments is a revolutionary treatment as the result of a significant impact in the medical practice of lung cancer treatments. This new target therapy in recent years has displayed rapid impact with the development of knowledge in molecular markers as the guidance for medication [5].

The epidermal growth factor receptor (EGFR) gene mutation, which is one of the main accelerators

of cell growth, is the first targeted therapy and along with tyrosine kinase inhibitor shifted the era of systemic therapy to oncogenic driver mutations based therapy [6]. Erlotinib and gefitinib were the first line of EGFR tyrosine kinase inhibitor (EGFR-TKI) introduced in Indonesia and give significantly higher life expectations and with the decelerations of cancer cells growth, minimal side effect, and better quality of life compare with systemic therapy [7]. However, a side effect of the cytotoxic drugs still becomes a problem and is often associated with low compliance. Side effects including skin rash, diarrhea, alopecia, hematology toxicities, liver toxicities, and renal toxicities can be a serious impact on non-small-cell lung cancer (NSCLC) and shift the treatment of the patients to systemic therapy [8]. Even though this is not the first study assessing the side effect of the first line of EGFR-TKI treatment in lung adenocarcinoma, this is the first study published the official data of the side effect of the first line of EGFR-TKI in North Sumatera populations. Hence, this study aimed to assess the side effect of the use of gefitinib and erlotinib as the first line of EGFR-TKI in North Sumatera populations.

Methods

This study was a descriptive study with secondary data from the medical record in few centers of lung cancer in North Sumatera including Haji Adam Malik General Hospital, Santa Elizabeth Hospital, and Dr. Pirngadi Hospital. This study was approved by the Ethical Committee of Faculty of Medicine, Universitas Sumatera Utara, and conducted in 2019.

The sampling method of this study was total sampling that recruited all the chosen sample who met the inclusion criteria and did not have any exclusion criteria with the period of sampling time was from July 2017 to July 2019. The inclusion criteria of this study were lung adenocarcinoma patients confirmed by cytology and histopathology examinations, age >20 years old, have EGFR mutations confirmed by allele-specific polymerase chain reaction (PCR) for exon 19, 20, and 21 L858R, and L861Q consumed the first line of EGFR-TKI such as gefitinib and erlotinib, and have undergone RECIST procedure to evaluate the response of treatment and degree of toxicities. The exclusion criteria of this study were incomplete medical records including patient identity, smoking status data, cancer staging according to IASLC version 7, cytology or histopathology reports, and WHO checklist for the adverse event in using EGFR-TKI medications.

All data were collected and entered into SPSS software ver. 24.0. Since this study was an observation descriptive study, there were no analytical examinations performed.

Results

A total of 50 subjects enrolled in this study with the majority of subjects were in the age range of 50–60 years old (24%), Bataknese ethnics, had no smoking history (52%), and were in Stage IVA (62%) at the time of diagnosis. Further demographic characteristics are described in Table 1.

Table 1: Demographical characteristics of research subjects

Variable	n	%
Age (years)		
<40	6	12.0
40–60	27	54.0
>60	17	34.0
Gender		
Male	25	50.0
Female	25	50.0
Ethnics		
Bataknese	28	56.0
Javanese	21	42.0
Acehnese	1	2.0
Smoking status		
Smoker	24	48.0
Never smoker	26	52.0
Stage		
IIIa	4	8.0
IIIb	7	14.0
IIIc	1	2.0
Iva	32	64.0
IVb	6	12.0
Mutation		
Exon 19	31	62.0
Exon 21	19	38.0
EFGR-TKI		
Gefitinib	43	86.0
Erlotinib	7	14.0
Toxicity grading		
Grade 0	10	20.0
Grade I	23	46.0
Grade II	12	24.0
Grade III	4	8.0
Grade IV	1	2.0

EFGR-TKI: Epidermal growth factor receptor tyrosine kinase inhibitor.

Allele-specific PCR was performed and showed that exon 19 was found as the most common mutations (62%). After using the first generation of EGFR-TKI including erlotinib and gefitinib, the majority of subjects experienced Grade I toxicities (46%) involved skin (acneiform), as depicted in Table 2.

Table 2: Adverse events characteristics of the subjects with TKI-EGFR treatments

Adverse events	n = 50 (%)
Acne form	23 (46.0)
Xerosis	12 (24.0)
Diare	4 (8.0)
Scalp lesion	1 (2.0)

TKI-EGFR: Tyrosine kinase inhibitor epidermal growth factor receptor.

Discussion

Based on histopathological results, lungs tumor cells are divided into small-cell lung cancer and NSCLC in which the NSCLC is divided into subtypes, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and unclassified lung carcinoma [9]. Among these subtypes, the highest prevalence has been reported to be adenocarcinoma types [10].

Smoking is the main risk factor of lung cancer and gives the difference in molecular profiling compare with never smoker populations [11]. Yet, the expression of EGFR mutations is more common in never smoker population [12]. This is in line with this study that showed that 52% of subjects of this study were never smokers. This is in contrast with another study held in Indonesia that reported that 78% of the adenocarcinoma patients had a history of active smoker [13]. Although there was a shift of histopathological type of tobacco-induced lung cancer from squamous cell carcinoma to adenocarcinoma, EGFR mutations were still more common in never smokers. Meanwhile, in patients who have a smoking history, KRAS mutation was more common than EGFR mutations [14].

Our findings showed that the highest mutagenic status was found in exon 19 accounted for 31 people (62%), and this result is in accordance to Mia *et al*., that early age of EGFR mutagenic accounted for 36.9% [15]. Several studies about lung adenocarcinoma have shown EGFR mutation as it has been reported by Syahruddin *et al*., with 44% of mutation in which from this 44%, there were common EGFR mutation (ins/dels exon 19 and L858R) and uncommon EGFR mutations (G179X, T790M, and L861Q) which were around 57.1% and 29% in Indonesia, respectively [13]. Our data have shown that the highest population have been in Stage IV level accounted for 32 people (62%), and this result has the similar results conducted by Mia *et al*., with 98.5% of patients with advanced stages [15].

Toxicity reaction experienced by the patients with adenocarcinoma was observed on Grade I (acne form) with 23 people (46%). This finding is following to a study by Melosky *et al*., which have suggested that the highest percentage of toxicity was in acne form with 89.1% [16]. In a study conducted by Yoshida *et al*., the group with erlonib had higher AE including the rash form compared to that in the gefitinib group [17]. Meanwhile, Yang *et al*. have found that gefitinib demonstrated similar efficacy; however, the safety profile of gefitinib appears to be safer than that in erlotinib. Specifically, gefitinib is related to liver dysfunction with a 3/4 toxicity level; subsequently, a lower dosage is commonly prescribed. Therefore, the prescription of gefitinib appears to be drug discontinuation, total side effects, fatal and non-fatal, and certain specific side effects. More side effects include skin disorder, diarrhea, oral mucositis, asthenic condition, anorexia, nausea, vomiting, and gastrointestinal bleeding, which all of these side effects are observed in erlotinib. Abnormalities in liver function tests and pneumonitis have no differences in both groups. According to multivariate analysis, failure and early failure as well as drugs discontinuation due to the side effects independently are related to the usage of erlotinib [18]. This is in line with our study that showed that toxicities grading in 150 mg erlotinib are related to higher toxicities compared to those in 250 mg of gefitinib in daily usage.

Conclusion

In this study, the adverse event due to the usage of the first generation of EGFR-TKI is dominantly observed in skin disorders which are skin rash for 72% of cases. Toxicities degree of the medicines is commonly found in level 1-degree accounted for 46%.

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