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Profile of Dermatologic Side Effects of Tyrosine Kinase Inhibitor (EGFR-TKIs) in Lung Cancer Patients

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ABSTRACT

Background: Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKIs) drugs are commonly used target therapies in patients with advanced-stage non-small cell carcinoma lung cancer (NSCLC).

Objectives: This study aims to provide an overview of dermatologic side effects and quality of life index of NSCLC patients who received EGFR-TKIs targeted therapy at Dharmais Cancer Hospital.

Methods: This study used a cross-sectional design. Inclusion criteria were patients who received EGFR-TKIs targeted therapy, namely gefitinib, erlotinib, and afatinib, in September - October 2023, who were willing to be research subjects, and patients who were not in a medical emergency. In total, 52 patients filled out the dermatology life quality index (DLQI) questionnaire through interviews and medical records. Data evaluation was performed descriptively in the form of percentages.

Results: The most common occurrence of dermatologic side effects was skin hypersensitivity reactions with mild severity (grade 1) by 59.6%, moderate severity (grade 2) by 19.2%, and severe severity (grade 3) by 1.9%, and no drug dermatologic side effects by 19.2%. In comparison, the most DLQI was in the category of not affecting patient life. In general, side effects with moderate (grade 2) and severe (grade 3). The severity will decrease to mild severity (grade 1) when already getting topical corticosteroid drugs or combinations with oral antibiotics and antihistamine drugs.

Conclusion: The most severe side effect was grade 1, which slightly affected the patient's quality of life. Education and monitoring of side effects and management of symptoms are necessary to reduce the severity and improve patients' quality of life.

Keywords: Dermatologic side effects; DLQI; EGFR-TKIs; Non-small cell lung cancer (NSCLC)

INTRODUCTION

Lung cancer is the leading cause of malignancy in the world, accounting for up to 13 percent of all cancer diagnoses. In addition, lung cancer also causes one-third of all cancer deaths in men.[1] In the United States, there were an estimated 213,380 new cases and 160,390 deaths from lung cancer in 2007. Based on the WHO cancer profile report, lung cancer is the highest contributor to the incidence of cancer in men in Indonesia, followed by colorectal, prostate, liver, and nasopharyngeal cancer, and is the fifth most significant contributor to cases in women after breast, cervical-uterine, colorectal, and ovarian cancer. Cancer registry data from Dharmais Hospital in 2003-2007 showed that trachea, bronchus, and lung cancer was the second most common malignancy in men (13.4%) after nasopharynx (13.63%). They were the cause of most cancer deaths in men (28.94%).[1] World Health

Organization (WHO) epidemiological studies show that nearly 85% of lung cancers are non-small cell carcinoma lung cancer.[1]

About 40% of lung cancer cases in Asia have epidermal growth factor receptor (EGFR) mutations.[2] Tyrosine kinase inhibitors (TKIs) are one of the commonly used targeted therapies for NSCLC with Epidermal Growth Factor Receptor (EGFR) mutations. In recent decades, the treatment of lung cancer with epidermal growth factor receptor (EGFR) mutations has been revolutionized, starting from the first generation of erlotinib, gefitinib, and icotinib, the second generation of dacomitinib and afatinib, and the third generation of osimertinib. Gefitinib, erlotinib, and afatinib are the first- and second-generation EGFR-TKIs most commonly used for the treatment of NSCLC, and they are in the national formulary.[3] These targeted therapies are aimed at molecular mechanisms that contribute to cancer development and progression. Although target therapy is significantly better than chemotherapy, it often causes side effects.[4,5] Previous studies have consistently shown that Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) are well tolerated but show some adverse events, including skin, gastrointestinal tract, liver, and lung.[2]

The most commonly observed side effect of treatment with targeted therapy is skin toxicity.[6] A severe and prolonged degree of skin pain can affect the patient's quality of life, including the patient's physical, emotional, and psychological condition and well-being.[6,7] All dermatologic effects due to treatment with EGFR-TKIs are reversible and asymptomatic. If treated promptly, the side effects are lower and can usually help improve quality of life.[8] The previous study reported in August 2018-December 2019 showed that out of a total of 146 NSCLC patients who received EGFR-TKI therapy in the first 3 months after diagnosis, about 93.2% of patients had skin toxicity. About 70% of patients had skin toxicity in the form of xerosis and pruritus. About 50% had toxicity in the form of papulopastular eruptions and paronycia.[9] These skin toxicities have a significant impact on the quality of life of advanced-stage NSCLC patients receiving EGFR-TKI therapy.[7,10] The quality of life of NSCLC patients who experienced dermatologic side effects was measured using the Dermatology Life Quality Index (DLQI) questionnaire in accordance with the Clinical Practice Guidelines for Dermatologists in Indonesia.[11] The Dermatology Life Quality Index (DLQI) questionnaire consists of 10 questions covering physical symptoms and feelings, daily activities, recreation, and work/ school.[12] The University of Indonesia has validated the Indonesian language of the DLQI, with validity and reliability test results considered good, so the questionnaire is a quality of life measure for patients experiencing skin toxicity.[13]

Therapy to treat dermatologic adverse events depends on the severity of the adverse event. The severity of drug side effects and their definitions can be seen based on the CTCAE (Common Terminology Criteria for Adverse Event) Version 5.0 criteria.[14,15] Grade 1 dermatologic adverse events (macular or papular eruption or erythema) without symptoms will be treated with topical steroids twice daily or topical antibiotics clindamycin 1-2%, erythromycin 1-2%, or metronidazole 1%. Patients with grade 2 dermatological side effects (macular or papular eruptions or erythema with pruritus or with other associated symptoms), localized desquamation, or lesions covering <50% of body surface area are treated with oral antibiotics (doxycycline 100 mg) 2x daily for 6 weeks or minocycline 100 mg twice daily and topical steroids twice daily. Patients with grade 3 adverse events (severe, generalized erythroderma or macular, papular, or vesicular eruptions covering 50% of the body surface area, generalized exfoliative, ulcerative, or bullous dermatitis, will be treated with oral antibiotics (doxycycline 100 mg twice daily, minocycline 100 mg twice daily) for 6 weeks with topical steroids twice daily with discontinuation of TKI treatment and then resumed when the degree of adverse events switches to grade 2.[14] The previous study reported that patients who received EGFR therapy (cetuximab, erlotinib, lapatinib, panitumumab, or gefitinib) were given the skindex-16 questionnaire.[16] The grade of side effects assessed using NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 3.0, namely pruritus grade, xerosis grade, paronychia grade, alopecia grade, telangiectasia grade, and mucositis grade. [16] The results of this study were that toxicity, including rash, xerosis, paronychia, and pruritus, affected quality of life, and the rash had a greater impact on reducing quality of life than other toxicity.[16] The other study, which involved a critical review of journals, aimed to investigate the impact of dermatology's side effects on quality of life by using targeted therapy.[17]. Maintaining a good quality of life is highly important in patients receiving EGFR-TKI to achieve good treatment compliance.[18] However, no appropriate methods have been established to evaluate the degree to which skin condition affects patient quality of life during EGFR-TKI therapy.[18] Therefore, it is interesting to investigate the profile and overview of dermatologic side effects and quality of life index of NSCLC patients who received EGFR-TKI targeted therapy, especially at Dharmais Cancer Hospital, Jakarta.

METHODS

Study design

This study is an observational study with a cross-sectional design. It used primary and secondary data from 52 Patients with a diagnosis of advanced-stage NSCLC who were receiving one of the EGFR-TKI therapies, namely gefitinib, erlotinib, or afatinib, from September to October 2023 at Dharmais Cancer Hospital. The sampling technique used the purposive sampling technique and consecutive method, where samples that met the inclusion criteria were determined as research subjects.

Population and samples

The study was conducted on 52 patients who were the total number of non-small cell carcinoma lung cancer patients who received EGFR-TKI therapy during the study period. The inclusion criteria of this study were as follows: a) Patients with a diagnosis of advanced non-small cell carcinoma lung cancer (NSCLC) who received EGFR-TKIs targeted therapy, namely gefitinib, erlotinib, and afatinib in the period September - October 2023 at Dharmais Cancer Hospital; b) Willing to become research respondents; c) No dermatological diseases before using EGFR-TKI class drugs; d) Patients who are easy to communicate with. Patients who are easy to communicate with. Patients in medical emergencies were excluded.

Study instruments

The instruments used in this study were the quality of life questionnaire DLQI (Dermatology Life Quality Index) and a data collection sheet containing patient identity in the form of initials name, date of birth, medical record number, stage of lung cancer, ECOG PS Score and date of first use of EGFR-TKIs class drugs and informed consent to research participation. The use of this data collection sheet is intended to facilitate data collection during the study.

Data collection

The degree of severity of dermatologic side effects is the value of dermatologic side effects of patients undergoing lung cancer treatment after the use of drugs during the last week, divided into three degrees, namely Degree 1: Treated with topical steroid or topical antibiotic, second degree: Treated with oral antibiotics for 6 weeks and topical steroids, third degree: Treated with oral antibiotics for 6 weeks and topical steroids and discontinuation of EGFR-TKIs treatment. For quality of life, namely a person's ability to carry out his life functions in normal activities according to health conditions or existing complaints according to his perceptions using a quality of life questionnaire (Dermatology Life Quality Index) with a score of 0-1: Does not affect the patient's entire life, scoring 2-5: Affects the patient's life slightly, scoring 6-10: Moderately affects the patient's life, scoring 11-20: Strongly affects the patient's life, scoring 21-30: Extremely affecting the patient's life.[12,19]

Data Analysis

Data analysis was carried out by describing patient characteristic data, including age, sex, education level, disease stage, comorbidities, and Eastern Cooperative Oncology Group Performance Scale (ECOG PS) scores. The ECOG Performance Scale consists of numbers 0 to 5, where number 0 means that the patient is fully active and can carry out activities as before the disease without obstacles. An ECOG scale score of 1 means that the patient has limitations in doing strenuous activities but can still be ambulatory and can do light work such as household chores or light office work. An ECOG scale score of 2 means that the patient is ambulatory and able to care for themselves but unable to perform work and, less than 50% of the time, must lie down. An ECOG scale score of 3 means that the patient is only able to care for themselves in a limited way and, more than 50% of the time, must lie or sit. An ECOG scale score of 4 means the patient must lie down continuously, while a score of 5 means the patient has died. Data regarding the description of side effects of EGFR-TKIs were analyzed descriptively in the form of percentages.

RESULTS AND DISCUSSION

Patient Characteristics

The EGFR-TKIs drug administration in patients with lung cancer type NSCLC involved 52 patients during the study period. Data on patient demographic characteristics can be seen in Table I, which includes sex, age, education level, disease stage, comorbidities, EGFR-TKI drugs, Eastern Cooperative Oncology Group Performance Scale (ECOG PS) scores, and Dermatology Life Quality Index (DLQI) scores.

Table I. Demographic Characteristics of NSCLC Type Lung Cancer Patients at Dharmais Cancer Hospital

Characteristics	Number of patients (n)	Percentage (%)
Age in years		
≤50 years	13	25
>50 years	39	75
Education		
Primary School	4	7.7
Junior School	7	13.5
High School	30	57.7
Bachelor	6	11.5
Magister	5	9.6
Sex		
Male	20	38.5
Female	32	61.5
Stage		
IIIB	17	32.7
IV	35	67.3
Comorbidities		
Without comorbidities	35	67.3
With comorbidities	17	32.7
EGFR-TKI Drug Types		
Gefitinib	28	53.8
Erlotinib	4	7.7
Afatinib	20	38.5
ECOG		
0	3	5.8
1	27	51.9
2	22	42.3
Severity of Dermatologic Side Effect		
No skin side effects	10	19.2
Mild severity (*grade 1*)	31	59.6
Moderate severity (*grade 2*)	10	19.2
Severe severity (*grade 3*)	1	1.9
DLQI Score		
Does not affect the patient's life	16	30.8
Slightly affects the patient's life	15	28.8
Moderate impact on patient's life	7	13.5
Dramatically impact on patient's life	12	23.1
Extreme impact on patient's life	2	3.8

Description: ECOG: Eastern Cooperative Oncology Group, DLQI: Dermatology Life Quality Index

In the description of Table I, it is known that the average age of non-small cell carcinoma lung cancer (NSCLC) patients who received EGFR-TKIs therapy was >50 years, which is about 75% of the total sample. This is in accordance with the research of several studies, where in the study, it was reported that the average age of NSCLC patients who received EGFR-TKIs therapy was 65.4±12.1.[9,20,21] Another study, conducted at Dr. Soetomo Hospital, Surabaya, East Java, from January 2016 to August 2018, also stated that the average age of those who used gefitinib therapy was 56, and the average age of those who used erlotinib was 59.[22] Table I also presents that most NSCLC patients are female, around 32 patients or 61.5%. In the previous study, out of 146 research subjects, there were about 95 (65.1%) female patients[8], whereas in the other study, there were about 56 (59.6%) women and about 38 (40.4%) men.[22]

The level of education presented in Table I was primarily high school education, reaching 57.7%. This indicates a relatively good level of education in receiving education about the disease and its treatment. The severity or stage of lung cancer is grouped into stage IIIB and stage IV. The most severe stage is stage IV metastases, which is 67.3%. This result is in line with the previous study conducted in four hospitals in Taiwan

from August 2018 to December 2019, patients who received EGFR-TKIs stage IV therapy 114 (94.2%) patients, and stage IIIB 7 (5.8%) patients.[7]

Comorbidities are additional clinical conditions that have occurred together or possibly during the clinical course of a patient.[18] This study shows that the most extensive sample population is patients who do not have comorbidities, namely 69.2%. Whereas in the previous study, the comorbid status in the sample population used the SCS (Simplified Comorbidity Score) score. The sample population who had an SCS score <9 was 117 (96.7%) patients. In comparison, the SCS score ≥9 was 4 (3.3%) patients[10]. This study also described the influence between SCS scores and the quality of life of lung cancer patients, but the results were not significant. In contrast to breast cancer patients, a high comorbid index correlates with worsening quality of life.[7]

Table I also illustrates that the most widely used EGFR-TKIs drug is gefitinib, used by 28 (53.8%) patients, followed by afatinib, used by 20 (38.5%) patients, and erlotinib, used by 4 (7.7%) patients. The most common performance status (ECOG PS) was ECOG 1 was 27 (51.9%), while ECOG 2 was 22 (42.3%) and ECOG 0 was 3 (5.8%). A similar result also reported that the majority of ECOG PS is ECOG PS 0-1 (89.2%).[7] Another study reported that the majority of ECOG PS was 0, with 108 (74%) subjects.[9] Meanwhile, the results of filling out the Dermatology Life of Quality Index (DLQI) questionnaire were the most in the category of not affecting the patient's quality of life, namely 16 (30.8%), followed by the category of slightly affecting the patient's life 15 (28.8%), the category of moderate effect on the patient's life as many as 7 (13.5%), the category of significantly affecting the patient's life as many as 12 (23.1%) patients and very extreme affecting the patient's life as many as 2 (3.8%).

Incidence of Drug Side Effects

Table II describes that 52 patients who received EGFR-TKI therapy mostly experienced dermatologic side effects, whereas 43 (80.8%) patients experienced dermatologic side effects from mild (grade 1) to severe (grade 3). In comparison, 9 (19.2%) patients did not experience dermatologic side effects. The results are also similar to those of the previous study.[9] The study found that 136 (93.2%) patients experienced dermatologic side effects ranging from mild to severe (grade ≥1)[8]. This study also showed that the highest degree of severity of dermatological side effects was mild (grade 1), namely 31 (59.6%) patients. This was followed by moderate severity of dermatologic side effects (grade 2) with 10 (19.2%) patients and severe degree (grade 3) with 1 (1.92%) patient.

Table II shows that afatinib caused the most skin side effects, ranging from mild to severe, followed by gefitinib and erlotinib. These results are comparable to those of previous research.[2] The study is a systematic review and network meta-analysis registered in the Prospective Register of Systematic Reviews (PROSPERO). It consists of 40 randomized controlled trial studies involving 13,352 patients, concluding that toxicity is generally caused more by dacomitinib and afatinib than by osimertinib and gefitinib.[2] Another study reported that the group using afatinib had the highest SSI (Skin Symptom Impact) score when compared to the erlotinib and gefitinib groups.[9] Meanwhile, the gender that experienced more side effects of mild to severe severity was female. The percentage of age that experienced milder to severe side effects was ≤50 years old. The education of the research subjects who experienced the most side effects was elementary school, followed by junior high school, undergraduate, graduate, and high school. The percentage of research subjects with stage IV experienced more dermatologic side effects, research subjects without comorbidities experienced more dermatologic side effects, and research subjects with ECOG 2 experienced milder to severe side effects.

Table III shows that most of the subjects who experienced side effects of mild severity (grade 1), which slightly affected the patient's quality of life, followed by DLQI, which moderately or severity affected the quality of life patient's life. Furthermore, it is followed by DLQI, which does not affect the patient's quality of life and is very extreme in affecting the patient's life. The majority of research subjects who experienced side effects of moderate severity had a DLQI, which greatly affected the patient's quality of life, and research subjects who experienced side effects with severe severity had a DLQI, which greatly affected the patient's quality of life.

A previous study reported that dermatological side effects, such as pruritus accompanied by pain with a severity grade of ≥ 3 or pruritus with a severity grade of > 7, were associated with worsening quality of life.[7] The same report also showed that of the 21 studies identified, 6 studies analyzed the relationship between the intensity of dermatological symptoms and the severity of toxicity on quality of life.[17] The results of this research showed that 4 studies had significant relationships and positive correlations, while the other 2 studies had insignificant relationships and negative correlations in larger samples. The same study also reported in research

Table II. Incidence of Dermatologic Side Effects of NSCLC at Dharmais Cancer Hospital

Patient Demographics	Skin side effects n (%)				Total Skin side effects n (%)
	No skin side effect (%)	Mild	Moderate	Severe	
Name of Medicine					
Gefitinib	6(21.43)	18(64.29)	4(14.29)	0	22(78.58)
Erlotinib	1(25)	2(50)	1(25)	0	3(75)
Afatinib	3(15)	11(55)	5(25)	1(5)	17(85)
Sex					
Male	5 (25)	12(60)	2(10)	1(5)	15(75)
Female	5(15.63)	19(59.38)	8(25)	0	27(84.38)
Age					
≤50 years	2(15.38)	6(46.15)	4(30.77)	1(7.7)	11(84,62)
>50 years	8(20.51)	25(64.10)	6(15.38)	0	31(79.48)
Education					
Primary school	0	3(75)	1(25)	0	4(100)
Junior school	1(14.29)	5(71.43)	1(14.29)	0	6(85.72)
High school	7(23.33)	17(56.67)	6(20)	0	23(76.67)
Bachelor	1(16.67)	3(50)	1(16.67)	1(16.67)	5(83.34)
Magister	1(20)	3(60)	1(20)	0	4(80)
Stage					
IIIB	4(23.53)	9(52.94)	3(17.65)	1(5.88)	13(76.47)
IV	6(17.14)	22(62.86)	7(20)	0	29(82.86)
Comorbidities					
None	5(14.29)	21(58.33)	8(22.22)	1(2.78)	30(85.71)
With Comorbidities	5(29.41)	10(58.82)	2(11.76)	0	12(70.59)
ECOG					
0	1(33.33)	1(33.33)	1(33.33)	0	2(66.66)
1	6(22.22)	15(55.56)	6(22.22)	0	21(77.78)
2	3(13.64)	15(68.18)	3(13.64)	1(4.55)	19(86.36)

Description: ECOG: Eastern Cooperative Oncology Group, DLQI: Dermatology Life Quality Index

Table III. Incidence of Side Effects of NSCLC with Quality of Life

Degree of skin side effects (n)	Does not affect the patient's life	Slightly affects the patient's life	Moderate impact on patient's life	Greatly affects the patient's life	Very extremes affecting the patient's life	Total
No side effect	10(100)	0	0	0	0	10
Mild severity	5(16.13)	13(41.94)	6(19.35)	6(19.35)	1(3,23)	31
Moderate severity	1(10)	2(20)	1(10)	5(50)	1(10)	10
Severe severity	0	0	0	1(100)	0	1
TOTAL	16	15	7	12	2	52

Description: DLQI: Dermatology Life Quality Index

of 32 patients showed a significant correlation between skin toxicity of EGFR-TKI drugs in the form of acneiform rash, xerosis, and pruritus in different weeks since the drug was used.[10 9]

CONCLUSION

This study revealed that the most grade of side effect was grade 1 which slightly affected the patient's quality of life. The important role of the pharmacist is to provide information on side effects that may occur and manage these side effects to improve the quality of life of patients.

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STATEMENT OF ETHICS

This study has received ethical approval from the Research Ethics Committee of Dharmais Cancer Hospital No. 286/KEPK/VIII/2023.

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