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DLCO and Spirometry in non-small cell lung cancer patients receiving EGFR-TKI in Indonesia

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Abstract

English:

Introduction: *EGFR-TKI is the treatment of choice in non-small cell lung cancer (NSCLC) with EGFR mutation in exon 19 or 21. The influence of EGFR-TKI therapy on lung function is still unrecognizable in NSCLC patients.*
Objectives: *This prospective study aims to examine the influence of EGFR-TKI therapy on lung function of lung adenocarcinoma patients with a single mutation in EGFR exon 19 or 21 at Persahabatan National Respiratory Center Hospital Jakarta, Indonesia. The pulmonary function test (PFT), including spirometry and diffusing capacity (DLCO), was performed before and after three months of EGFR-TKI therapy. After three months, the patients were divided into groups based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria and the change of PFT was compared before and after therapy.*
Results: *Among twenty lung cancer patients enrolled, we found increase of predicted mean FVC value from 60.6% to 68.25% (p=0.03), mean predicted FEV1 value from 59.7% to 67.05% (p=0.036), mean DLCO from 11.55 ml/minute/mmHg to 13.72 ml/min/mmHg (p=0.004), and predicted DLCO from 53.4% to 63.85% (p=0.03). The increase of mean predicted DLCO was greatest in the partial response group, which was 16.43% (p=0.056).*
Conclusion: *This study found that the majority of NSCLC patients with single EGFR exon 19 or 21 mutation had significantly improved lung function after EGFR-TKI therapy. Lung function test might become a beneficial tool to evaluate the effectiveness of EGFR-TKI in NSCLC patients, especially in clinical setting where computerized tomography (CT) scan is not available.*

Keywords

NSCLC • EGFR-TKI • Spirometry • DLCO

DLCO și spirometria la pacienții cu cancer pulmonar NSCLC care primesc EGFR-TKI în Indonezia

Rezumat

Romanian:

Introducere: *EGFR-TKI reprezintă tratamentul de elecție în cancerul pulmonar cu celule non-mici (NSCLC) cu mutație EGFR în exonul 19 sau 21. Influenta terapiei EGFR-TKI asupra funcției pulmonare este încă neclară în cazul pacienților cu NSCLC.*
Obiective: *Acest studiu prospectiv își propune să examineze influența terapiei EGFR-TKI asupra funcției pulmonare la pacienții cu adenocarcinom pulmonar având o singură mutație în exonul 19 sau 21 al genei EGFR, la Persahabatan National Respiratory Center Hospital din Jakarta, Indonezia. Testele funcționale pulmonare (PFT), incluzând spirometria și capacitatea de difuziune prin membrana alveolo-capilară a monoxidului de carbon (DLCO), au fost efectuate înainte și după trei luni de terapie EGFR-TKI. După aceste trei luni, pacienții au fost împărțiți în grupuri pe baza criteriilor de Evaluare a Răspunsului în Tumori Solide (RECIST), iar schimbările în PFT au fost comparate înainte și după terapie.*
Rezultate: *La cei douăzeci de pacienți cu cancer pulmonar incluși în studiu, am constatat o creștere a valorii medii prognozate a Capacității Vitale Forțate (FVC) de la 60.6% la 68.25% (p=0.03), valoare medie prognozată a Volumului Expirator Forțat într-o secundă (FEV1) de la 59.7% la 67.05% (p=0.036), DLCO medie de la 11.55 ml/minute/mmHg la 13.72 ml/min/mmHg (p=0.004), și DLCO prognozată de la 53.4% la 63.85% (p=0.03). Creșterea DLCO medie prognozată a fost cea mai mare în grupul de răspuns parțial, și anume 16.43% (p=0.056).*

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Concluzie: *Acest studiu a constatat că majoritatea pacienților cu NSCLC având o singură mutație EGFR în exonul 19 sau 21 au avut o îmbunătățire semnificativă a funcției pulmonare după terapia cu EGFR-TKI. Testul funcției pulmonare ar putea deveni un instrument benefic pentru evaluarea eficacității EGFR-TKI la pacienții cu NSCLC, în special în mediul clinic unde tomografia computerizată (CT) nu este disponibilă.*

Cuvinte-cheie

NSCLC • EGFR-TKI • Spirometrie • DLCO

Introduction

Epidermal growth factor (EGF) is a growth factor that could stimulate the growth of cancer cells through the epidermal growth factor receptor (EGFR) pathway. EGFR signaling has a vital role in lung cancer progression. Therefore, researchers have sought therapy that could inhibit tyrosine kinase activity in EGFR. Tyrosine kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC) lung cancer patients significantly has a better response rate (RR), progression-free survival (PFS) and lower toxicity than chemotherapy [1].

Gefitinib and erlotinib are EGFR-TKI with side effects including skin rash, diarrhea, and nterstitial lung diseases (ILD). Interstitial lung diseases as one of the severe side effects has become the main focus of research worldwide. The global incidence of ILD due to gefitinib is 1%. However, the prevalence of ILD in Japan is higher, reaching up to 2.4 to 8.3%. Furthermore, the incidence of ILD induced by erlotinib was 2.3% to 4.3% [2,3].

The interval of disease onset of gefitinib-induced ILD varies across studies. A retrospective analysis in Japan reported that more than 75% of ILD occurred in the first three months after gefitinib therapy, and most occurred within the first four weeks [4].

A study in Taiwan showed that the median time interval from the start of gefitinib administration to the incidence of ILD was 41 days and 84% of interstitial lung disease occurs within the first two months of gefitinib administration and if the interval of EGFR-TKI administration to ILD onset is rapid, the prognosis worsens [5].

Despite the evidence that EGFR-TKI may induce ILD, the influence of EGFR-TKI on lung function is elusive. This study investigated the effect of EGFR-TKI on lung function before and after EGFR-TKI therapy to give the insight regarding the impact of EGFR-TKI to the lung.

Objectives

The purpose of this study was to investigate the effect of EGFR-TKI on lung function and to explicate the impact of EGFR-TKI to the lung.

Materials and Methods

Participant and Study Design

This was a observational study of non-small cell lung cancer patients with EGFR mutation in exon 19 or 21 who was given EGFR-TKI therapy from September 2018 to June 2019 in Persahabatan National Respiratory Center Hospital in Indonesia. Patient who had receive radiotherapy and unable to performed lung function test properly were excluded.

Data collection

The baseline characteristics were collected through interview and from the medical records. The baseline characteristics examined were sex, age, weight, height, smoking history (using Brinkmann index), body mass index (BMI), type of mutation (Exon 19 or Exon 21), type of EGFR-TKI (gefitinib, erlotinib, and afatinib), and staging. The Response Evaluation Criteria in Solid Tumors (RECIST) criteria was used to evaluate the cancer progression and the data were collected after three months of therapy.

Clinical and Pulmonary Function Test

All the participant underwent lung function test (Spirometry and DLCO) before and three months after the therapy. Spirometry was examined according to international guidelines of American Thoracic Society (ATS) [6]. The DLCO was performed using single breath technique by Easyone™ Pro Lab and the procedure done according to ATS/European Respiratory Society (ERS) guidelines [7]. Spirometry was used to measure initial mean FVC, mean FVC prediction, initial mean FEV_1, mean FEV_1 prediction, and FEV_1/FVC ratio. Determination of obstructive was based on FEV_1/FVC value less than or equal to 75% while restrictive was based on the predicted FVC value below 80%. The DLCO was used to measure DLCO absolute, %DLCO, and % DLCO/VA.

Statistical Analysis

The numerical variable was expressed as the mean and standard deviation, and the comparison analysis were performed using unpaired t-tests and Pearson correlation. For categorical variable, we expressed the data as count (percentage) and

performed bivariate analysis using Chi-square. Statistical analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA). Statistically significant were defined as $p<0.05$.

Results

Among 57 lung adenocarcinoma patients with EGFR mutation in exon 19 or 21, only 20 patients were able to perform pulmonary function tests before and after three months of therapy, as illustrated in **Figure 1**. Collectively, 20 patients were analyzed since these patients had a complete set of data including lung function tests and chest CT scan. The demographic characteristics were summarized in **Table 1.** The highest change of predicted DLCO was observed in smoker patients with moderate Brinkmann index (18.75 ± 10.43%).

RECIST

Of 20 patients treated with EGFR-TKI therapy, 8 patients (40%) with gefitinib, 8 patients (40%) with erlotinib, and 4 patients (20%) with afatinib. Based on RECIST criteria three months after EGFR-TKI treatment, there were 7 patients (35%) with partial response, 10 patients (50%) with stable disease, and 3 patients (15%) with progressive disease. Of 8 patients who received gefitinib, 1 patient (12.5%) had progressive disease, 5 patients (62.5%) had stable disease, and 2 patients (25%) had partial response. Of 8 patients who received erlotinib, 2 patients (25%) had progressive disease, 3 patients (37.5%) had stable disease, and 3 patients (37.5%) had partial response. Of 4 patients who received afatinib, 2 (50%) patients had stable disease and 2 patients (50%) had partial response patients. One patient who received afatinib had pneumonitis.

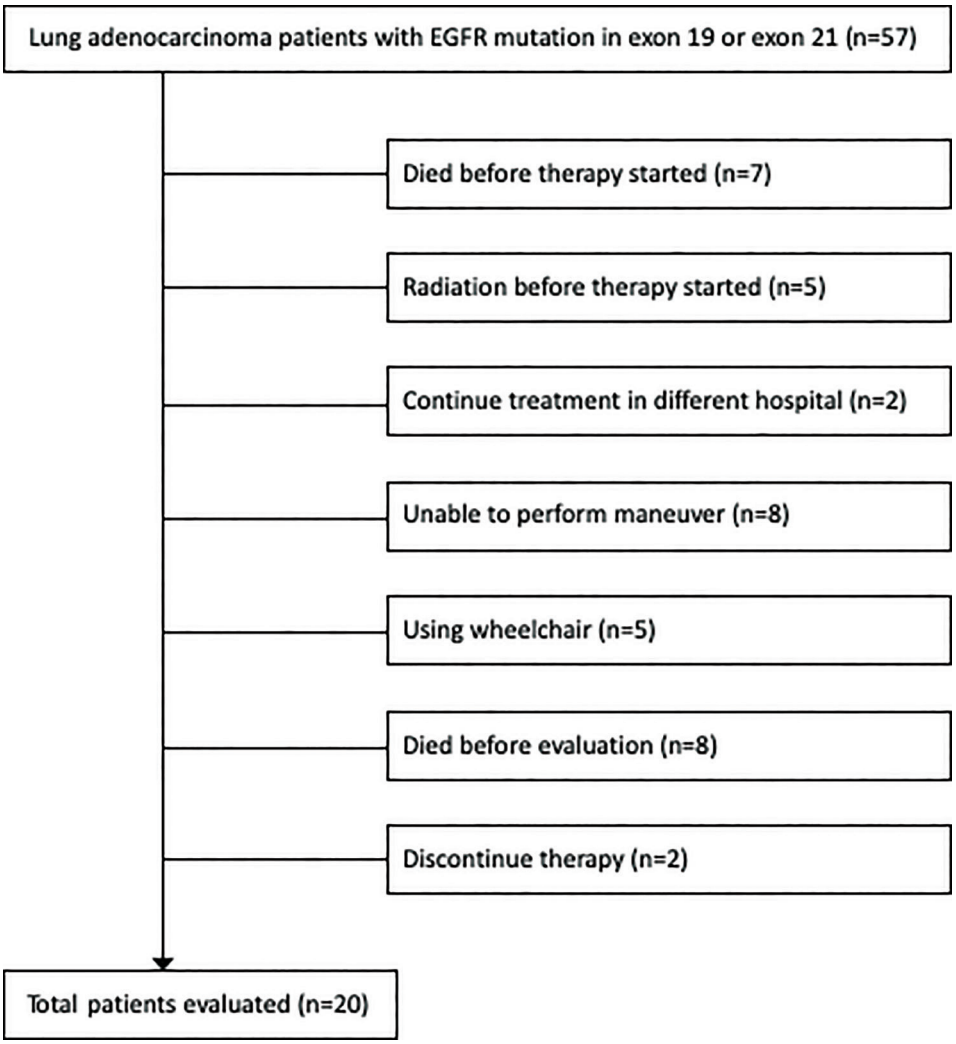

Figure 1. Research participant. **Abbreviations:** EGFR, epidermal growth factor receptor

Table 1. Patients Charactertistics

Variable	n (%)
Sex, Male	10 (50)
Age	
Highest	76
Lowest	37
Mean	54.8
Smoking history	
Smoker	10 (50)
Non-smoker	10 (50)
BMI	
<18.5	4 (20)
18.5-24.9	12 (60)
>25	4 (20)
Mutation type	
Exon 19	11 (55)
Exon 21	9 (45)
EGFR-TKI	
Gefinitib	8 (40)
Erlotinib	8 (40)
Afatinib	4 (20)
Stage	
IIIB	2 (10)
IV	18 (90)
RECIST	
Partial Response	7 (35)
Stable Response	10 (50)
Progressive Response	5 (15)
Pneumonitis incidence	19 (95)

Abbreviations: RECIST Response Evaluation Criteria in Solid Tumors, **EGFR** Epidermal Growth Factor Receptor, **EGFR-TKI** Epidermal Growth Factor Receptor Tyrosine kinase inhibitor.

Table 2. Spirometry Characteristics

Variable	Pretreatment	Post-treatment
FVC (ml)	1651 ± 560	1830 ± 589
%FVC	60.601651 ± 56016.87	68.25 ± 15.61
FEV_1 (ml)	1263 ± 429	1394 ± 502
FEV_1 (ml)	59.70 ± 18.66	67.05 ± 16.88
FVC/ FEV_1	78.55 ± 14.39	80.09 ± 14.12
Spirometry Results[1]		
Obstructed	6 (30)	5 (25)
Restricted	15 (75)	14 (70)

Abbreviations: FVC Forced Vital Capacity, **FEV_1** Forced Expiratory Volume 1-second.

[1]Described as count (percentage).

Table 3. Characteristics of Lung Function Based on the DLCO Test

Variable	Pretreatment	Post-treatment
DLCO absolute (ml)	11.55 ± 3.67	13.72 ± 4.62
%DLCO	53.40 ± 12.99	63.85 ± 15.94
%DLCO/Va	95.70 ± 24.86	100.5 ± 24.58
DLCO Results[1]		
Normal	1 (5)	5 (25)
Decreased	19 (95)	15 (75)

Abbreviations: DLCO Diffusing Capacity, **VA** Alveolar Volume.

[1]Described as count (percentage).

Spirometry

The initial mean FVC value was 1651 ± 560 ml and initial predicted mean FVC value was 60.6 ± 16.87%. The baseline mean FEV_1 value was 1263 ± 429 ml and predicted mean FEV_1 value was 59.7 ± 18.66%. The initial mean FEV_1/FVC value was 78.55 ± 14.39%. Initial spirometry examination showed 6 (30%) obstructive patients and 15 (75%) restrictive patients with 1 patient showed both obstructive and restrictive. Of those patients with restrictive disorders, 9 (60%) mild restriction, 6 (40%) moderate restriction, and no severe restriction.

After three months of therapy with EGFR TKI, mean FVC value was 1803 ± 589 ml and mean predicted FVC value was 68.25 ± 15.61%. Mean value FEV_1 value was 1394 ± 502 ml and predicted mean FEV_1 value was 67.05 ± 16.88%. Mean FEV_1/FVC value was 80.09 ± 14.12%. There were 5 (25%) obstructive patients and 14 (70%) restrictive patients, 1 (5%) patient had normal result. Spirometry results are described in **Table 2**.

DLCO

Mean absolute DLCO value before EGFR-TKI therapy was 11.55 ± 3.67 ml/min/mmHg. Mean predicted DLCO value before therapy was 53.4 ± 12.99%. Initial mean value of diffusing capacity divided by the alveolar volume (DLCO/VA) was 95.7 ± 24.86%. There were 19 (95%) patients with decreased DLCO results and only 1 (5%) patient with normal DLCO results. After three months therapy, mean absolute DLCO value was 13.72 ± 4.62 ml/minute/mmHg. Mean predicted DLCO value was 63.85 ± 15.94%. Mean predicted DLCO/VA value was 100.5 ± 24.58%. There were 15 (75%) patients with decreased DLCO results and 5 (25%) patients with normal DLCO. The detailed DLCO results are shown in **Table 3**.

Lung Function Changes Pre and Post-Treatment

The lung function was improved significantly ($p < 0.05$) in predicted FVC value, predicted FEV1, and absolute and predicted DLCO value after 3 months EGFR-TKI administration. There are increased of value in mean predicted FVC (7.65 ± 14.68%), mean FEV_1 (7.35 ± 14.06%), mean absolute DLCO (2.16 ± 2.92 ml/minute/mmHg), and mean predicted DLCO (10.45 ± 13.76%). The detailed of improvement of lung function test as shown in **Table 4**.

The Relationship between variables to changes in the value of DLCO

The relationship between categorical and numerical variables and changes in %predicted DLCO was analyzed. Changes

Table 4. Lung function Changes between Pre and Post-treatment

Variable	Mean Changes ± SD	p-value
Spirometry		
FVC	152.50 ± 370.91	0.082
%FVC	7.65 ± 14.68	0.031
FEV_1	131.50 ± 286.87	0.054
$\%FEV_1$ predicted	7.35 ± 14.06	0.036
FEV_1/FVC	1.50 ± 7.70	0.395
DLCO		
Absolute DLCO	2.16 ± 2.92	0.004
%DLCO Predicted	10.45 ± 13.76	0.003
%DLCO/VA Predicted	4.80 ± 22.44	0.351

Abbreviations: FVC Forced Vital Capacity, **FEV_1** Forced Expiratory Volume 1-second, **DLCO** Diffusing Capacity, **VA** Alveolar Volume

Table 5. Relationship Between Categorical Variables and Predicted DLCO

Variable	%DLCO Predicted Changes	p-value
Sex		
Male	13.40 ± 12.96	0.351
Female	7.50 ± 14.57	
Brinkmann Index		
Mild	12.90 ± 13.04	0.107
Moderate	18.75 ± 10.43	
Severe	0.20 ± 13.59	
EGFR Mutation		
Exon 19	13.00 (–19.00 to 26.00)	0.425
Exon 21	8.00 (–7.00 to 37.00)	
EGFR-TKI		
Gefitinib	7.37 ± 16.21	0.722
Afatinib	13.13 ± 14.01	
Erlotinib	11.25 ± 9.07	
RECIST		
Progressive disease	–5.67 ± 14.05	0.056
Stable disease	11.10 ± 11.92	
Partial Response	16.43 ± 12.16	

Abbreviation: EGFR Epidermal Growth Factor Receptor, **EGFR-TKI** Epidermal Growth Factor Receptor Tyrosine kinase inhibitor, **RECIST** Response Evaluation Criteria in Solid Tumors, **DLCO** Diffusing Capacity

in predicted DLCO value were 13.4 ± 12.96% in female, 7.5 ± 14.57% in male, 12.09 ± 13.04% in mild Brinkmann index, 18.75 ± 10.43 % in moderate Brinkmann index, and 0.2 ± 13.59% in severe Brinkmann index. Changes of predicted DLCO value based on EGFR mutation status and EGFR-TKI group were 13% in EGFR exon 19 mutations, 8% in EGFR exon 21 mutations, 7.37 ± 16.21% gefitinib, 13.12 ± 15.01% in patients who received erlotinib, 11.25 ± 9.07% in patients who received afatinib. Changes of predicted DLOC value based on RECIST criteria were 11.1 ± 11.92% in patients with stable disease and 16.43 ± 12.16% in patients with partial response. Predicted DLCO value in patients with progressive disease decreased up to 5.67 ± 14.05%. The results showed that the greatest improvement in DLCO values occurred in the female patient group, moderate Brinkmann index, exon 19, erlotinib, and patients with partial response. However, these results were not statistically significant (**Table 5**).

In this study, we found a significant correlation between age and FEV_1/FVC values with changes in absolute DLCO and predicted DCLO values. The younger the patients more likely had improvement of DLCO value after 3 months of EGFR-TKI. Furthermore, the greater the FEV1/FVC value, the more likely the DLCO values improved after the administration of EGFR-TKI. Complete information regarding the comparison between numerical variables and the changes in DLCO and was summarized in **Table 6**.

Table 6. Relationship of Numerical Variables to Changes in DLCO Value

Variable	Absolute DLCO		%DLCO Predicted	
	Coefficient	p-value	Coefficient	p-value
Age	–0.469	0.000	–0.451	0.046
Weight	–0.062	0.796	–0.021	0.931
Height	0.121	0,613	0.022	0.927
BMI	–0.169	0,476	–0.082	0.731
FVC	–0.03	0.901	–0.132	0.578
%FVC	–0.143	0,547	–0.189	0.426
FEV_1	0.222	0.347	0.119	0.618
$\%FEV_1$	0.142	0.551	0.068	0.774
Pretreatment FEV_1/FVC	0.504	0.024	0.462	0.039

Abbreviations: FVC Forced Vital Capacity, **FEV_1** Forced Expiratory Volume 1-second, **DLCO** Diffusing Capacity

Discussion

This study investigated the effect of EGFR-TKI therapy on pulmonary function in lung adenocarcinoma patients with EGFR mutation. The average age of the patient in this study was 54.8 ± 10.95 years with the youngest being 37 years old and the oldest being 76 years old, which was slightly different result compared to PIONEER study of the Chinese subgroup, which was 57.4 ± 11.4 years, with the youngest age being 20 years and the oldest being 83 years old [8]. In this study, we found 1 (5%) patients experiencing pneumonitis after receiving EGFR-TKI. Currently in Indonesia there is no data or studies looking for the prevalence of side effects of pneumonitis due to EGFR-TKI. Sequist et al reported the incidence of interstitial lung disease due to afatinib was 1.3% [9].

Mean FEV_1 value in this study was 1263 ± 429 ml, while predicted mean FEV_1 value in this study was 59.7 ± 18.66%. The spirometry examination in this study was not performed with maneuver to assess vital capacity. This related to the condition or ability of the patients to complete all examinations. Forced vital capacity examination is the most important examination in spirometry. Spirometry examination with forced vital capacity maneuver can assess the presence or absence of obstruction and its degree. Mean FVC value in the study patients before EGFR-TKI therapy was 1651 ±

560 ml and predicted mean FVC value was 60.6 ± 16.87%. Predicted FVC value is used to determine the degree of restriction. Mean FVC and predicted FVC values in this study were similar with the previous study by Fathana et al which involved 52 patients with newly diagnosed lung cancer who had mean FVC value of 1664 ± 657 ml and mean predicted FVC value was 57% [10]. These data showed that restriction commonly occurred in lung cancer patients.

In this study, we found no significant improvement of mean FVC value after 3 months therapy. However, there was a significant improvement of predicted FVC value after 3 months of EGFR-TKI therapy. Mean predicted FVC value after 3 month EGFR-TKI therapy increased from 60.6 ± 16.87% to 68.25 ± 15.61% and mean predicted FVC value after 3 months EGFR-TKI therapy was 7.65. ± 14.68%. Currently, we did not find any comparative studies that have assessed changes in lung function in lung adenocarcinoma patients receiving EGFR-TKI therapy. However, we found a similar study that assessed changes in lung function in lung cancer patients receiving intravenous chemotherapy. Our study showed similar result, which was the improvement in predicted FVC value, compared to the previous study which showed the significant improvement of predicted FVC value after 3 cycles of chemotherapy [11].

The mean value of FEV_1/FVC in this study was 78.55 ± 14.39% which was just above the upper limit of obstruction value, 75%. We found an improvement in mean FEV_1/FVC value up to 1.5 ± 7.7% 3 months after EGFR-TKI therapy. However, this improvement was not statistically significant ($p>0.05$) which may be caused by the small increase of mean FEV_1/FVC and moreover the reduction number of patients with obstruction 3 months after EGFR-TKI therapy.

Three months after EGFR-TKI therapy, mean FEV_1 value was improved with the average of 131.5 ± 286 ml. This too was also not statistically significant ($p>0.05$). In contrast, previous study by Takeda et al showed a significant increase of mean FEV_1 ($p<0.05$) in lung cancer patients three months after treatment, which including resection, chemoradiation, and chemotherapy alone [12]. This discrepancy with our results might be due to mean FEV_1 value in our study before therapy was already quite low compared and most of the patients in our study were in stage 4 while patients in Takeda et al study were in stage 2B to 3B who underwent neoadjuvant therapy.

Our study showed that after 3 months of EGFR-TKI therapy, mean predicted FEV_1 value was significantly increased to 67.05 ± 16.88% with the mean value of change of 7.35 ± 14.06% ($p<0.05$). Similar result was previously reported in NSCLC patients after receiving cisplatin and gemcitabine chemotherapy for 3 cycles which showed the increased of mean predicted FEV_1 value from 78.1% to 87.5%.[11]

Another interesting finding in our study was the significant improvement in absolute DLCO and predicted DLCO values after 3 months of EGFR-TKI ($p<0.05$), which were up to 13.72 ± 4.62 and 10.45 ± 13.76%, respectively. Moreover, we found an improvement of mean DLCO/VA value to 100.5 ± 24.58% after EGFR-TKI therapy, but it was not statistically significant. To our knowledge, there are no studies had been done to asses changes in lung function in lung adenocarcinoma patients before and after receiving EGFR-TKI therapy. Previous study had assessed lung function in lung cancer patients before and after chemotherapy or chemoradiation [12].

Lung cancer patients who received cisplatin-based chemotherapy usually have an improvement in spirometry but a decrease in DLCO values [12]. Our study revealed a significant improvement in both absolute DLCO and predicted DLCO value 3 months after EGFR-TKI therapy. Moreover, the highest increase of predicted DLCO value was observed in patients with partial response according to RECIST criteria. Furthermore, an increase of predicted DLCO value was also found in patients with stable disease. On the other hand, patients with progressive disease had worsening of predicted DLCO mean value. Based on these results, we suggested that lung function in lung cancer patients was influenced by the response to therapy. In contrast, previous study showed a decrease in the value of DLCO despite the response to chemotherapy. Lung tumors can cause lung function disorders in 2 ways, namely non-obstructive disorders in the form of decreased lung volume and diffusion barriers and obstructive disorders due to intraluminal tumor growth and airway compression. The DLCO value is influenced by the volume of inspired air (a large inspired air volume will increase the DLCO value). Chemotherapy in lung cancer patients can reduce the size of the tumor mass [13].

Our study showed that predicted DLCO value change in women after EGFR-TKI therapy for three months was greater than those in male even though statistically the relationship between sexes with the value of the predicted DLCO change was not significant ($p> 0.05$). The better improvement of mean predicted DLCO value in female group might be associated with a better EGFR-TKI response in female patients. The fact that EGFR-TKI response was better in female population, East Asian ethnicity, non-smokers, adenocarcinoma histology, and EGFR mutations positive has been reported previously [14].

Change of predicted DLCO value based on the type of mutation in this study was greatest in patients with exon 19 mutation (13%) compared to exon 21 (8%). However, there was no significant relationship ($p>0.05$) between the type of mutation and the predicted DLCO change value. This results were consistent with previous study showing no relationship between the effectiveness of types of EGFR-TKI with the predicted DLCO change value [15].

Our study found that there was a significant relationship between the age of with the absolute DLCO change value and the predicted DLCO. The younger patients are more likely to have improved the DLCO value or a good response to the administration of EGFR-TKI. In contrast, Shang et al reported that poor response or effectiveness of EGFR-TKI in young patients (<50 years). Patients aged younger or less than 50 years had the lowest PFS rate of 7.3 months compared to patients aged above and a lower response rate of 70.4% compared to 80.6%. However, the relation between age and the effectiveness of EGFR-TKI is elusive. EGFR mutation is uncommonly found in younger patients than older one. This is indirectly related to the lower EGFR-TKI response. The main issue regarding the effectiveness of the EGFR-TKI in this study compared with Shang et al is that the entire patients in both study combined had mutations in exons 19 and 21 [16].

The magnitude of the change in mean and predicted DLCO values in this study was not influenced by the predicted FVC, FEV_1 and FEV_1 values. The improvement of lung function in lung cancer patients both from spirometry and DLCO examinations in this study was influenced by tumor response to EGFR-TKI therapy. Based on these findings, we concluded that the better the EGFR-TKI response might reduced the tumor volume and therefore resulting greater improvement in spirometry, absolute DLCO, and predicted DLCO values. One patient in our study had good response (partial response) to EGFR-TKI. However, the DLCO value did not show any improvement. We suggest that this could be due to the side effects of EGFR-TKI which was pneumonitis. Another patient with progressive disease had an increment in DLCO value and was thought to be related to the delay in CT scan examination for RECIST. The patient was only evaluated for RECIST during the fifth month of therapy.

Our study revealed a significant relationship between FEV_1/FVC value and change in the mean DLCO and predicted DLCO values. The greater FEV_1/FVC value, the greater DLCO value which was improved after the administration of EGFR-TKI. Lung tumors can cause lung function disorders in two ways, non-obstructive disorders in the form of decreased lung volume along with diffusion barriers and obstructive disorders due to intraluminal tumor growth and compression of the airways. Most cancer patients are smokers and may developed COPD. The DLCO value of COPD patients is directly proportional to the degree of obstruction. The more severe the obstruction in COPD patients, the lower the DLCO value [17].

This study encountered some limitation, including the small sample size and unbalanced of EGFR-TKI administration to research patients, the high drop out rate during the study period. Further research is recommended to truly established the effect of EGFR-TKI in lung function.

Conclusion

In lung adenocarcinoma patients with EGFR mutation who received EGFR-TKI therapy, the lung function significantly improved three months after therapy. In clinical setting where CT scan is not available, lung function testing might become the valuable tool to evaluate therapy in lung cancer.

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Institutional Review Board Statement

The study was approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia (Ethic number 0676/UN2.F1/ETIK/2018).

Informed Consent Statement

Informed consent was obtained from all participants in the study.

Patient Consent

Written informed consent was obtained from the patients for publication of this case series. A copy of the written consent is available for review of request.

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Wang BC, Zhang WX, Kuang BH etc. The efficacy and tolerability of combining pemetrexed-based chemotherapy with gefitinib in the first-line treatment of non-small cell lung cancer with mutated EGFR: A pooled analysis of randomized clinical trials. PLoS One 2022;17(10):e0275919.
2. Harada C, Kawaguchi T, Ogata-Suetsugu S etc. EGFR tyrosine kinase inhibition worsens acute lung injury in mice with repairing airway epithelium. Am J Respir Crit Care Med 2011;183(6):743-751.
3. Gemma A, Kudoh S, Ando M etc. Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer. Cancer Sci 2014;105(12):1584-1590.
4. Muller NL, White DA, Jiang H etc. Diagnosis and management of drug-associated interstitial lung disease. Br J Cancer 2004;91 Suppl 2(Suppl 2):S24-30.
5. Chang SC, Chang CY, Chang SJ etc. Gefitinib-related interstitial lung disease in Taiwanese patients with non-small-cell lung cancer. Clin Lung Cancer 2013;14(1):55-61.
6. Graham BL, Steenbruggen I, Miller MR etc. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019;200(8):e70-e88.
7. Graham BL, Brusasco V, Burgos F etc. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017;49(1).
8. Shi Y, Li J, Zhang S etc. Molecular Epidemiology of EGFR Mutations in Asian Patients with Advanced Non-Small-Cell Lung Cancer of Adenocarcinoma Histology - Mainland China Subset Analysis of the PIONEER study. PLoS One 2015;10(11):e0143515.
9. Sequist LV, Yang JC, Yamamoto N etc. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31(27):3327-3334.
10. Fathana FB, Yunus F, Andarini SL etc. Prevalens penyakit paru obstruksi kronik (PPOK) dan emfisema berdasarkan pemeriksaan spirometri dan Computed Tomography Scanning (CT-Scan) toraks pada pasien kanker paru di Rumah Sakit Umum Pusat Persahabatan. Jakarta, Indonesia: University of Indonesia; 2019.
11. Leo F, Solli P, Spaggiari L etc. Respiratory function changes after chemotherapy: an additional risk for postoperative respiratory complications? Ann Thorac Surg 2004;77(1):260-265; discussion 265.
12. Takeda S, Funakoshi Y, Kadota Y etc. Fall in diffusing capacity associated with induction therapy for lung cancer: a predictor of postoperative complication? Ann Thorac Surg 2006;82(1):232-236.
13. Pinson P, Klastersky J. The value of lung function measurements for the assessment of chemotherapy in lung cancer patients. Lung Cancer 1998;19(3):179-184.
14. Yang Z, Hackshaw A, Feng Q etc. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis. Int J Cancer 2017;140(12):2805-2819.
15. Lim SH, Lee JY, Sun JM etc. Comparison of clinical outcomes following gefitinib and erlotinib treatment in non-small-cell lung cancer patients harboring an epidermal growth factor receptor mutation in either exon 19 or 21. J Thorac Oncol 2014;9(4):506-511.
16. Wu SG, Chang YL, Yu CJ etc. Lung adenocarcinoma patients of young age have lower EGFR mutation rate and poorer efficacy of EGFR tyrosine kinase inhibitors. ERJ Open Res 2017;3(3).
17. Bailey KL. The importance of the assessment of pulmonary function in COPD. Med Clin North Am 2012;96(4):745-752.