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# COMPARISON OF THERAPEUTIC RESPONSES OF LUNG ADENOCARCINOMA PATIENTS RECEIVED TARGETED THERAPY

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**ABSTRACT**
**Background:** Targeted therapy with tyrosine kinase inhibitors (TKIs) were used to treat lung adenocarcinoma patients with EGFR mutation positive. EGFR mutations at exon 19 and exon 21 are classified as classical/common mutations, while mutations other than those exons are classified as rare/uncommon mutations. This study aims to compare the therapy responses of lung adenocarcinoma patients received TKI generation I (gefitinib and erlotinib) and TKI generation II (afatinib) in Makassar, as well as analyzed factors such as age, sex, tumor stage, type of EGFR mutation and comorbidity to therapy responses.
***Methods*:** This study is a retrospective observational using secondary data from Lung Adenocarcinoma patient medical records at Wahidin Sudirohusodo Hospital Makassar in 2016 - 2020, involved 84 patients aged 28-83 years who received targeted therapy. The subjective response was determined by the Eastern Cooperative Oncology Group (ECOG) score, while the objective response was determined by the Response Evaluation Criteria In Solid Tumor (RECIST) guidelines version 1.0. The statistical test used were Pearson's Chi-Square. The results were considered significant if p-value <0.05.
***Results*:** Subjective response from PS2 to PS1 and from PS2 to PS0 were significantly higher in common mutations than in uncommon mutations ($p<0.05$). While subjective response was shown higher in TKI generation II than in TKI generation I but not statistically significant ($p=0.464$). The objective response of Progressive Disease (PD) was shown significantly higher in TKI generation I than in TKI generation II ($p<0.05$), and the objective response of PD was obtained significantly higher in uncommon mutations than in common mutations ($p<0.05$). Factors such as age, gender, tumor stage and comorbidities did not have a significant correlation to objective and subjective responses.
***Conclusions*:** Targeted therapy with TKI generation II provided a significantly better objective response than TKI generation I. The type of EGFR mutation "common/classical mutation" provides a better therapeutic response regardless of the type of TKI targeted therapy received.
**Keywords: Lung adenocarcinoma, EGFR-TKI, therapy response**

## Introduction

The most common type of lung cancer is adenocarcinoma (comprises around 40% of all lung cancer).[1,2] Targeted therapy is given to NSCLC patients with positive epidermal growth factor receptor (EGFR) mutations that sensitive to EGFR-tyrosine kinase inhibitors (TKI).[2,3] The National Comprehensive Cancer Network (NCCN) recommends oral EGFR-

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TKIs as first line, such as gefitinib, erlotinib (first generation TKI), and afatinib (second generation TKI).[4,5] The second generation TKI (afatinib) provides better clinical effectiveness as first-line therapy for patients with advanced lung adenocarcinoma than the first generation EGFR-TKI (gefitinib and erlotinib), because the second generation TKI has a wider spectrum and stronger binding ability.[6]

There are 28 exons on the EGFR that formed proteins that are distributed across cell membranes of various epithelial cells.[7] Mutations in exon 19 ( exon 19 insertion/deletion) and L858R point mutation in exon 21 (exon 21 L858R) are the most common types of EGFR mutations[2,8,9] and classified as classic mutations ("classical mutation patterns"). Mutations other than exon 19 or exon 21 L858R are classified as "uncommon mutation patterns" and are less effective against treatment with EGFR-TKIs than classic mutations.[2,9]

Younger lung adenocarcinoma patients (≤50 years) had tumours with a lower EGFR mutation rate but more uncommon mutation types so that poorer treatment response.[10] EGFR mutations are found much higher proportions in female patients, Asian populations, and nonsmokers.[1,11] Several studies have shown that a larger proportion of women than men among patients with adenocarcinoma are non-smokers, and lung cancer in non-smokers responds better to treatment and lives longer than smokers.[12]

Most lung cancers are diagnosed at an advanced stage, both locally and metastasized (stage IIIb and stage IV).[13,14] Yun Oh et al reported that reported that tumor size and number of metastatic sites were predictors of poor outcome in patients with NSCLC.[14]

The level of response to therapy consists of a subjective response, which can be assessed based on the patient's clinical (performance status based on the Karnofsky or WHO score)[3] and the Eastern Cooperative Oncology Group (ECOG)[15,16], as well as an objective response assessed from the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.0 based on the size of the primary tumor or measurable lesions and the presence or absence of new lesions.[17,18]

Based on this background and very limited reports regarding the therapeutic response of lung adenocarcinoma patients who received targeted therapy in Makassar, we interested in conducting this study.

## Method

### Research design

This study is a retrospective observational study using secondary data from lung adenocarcinoma patient medical records who received targeted therapy at Wahidin Sudirohusodo Hospital, Makassar.

### Research subject

Research subjects were taken with a consecutive sampling approach on subjects with lung adenocarcinoma who received targeted therapy TKI generation I (gefitinib and erlotinib) and TKI generation II (afatinib) at the Wahidin Sudirohusodo Hospital since 2016-2020 who met the research criteria. Inclusion criteria were age ≥18 years, lung

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adenocarcinoma patients with positive EGFR mutations who received targeted therapy with gefitinib, erlotinib and afatinib, and complete medical records for the study.

**Research Data Collection**

Research subjects were lung adenocarcinoma patients who met the research criteria and then we collected data on age, sex, tumor stage, comorbidities, types of EGFR mutations, and data related to subjective and objective responses of subjects after receiving targeted therapy for the first 3 months based on medical record status. We analyzed subjective responses based on the ECOG Performance Scale scoring criteria, and objective responses were analyzed based on the RECIST version 1.0 criteria.

**Data analysis**

Data analysis was performed using SPSS version 25.0. The statistical test used Pearson Chi-Square test, where the results were considered significant if the p value <0,05.

**Research Permit and Ethical Eligibility**

This research protocol has been approved by the Health Research Ethics Committee, Medical Faculty, Hasanuddin University Makassar, according to the ethical approval recommendation letter number: 733/UN4.6.4.5.31/PP36/2020.

**Results**

This study included 84 subjects with with most of the subjects were male (51.2%), with a mean age of 58.58±11.76 years. Subjects studied were in the age range of 28-83 years, which grouped by age 20-50 years (21.4%), 51-64 years (48.8%), and ≥65 years (29.8%). Most of the subjects had comorbidities (51.2%) and based on the American Joint Committee on Cancer (AJCC) 2017 version 8, the most studied subjects were at stage IV (96.4%). Subjects with common/classical mutations were 56 subjects (66.7%) and with uncommon mutations were 28 subjects (33.3%). Subjects who received first generation TKIs (Gefitinib and Erlotinib) were 58 subjects (69%) while 26 subjects received second generation TKI (Afatinib) (31%).

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**Table 1. Distribution of subject characteristics (n=84)**

| Variable | | n | % |
|---|---|---|---|
| Age (years) | 20-50 | 18 | 21,4 |
| | 51-64 | 41 | 48,8 |
| | ≥65 | 25 | 29,8 |
| Gender | Male | 43 | 51,2 |
| | Female | 41 | 48,8 |
| Comorbid | None | 41 | 48,8 |
| | Yes | 43 | 51,2 |
| Tumor stage | III | 3 | 3,6 |
| | IV | 81 | 96,4 |
| Type of EGFR mutation | *Common/classical mutations* | 56 | 66,7 |
| | *Uncommon mutations* | 28 | 33,3 |
| Targeted therapy | TKI Generation I | 58 | 69,0 |
| | TKI Generation II | 26 | 31,0 |

TKI= *Tyrosine Kinase Inhibitor*

In the analysis of the correlation between target therapy and subjective response, the correlation was not significant between TKIs generations I and II with subjective responses changes from PS2 to PS1 and from PS1 to PS0 (p=0.464), this can be seen in **table 2**.

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**Table 2. Correlation targeted therapy with subjective response**

| Targeted Therapy | | Subjective Response | | | | Total | p value |
|---|---|---|---|---|---|---|---|
| | | PS 2 to PS 1 | PS 2 to PS 0 | PS 1 to PS 0 | PS not changed | | |
| TKI generation I | n | 21 | 1 | 4 | 32 | 58 | 0,464 |
| | % | 36,20% | 1,70% | 6,90% | 55,20% | 100,00 % | |
| TKI generation II | n | 11 | 2 | 2 | 11 | 26 | |
| | % | 42,30% | 7,70% | 7,70% | 42,30% | 100,00 % | |
| Total | n | 32 | 3 | 6 | 43 | 84 | |
| | % | 38,10% | 3,60% | 7,10% | 51,20% | 100,00 % | |

PS= *performance status;* TKI= *Tyrosine Kinase Inhibitor*

In the analysis of the correlation between confounding factors and subjective responses, there was a significant correlation between the types of EGFR mutations on changes in subjective responses from PS2 to PS1 and from PS2 to PS0 (p=0.000), but not significant in age (p=0.822), gender (p=0.933), comorbidities (p=0.732), and tumor stage (p=0.919), **it can be seen in table 3.**

**Table 3. Correlation confounding factor to subjective response**

| Variable | Subjective Response | | | | | | | | Total | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PS 2 to PS 1 | | PS 2 to PS 0 | | PS1 to PS 0 | | PS not changed | | | | |
| | n | % | n | % | n | % | n | % | n | % | |
| **Gender** | | | | | | | | | | | |
| Male | 17 | 39,5% | 1 | 2,3% | 3 | 7,0% | 22 | 51,2% | 43 | 100,0% | 0,933 |
| Female | 15 | 36,6% | 2 | 4,9% | 3 | 7,3% | 21 | 51,2% | 41 | 100,0% | |
| **Age (years)** | | | | | | | | | | | |
| 20 - 50 | 7 | 38,9% | 0 | 0,0% | 1 | 5,6% | 10 | 55,6% | 18 | 100,0% | |
| 51 - 64 | 17 | 41,5% | 2 | 4,9% | 4 | 9,8% | 18 | 43,9% | 41 | 100,0% | 0,822 |
| ≥ 65 | 8 | 32,0% | 1 | 4,0% | 15 | 60,0% | 1 | 4,0% | 25 | 100,0% | |
| **Type of EGFR mutation** | | | | | | | | | | | |
| *Common Mutations* | 30 | 53,6% | 3 | 5,4% | 3 | 5,4% | 20 | 35,7% | 56 | 100,0% | 0,000 |
| *Uncommon Mutations* | 2 | 7,1% | 0 | 0,0% | 3 | 10,7% | 23 | 51,2% | 28 | 100,0% | |

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| Variable | Subjective Response | | | | | | | | Total | | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PS 2 to PS 1 | | PS 2 to PS 0 | | PS1 to PS 0 | | PS not changed | | | | |
| | n | % | n | % | n | % | n | % | n | % | |
| **Comorbid** | | | | | | | | | | | |
| None | 17 | 41,5% | 2 | 4,9% | 2 | 4,9% | 20 | 48,8% | 41 | 100,0% | 0,732 |
| Yes | 15 | 34,9% | 1 | 2,3% | 4 | 9,3% | 23 | 53,5% | 43 | 100,0% | |
| **Tumor Stage** | | | | | | | | | | | |
| Stage III | 1 | 33,3% | 0 | 0,0% | 0 | 0,0% | 2 | 66,7% | 3 | 100,0% | 0,919 |
| Stage IV | 31 | 38,3% | 3 | 3,7% | 6 | 7,4% | 41 | 50,6% | 81 | 100,0% | |
| Total | 32 | 38,1% | 3 | 3,6% | 43 | 51,2% | 6 | 7,1% | 84 | 100,0% | |

PS= *performance status*; EGFR= *Epidermal Growth Factor Receptor; Common mutations*= mutation at exon 19 or 21 L858R*; Uncommon mutations*= mutation at exon 18 or 20

In the analysis of the correlation between target therapy and objective response, there was a significant correlation between generation I and II TKIs on the objective response to progressive disease (PD) (p = 0.040), this can be seen in **table 4**.

**Table 4. Correlation targeted therapy with objective response**

| Targeted Therapy | | Objective Response | | Total | P value |
|---|---|---|---|---|---|
| | | CR,PR,SD | PD | | |
| TKI generation I | n | 42 | 16 | 58 | 0,040 |
| | % | 72,40% | 27,60% | 100,00 % | |
| TKI generation II | n | 24 | 2 | 26 | |
| | % | 92,30% | 7,70% | 100,00 % | |
| Total | n | 66 | 18 | 84 | |
| | % | 78,60% | 21,40% | 100,00 % | |

*CR= Complete Response; PR= Partial Response; SD= Stable Disease; PD= Progressive Disease; TKI= Tyrosine Kinase Inhibitor*

In the analysis of the correlation of confounding factors to the objective response, there was a significant correlation between the types of EGFR mutations in the objective

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response to PD (p=0.000), but not significant for age (p=0.978), gender (p=0.909), comorbidities (p=0.518), and tumor stage (p=0.357), it can be seen in **table 5**.

**Table 5. Correlation confounding factor to objective response**

| Variable | Objective Response | | | | Total | | P value |
|---|---|---|---|---|---|---|---|
| | CR, PR, SD | | PD | | | | |
| | n | % | n | % | n | % | |
| **Gender** | | | | | | | |
| Male | 34 | 79,1% | 9 | 20,9% | 43 | 100,0% | 0,909 |
| Female | 32 | 78,0% | 9 | 22,0% | 41 | 100,0% | |
| **Age (years)** | | | | | | | |
| 20 - 50 | 14 | 77,8% | 4 | 22,2% | 18 | 100,0% | |
| 51 - 64 | 32 | 78,0% | 9 | 22,0% | 41 | 100,0% | 0,978 |
| ≥65 | 20 | 80,0% | 5 | 20,0% | 25 | 100,0% | |
| **Type of EGFR mutation** | | | | | | | |
| *Common Mutations* | 51 | 91,1% | 5 | 8,9% | 56 | 100,0% | 0,000 |
| *Uncommon Mutations* | 15 | 53,6% | 13 | 46,4% | 28 | 100,0% | |
| **Comorbid** | | | | | | | |
| None | 31 | 75,6% | 10 | 24,4% | 41 | 100,0% | 0,518 |
| Yes | 35 | 81,4% | 8 | 18,6% | 43 | 100,0% | |
| **Stadium Tumor** | | | | | | | |
| Stage III | 3 | 100,0% | 0 | 0,0% | 3 | 100,0% | 0,357 |
| Stage IV | 63 | 77,8% | 18 | 22,2% | 81 | 100,0% | |
| Total | 66 | 78,6% | 18 | 21,4% | 84 | 100,0% | |

CR= *Complete Response*; PR= *Partial Response*; SD= *Stable Disease*; PD= *Progressive Disease*; EGFR= *Epidermal Growth Factor Receptor; Common mutations*= mutation at exon 19 or 21 L858R*; Uncommon mutations*= mutation at exon 18 or 20

## Discussion

In this study, the percentages from PS2 to PS1 and from PS1 to PS0 were found to be higher in targeted therapy with TKI generation II (42.3% and 7.7%, respectively) than in targeted therapy with TKI generation I (36.2% and 6.9%, respectively), but not statistically significant (Table 2). There are no similar studies assesing the correlation of targeted therapy with subjective responses. Yu-Feng Wei et al showed that patients treated with afatinib had statistically significant improvement in symptoms and quality of life within 4 weeks of starting therapy (from 41.7% to 50.0%) compared with gefitinib (still 44.6% during 4 weeks of therapy), which was assessed by the Lung Cancer Subscales (LCS).[14]

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Yao-Yu Hsieh et al reported the results of several comparisons showing that Afatinib (TKI generation II) had better treatment effectiveness than Gefitinib and Erlotinib (TKI generation I). This may be because patients receiving afatinib had a relatively better ECOG PS, because ECOG PS is a strong prognostic factor in patients with lung cancer.[19] Ming-Yi Huang et al also found better clinical effectiveness on Afatinib (TKI generation II) than Gefitinib and Erlotinib (TKI generation I). Afatinib as TKI generation II has a wider spectrum and stronger binding ability, and theoretically can have better efficacy than TKI generation I (gefitinib and erlotinib).[6]

This study shows that there is a significant correlation between the types of EGFR mutations to subjective responses where the percentage from PS2 to PS1 and from PS2 to PS0 is found to be the highest in common/classical mutations (53.6% and 5.4%, respectively) than uncommon mutations (7.1% and 0%, respectively) (Table 3). There are no similar studies assesing the correlation of EGFR mutations to subjective responses. Uncommon mutations and common mutations have similar clinicopathological features, but uncommon mutations have lower sensitivity and lower response to EGFR-TKI treatment than common mutations. Previous studies by Dan Cheng et al and JL Kuiper et al reported that patients with uncommon mutations were less responsive than those with common mutations, as showed by their shorter (progression-free survival) PFS after EGFR-TKI treatment. Medical-based evidence is only available from retrospective studies and case reports with small samples due to the low incidence of patients with uncommon mutations, and only a small number of relevant studies have been published to date.[20] The results of our study also showed that age, gender, tumor stage and comorbidities did not have a significant correlation to subjective response.

This study showed a significant correlation between targeted therapy and objective response, where the percentage of progressive disease (PD) was found to be highest in subjects receiving targeted therapy with first-generation TKI (27.6%) than subjects receiving targeted therapy with second-generation TKI (7.7%) (Table 4).This is in line with the study conducted by Noorwati Sutandyo et al which showed the the percentage of PD was found to be highest in subjects receiving targeted therapy with first-generation TKI, gefitinib (64.3%) and erlotinib (25%) than second-generation TKI, afatinib (10.7%).[21] This study is also similar to research by Ichidai Tanaka et al, Sojung Park et al and Yi-Cheng Shen et al where the percentage of PD was found to be highest in subjects who received first-generation TKI than second-generation TKI.[22,23,24] The objective response was lower in TKI generation I (gefitinib and erlotinib) than in TKI generation II (afatinib) because TKI generation I reversible inhibited EGFR tyrosine kinase while TKI generation II irreversible inhibited the erythroblastosis oncogene B (ErbB) receptor. In addition, afatinib has the capacity to block signaling through all HER homodimers and heterodimers on the cell surface (wider inhibitory profile) than erlotinib and gefitinib.[25,26] Studies conducted by LUX-Lung 7, ARCHER 1050 and FLAURA have shown that second and third generation TKI-EGFRs are superior to first-generation TKIs as a first-line treatment option for patients with positive EGFR mutations.[25]

This study shows that there is a significant correlation between the types of EGFR mutations to the objective response, where the percentage of PD was found to be the

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highest in subjects with "uncommon mutations" (46.4%) than "common/classical mutations" (8.9%) ( Table 5). This is in line with the study by Sojung Park et al which showed that the percentage of PD was found to be the highest and statistically significant in subjects with “uncommon mutations” (26.5%) than “common/classical mutations” (9.6%).[23] This is also similar to study conducted by Pawel Krawczyk et al that found the highest percentage of PD in “uncommon mutations” (30.8%) compared to “common mutations” (13.2%).[27] Analysis of EGFR-TKI activity against uncommon mutations showed that this mutation was more sensitive to EGFR-TKI generation II with varying sensitivity to afatinib and resistant to EGFR-TKI generation I so that the objective response to PD was higher in uncommon types of EGFR mutations than common/classical mutations.[9] Our results also showed that age, gender, tumor stage and comorbidities did not have a significant correlation to objective response.

## Conclusion

In this study found that lung adenocarcinoma subjects with positive EGFR mutations who received targeted therapy with TKI generation II (afatinib) provided objective response that was significantly better than TKI generation I (gefitinib and erlotinib). The type of EGFR mutation "common/classical mutation" gave a better therapeutic response regardless of the type of TKI target therapy used.

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