Health-related quality of life in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutation with tyrosine kinase inhibitors treatment: a systematic review

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ABSTRACT

Tyrosine Kinase Inhibitors (TKIs) have been recommended by the National Comprehensive Cancer Network (NCCN) as first-line therapy in Non-Small Cell Lung Cancer (NSCLC) patients with EGFR mutations. In addition to prolonging Progression-Free Survival and Overall Survival, one of the treatment goals also considers improving the health-related quality of life (HRQOL), which can help to achieve the patients’ treatment targets. Several systematic review studies related to HRQOL in advanced NSCLC patients have already been carried out, but there are only a few studies of HRQOL in NSCLC patients who experience EGFR mutations and are treated with TKIs in their specific treatment. This Systematic review aims to provide an overview of the impact of TKIs on HRQOL. Relevant studies were identified from Science Direct, PubMed, and Scopus. They were limited to articles explaining TKIs as first-line therapy, written in English, not a systematic review or meta-analysis, and not containing incomplete text. Electronic data-based search produced 112 articles, with 21 articles matched the title and abstract, yet only nine articles met the inclusion and exclusion to be reviewed. In general, the impact of HRQOL on TKIs is better than platinum and placebo-based chemotherapy. Afatinib, erlotinib, and gefitinib further improved HRQOL compared to platinum and placebo-based chemotherapy seen from the improvements in symptoms, physical function, and social function scale. However, gefitinib vs erlotinib showed no significant difference in patients’ the quality of life. TKIs provide better HRQOL than platinum and placebo-based chemotherapy.

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INTRODUCTION

Lung cancer is one type of cancer that has a high incidence and the leading cause of cancer deaths worldwide (Ferlay et al., 2015). Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung can-
cer, which is 85% of all lung cancer events, which is about 80%, is advanced (IIIB / IV). The incidence of epidermal growth factor receptor (EGFR) often occurs in advanced NSCLC patients, around 10-15% of cases in western countries, and up to 50% in Asian countries (Shi et al., 2015). First-line therapy is often used for NSCLC patients with EGFR mutations in the Tyrosine kinase inhibitor (TKIs) such as gefitinib, erlotinib, afatinib, and osimertinib. TKIs have superior Progression-Free Survival (PFS) compared to platinum-based chemotherapy (Ettinger et al., 2017). One of the treatment goals in NSCLC patients with EGFR mutations in addition to prolonging Progression-Free Survival and Overall Survival (OS), also considering HRQOL, where improvement in HRQOL can help achieve patient treatment targets (William et al., 2009). Measurement of Health-Related Quality of Life can help clinicians in making decisions regarding the care and treatment of patients. Besides, it can also be an additional tool for estimating and assessing the risks and benefits of new treatments, where HRQOL can measure the extent to which diseases and therapies received by patients have an impact on the lives of patients (Mckenna, 2011; Damm et al., 2013; Lemonnier et al., 2014). Several systematic review studies related to HRQOL in advanced NSCLC patients have been carried out, in which the study presents HRQOL in NSCLC from both RCT studies, health state utility in metastatic patients, evaluation of measuring instruments/questionnaires most widely used in HRQOL measurements, and HRQOL in NSCLC patients using chemotherapy regimens (Claassens et al., 2011; Matsuda et al., 2012; Damm et al., 2013; Paracha et al., 2018). However, as far as the researchers observed, a systematic review of HRQOL in NSCLC patients had experienced an EGFR mutation and used tyrosine kinase inhibitors in their specific treatment. It is necessary to discuss this further, which is expected to help clinicians in choosing the optimal therapy for NSCLC patients who have EGFR mutations. This study aims to provide an overview of the effects of tyrosine kinase inhibitors on HRQOL.

MATERIALS AND METHODS

Literature searches were conducted in Science Direct, PubMed, and Scopus to identify all articles related to HRQOL in NSCLC patients who experienced EGFR mutations with the treatment of TKIs. The search used the terms and strategies as follows: “Health-Related Quality of Life” AND “Tyrosine Kinase Inhibitor” AND “Non-Small Cell Lung Cancer EGFR Mutation”. The duration of the article search is limited from 2009 to 2019. Literature search based on article selection is provided in Figure 1. The inclusion criteria in this study were: (1) Research that describes Tyrosine Kinase Inhibitors (TKIs) as first-line therapy; (2) Articles that use English. The exclusion criteria in this study were: (1) systematic review and meta-analysis; (2) Research with no full text available (both articles in abstract form, or proceedings). Data were extracted independently, using a standard form to combine data from several selected studies. Data extracted included: first author, year of publication, country, number of patients, treatment, instruments, and HRQOL results.

RESULTS AND DISCUSSION

Searching for Result

The steps in searching for articles in this study have been presented in the PRISMA diagram in Figure 1. As explained in the figure, the total number of articles that have been identified from the database used as many as 122 articles, consisting of PubMed (3 articles), Science Direct (112 articles), and Scopus (7 articles). Titles and abstracts of 122 articles were independently identified assessed by four authors; there were 21 articles selected based on titles and abstracts (12 articles were excluded because they did not fit the inclusion and exclusion criteria). This study used 9 articles for review.

Scoring Characteristic

This research was conducted in several countries such as Hong Kong, China, Italy, Canada, South Korea, Japan, Thailand, Taiwan, North America, Europe, Seoul, Spain, USA, and Germany.

HRQOL Measurement

There were nine studies related to HRQOL in NSCLC patients with EGFR mutations, and using several instruments inpatient HRQOL measurements, can be seen in Table 1. Instruments used in this study were Functional Assessment of Cancer Therapy Lung (FACT-L), Trial Outcome Index (TOI), Lung Cancer Subscale (LCS), the European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire Core 30 items (QLQ-C30), the EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13), and the European Quality of Life 5 Dimension 5 Level (EQ 5D 5L).
<table>
<thead>
<tr>
<th>No</th>
<th>Authors</th>
<th>Negara</th>
<th>Patient</th>
<th>Treatment</th>
<th>Instrument</th>
<th>HRQoL outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mckenna et al., 2011</td>
<td>Hong kong, China</td>
<td>1151</td>
<td>Gefitinib (250 mg/day) Carboplatin/paclitaxel (200 mg/m2)</td>
<td>Functional Assessment of Cancer Therapy-Lung (FACT-L)</td>
<td>-FACT-L: 70.2% (gefitinib) vs 44.5% (carboplatin/paclitaxel) -Trial Outcome Index (TOI) -Lung Cancer Sub-scale (LCS)</td>
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<td></td>
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<td></td>
<td>TOI: 70.2% (gefitinib) vs 38.3% (carboplatin/paclitaxel) LCS: 75.6% (gefitinib) vs 53.9% (carboplatin/paclitaxel)</td>
</tr>
<tr>
<td>2</td>
<td>Lamers et al., 2012</td>
<td>Italy dan Canada</td>
<td>630</td>
<td>Erlotinib (150 mg/day) Cisplatin (80 mg/m2) Gemcitabine 1200 mg/m2</td>
<td>The EORTC Quality of Life Questionnaire Core 30 items (QLQ-C30)</td>
<td>In erlotinib the most common effects are vomiting, constipation, and allergies, whereas platinum-based chemotherapy: pain, dyspnea, diarrhea Improved quality of life (general quality of life and physical function) is better than chemotherapy. Patients using gefitinib and erlotinib decreased in quality of life but did not show a significant difference between the two groups The QOL scale has the same slope between the two arms except for peripheral neuropathy (p = 0.0349)</td>
</tr>
<tr>
<td>3</td>
<td>Kim et al., 2012</td>
<td>South Korea</td>
<td>96</td>
<td>Gefitinib (250 mg/day) Erlotinib (150 mg/day)</td>
<td>The EORTC Quality of Life Questionnaire Core 30 items (QLQ-C30)</td>
<td></td>
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### Table 1 continued

<table>
<thead>
<tr>
<th></th>
<th>Country/Region</th>
<th>n</th>
<th>Treatment</th>
<th>Quality of Life Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>(Wu et al., 2013) China, Jepang, Hongkong, Thailand, Taiwan</td>
<td>94</td>
<td>Gefitinib (250 mg/day)</td>
<td>- Functional Assessment of Cancer Therapy-Lung (FACT-L) - Trial Outcome Index (TOI) - Lung Cancer Subscale (LCS)</td>
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<td></td>
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<td>- FACT-L: 33.7% (tumors progression) vs 16.3% (tumors did not progress) - TOI: 33.7% (tumors progression) vs 13.2% (tumors did not progress) - LCS: 31.7% (tumors progression) vs 15.5% (tumors did not progress)</td>
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<tr>
<td></td>
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<td>- There was a decrease in HRQoL in patients who tumors progress compared to those who did not progression</td>
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<tr>
<td>5</td>
<td>(Hirsh et al., 2013) North America, Europe, Asia</td>
<td>585</td>
<td>Afatinib (40 mg/day) Placebo</td>
<td>- Quality of Life Questionnaire Core 30 items (QLQ-C30) - European Quality of Life 5 Dimensions 5 Level (EQ-5D)</td>
</tr>
<tr>
<td></td>
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<td>- Overall, improvements were observed For the quality of life status (38% (afatinib) vs 29% (placebo) with p &lt; 0.084) - Afatinib significantly (p &lt; 0.05) improved quality of life compared to placebo using the EQ-5D questionnaire</td>
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<table>
<thead>
<tr>
<th></th>
<th>Country</th>
<th>Study Period</th>
<th>Study Design</th>
<th>Medication</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
</table>
| 6 | China, Thailand, South Korea | Geater et al., 2015 | Phase 2 | Afatinib (40 mg/day), Cisplatin 1000 mg/m², Gemcitabine 75 mg/m² | - The EORTC Quality of Life Questionnaire Core 30 items (QLQ-C30)  
- The EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13) | Afatinib improves status health compared to cisplatin and gemcitabine with Status general health (p <0.0001), physical (p <0.0001), role (p = 0.013), and social function scale (p <0.001). Afatinib is better at decreasing delayed symptoms and good quality of life of the time from time to time compared cisplatin and gemcitabine |
| 7 | Italy | Cappuzzo et al., 2016 | Phase 2 | Gefitinib (250 mg/day) | - Functional Assessment of Cancer Therapy-Lung (FACT-L)  
- Trial Outcome Index (TOI)  
- Lung Cancer Subscale (LCS) | FACT-L shows improvement symptoms have a score of 8 (13.1%)  
TOI shows improvement in symptoms have a score of 1 (1.6%)  
CSF shows improvement in symptoms have a score of 7 (11.5%) |
<table>
<thead>
<tr>
<th>8</th>
<th>(Goss et al., 2016)</th>
<th>Canada, Taiwan, Seoul, South Korea, USA, Spain, Jepang</th>
<th>119</th>
<th>Osimertinib (80 mg/day)</th>
<th>-The EORTC Quality of Life Questionnaire Core 30 items (QLQ-C30)</th>
<th>-The EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13)</th>
<th>- Three-quarters of patients improve or remain stable regarding symptoms of cancer pulmonary (QLQ-LC13, n = 85) and inside the domain function of QLQ-C30 (n = 90) at week 54.</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>(Verschuer et al., 2017)</td>
<td>Germany</td>
<td>495</td>
<td>TKIs Platinum-based chemotherapy</td>
<td>-The EORTC QLQ-C30-LC13 questionnaires</td>
<td>-Median Time to deterioration (TTD) for general health status for TKIs of 8.7 months, chemotherapy for 6-7 months. -Median TTD for physical function, role, emotional, fatigue, nausea, dyspnea, and cough of the TKI group had a score (11.6, 7.6, 8.6 months) better than platinum-based chemotherapy (4.4, 4.0, 2.4 months).</td>
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</table>
HRQOL Results

Tyrosine Kinase Inhibitors have been recommended by the National Comprehensive Cancer Network (NCCN) as first-line therapy in the treatment of NSCLC that has an EGFR mutation, which also has superior PFS and OS than platinum-based chemotherapy, but also has superior HRQOL (Verschuer et al., 2017; Ettinger et al., 2017).

These HRQOL parameters are essential in ensuring overall effectiveness in clinical trials in cancer treatment, although most HRQOL is a secondary endpoint in the treatment of cancer patients (Fitieni et al., 2014).

In general, out of 9 studies conducted a review, showed that TKIs had better HRQOL than platinum or placebo-based chemotherapy can be seen in Table 1. This is because TKIs can improve physical function, role, and social function and can control symptoms of disease better than platinum-based chemotherapy (Thongprasert et al., 2011; Maio et al., 2012; Wu et al., 2013; Geater et al., 2015).

In studies of afatinib vs cisplatin/gemcitabine and gefitinib vs. carboplatin /paclitaxel, afatinib and gefitinib can provide significant improvement in symptoms of cough, dyspnea, and pain from lung cancer, where improvement is best in patients who experience early symptoms compared with asymptomatic patients (Wu et al., 2013; Geater et al., 2015).

In studies that were tested with placebo, afatinib could also delay symptoms of cough, dyspnea, and pain, but in a study conducted by (Kim et al., 2012), where comparing fellow TKIs, gefitinib and erlotinib, showed that there was no difference in the quality of life between gefitinib and erlotinib (Hirsch et al., 2013).

In addition to delaying symptoms, the side effects experienced by patients can affect HRQOL in NSCLC patients. In the TKIs group, the most common side effects are skin rashes and diarrhea (Wu et al., 2013; Geater et al., 2015; Verschuer et al., 2017). However, handling appropriate side effects and reducing doses in treatment can improve patient compliance in treatment and improve the quality of life of patients (Hirsch et al., 2013).

Disease development also has an impact on worsening HRQOL. In several studies that have been conducted, it shows that patients who experience tumor development consistently have a more inferior quality of life compared to patients without disease progression (Hirsch et al., 2013; Geater et al., 2015; Walker et al., 2017). The need to delay the development of disease in the treatment of patients, which is a way to maintain better HRQOL and reduce the symptom burden of patients with advanced NSCLC (Walker et al., 2017). Besides, psychological factors also had an impact on HRQOL. Patients who have high levels of depression can aggravate HRQOL, while patients who do not experience depression can slow disease progression and have an impact on the quality of life of patients (Walker et al., 2017; Prell et al., 2019). This is also following the meta-analysis study that has been carried out, where patients whose physical function is impaired but who have a higher emotional well-being show a better rate of recovery and survival compared to patients who experience low emotional stress/welfare (Lamers et al., 2012).

Figure 1: PRISMA Diagram

The limitation in this study is that the study provides information related to secondary endpoints, namely HRQOL, but does not explain other secondary endpoints such as the proportion of patients achieving disease control, and the objective response rate. This is because not all studies that have been reviewed present these data, as well as in measuring the quality of life in patients also using different instruments and there is no standard tool to assess reporting quality of life.

Also, this study only uses studies that have full text available, thus narrowing down relevant articles for review. However, to the best of our knowledge, discussions related to HRQOL in NSCLC patients who have experienced EGFR comprehensively have not been found. Some of the studies carried out were limited to NSCLC patients in general and patients receiving platinum-based chemotherapy, so this study is expected to increase knowledge in the selection of optimal therapy in NSCLC patients with the EGFR mutation.
CONCLUSIONS

Tyrosine kinase inhibitors provide a better HRQOL effect than platinum-based chemotherapy and placebo, but among the types of TKIs have a similar HRQOL effect.

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