RESEARCH ARTICLE

Comparison of the Efficacy and Safety of EFGR Tyrosine Kinase Inhibitor Monotherapy with Standard Second-line Chemotherapy in Previously Treated Advanced Non-small-cell Lung Cancer: a Systematic Review and Meta-analysis

Wei-Xiang Qi, Zan Shen, Feng Lin, Yuan-Jue Sun, Da-Liu Min, Li-Na Tang, Ai-Na He, Yang Yao*

Abstract

Purpose: To compare the efficacy and safety of epidermal growth factor receptor tyrosine kinase inhibitor monotherapy (EFGR-TKIs: gefitinib or erlotinib) with standard second-line chemotherapy (single agent docetaxel or pemetrexed) in previously treated advanced non-small-cell lung cancer (NSCLC). Methods: We systematically searched for randomized clinical trials that compared EGFR-TKI monotherapy with standard second-line chemotherapy in previously treated advanced NSCLC. The end points were overall survival (OS), progression-free survival (PFS), overall response rate (ORR), 1-year survival rate (1-year SR) and grade 3 or 4 toxicities. The pooled hazard ratio (HR) or risk ratio (RR), with their corresponding 95% confidence intervals (CI) were calculated employing fixed- or random-effects models depending on the heterogeneity of the included trials. Results: Eight randomized controlled trials (totally 3218 patients) were eligible. Our meta-analysis results showed that EGFR-TKIs were comparable to standard second-line chemotherapy for advanced NSCLC in terms of overall survival (HR 1.00, 95% CI 0.92-1.10; p=0.943), progression-free survival (HR 0.90, 95% CI 0.75-1.08, P=0.258) and 1-year-survival rate (RR 0.97, 95% CI 0.87-1.08, P=0.619), and the overall response rate was higher in patients who receiving EGFR-TKIs(RR 1.50, 95% CI 1.22-1.83, P=0.000). Sub-group analysis demonstrated that EGFR-TKI monotherapy significantly improved PFS (HR 0.73, 95% CI: 0.55-0.97, p=0.03) and ORR (RR 1.96, 95% CI: 1.46-2.63, p=0.000) in East Asian patients, but it did not translate into increase in OS and 1-year SR. Furthermore, there were fewer incidences of grade 3 or 4 neutropenia, febrile neutropenia and neutrotoxicity in EGFR-TKI monotherapy group, excluding grade 3 or 4 rash. Conclusion: Both interventions had comparable efficacy as second-line treatments for patients with advanced NSCLC, and EGFR-TKI monotherapy was associated with less toxicity and better tolerability. Moreover, our data also demonstrated that EGFR-TKI monotherapy tended to be more effective in East Asian patients in terms of PFS and ORR compared with standard second-line chemotherapy. These results should help inform decisions about patient management and design of future trials.

Keywords: Non-small-cell lung cancer - second-line - erlotinib - gefitinib - docetaxel - pemetrexed - meta-analysis

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Introduction

Lung cancer is still a leading cause of cancer-related deaths worldwide with a 5-year survival of less than 15% (Parkin et al., 2002; Schiller et al., 2002; Kim et al., 2012). Because the majority of people diagnosed with non-small cell lung cancer (NSCLC) are unsuitable for surgery, chemotherapy remains the cornerstone of treatment and prolongs survival with a positive impact on quality of life. However, the majority of patients with advanced NSCLC experience cancer progression after 3-6 months of first-line chemotherapy, and approximately 40% of them have progressive disease during the treatment (Passaro et al., 2011). Of note is that approximately 50% of patients progressing to first-line treatment still have a good performance status, which would make them suitable for second-line therapy (Stinchcombe et al., 2009). At present, although docetaxel and pemetrexed are still considered as standard second-line therapy in patients with good performance status (Fossella et al., 2000; Shepherd et al., 2000; Rossi et al., 2009), there is still much room for improvement in terms of efficacy as well as toxicity.

During the last decades, the second-line treatments for advanced NSCLC have evolved substantially, many trials have been conducted to evaluate the efficacy and safety of docetaxel-based or pemetrexed-based doublets...
therapies in previously treated advanced NSCLC. Though the combined meta-analyses results show that both doublet combination therapy significantly improved progression free survival (PFS) and overall response rate (ORR) compared with single agent chemotherapy, it do not translate into increase in overall survival (OS) (Qi et al., 2012; Qi et al., 2012). Recently, selective targeting of EGFR signaling pathways that contribute to the development and progression of NSCLC has the potential to provide antitumor efficacy with reduced toxicity compared with the conventional cytotoxic agents. Two EGFR TKIs, erlotinib (Tarceva; Genentech, San Francisco, CA) and gefitinib (Iressa; Astra-Zeneca, Wilmington, DE), have received approval for the treatment of advanced NSCLC in the second- or third-line setting worldwide (Shepherd et al., 2005; Thatcher et al., 2005). As both interventions share a common indication, we consider it particularly important to investigate the comparative effectiveness and safety of EGFR-TKIs and standard second-line chemotherapy.

Materials and Methods

Search strategy
We searched PubMed (up to March 2012), Embase (1980 to March 2012), the Cochrane Register of Controlled Trials and China National Knowledge Infrastructure (CNKI: up to March 2012) using various combinations of different terms “advanced NSCLC”, “docetaxel”, “pemetrexed”, “gefitinib”, “erlotinib”, “EGFR-TKIs”, “randomized” and “second-line”. We looked at posters from the annual meetings of the European Society of Medical Oncology (ESMO) and the American Society of Medical Oncology (ASCO) in the past 10 years. We did not set any language restrictions, and reference listed from relevant primary studies and review articles were also examined to find additional publications.

Study selection
The relevant clinical trials were manually selected carefully based on the following criteria: (1) trails comparing EGFR-TKIs monotherapy with standard second-line chemotherapy (single agent docetaxel or pemetrexed); (2) patients were pathologically confirmed of NSCLC and previously treated; (3) prospective phase II and III randomized controlled trials (RCTs); (4) The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. Statistical analysis of the overall hazard ratio (HR) for OS, and PFS, the risk ratio (RR) for overall response rate, 1-year SR, and grade 3 or 4 AEs was calculated using Stata version 12.0 software (Stata Corporation, College Station, Texas, USA). When OS and PFS could not be extracted from the original reports directly in several RCTs, we deciphered them from the survival curve as reported by Parmar et al. (1998). Between-study heterogeneity was estimated using the χ²-based Q statistic (Zintzaras et al., 2005). Heterogeneity was considered statistically significant when Heterogeneity < 0.05 or I² > 50%. If heterogeneity existed, data was analyzed using a random effects model.

Data extraction and Quality assessment
Two independent investigators reviewed the publications and extracted the data. The following information was extracted from each article: (1). Basic information from papers such as, year of publication, phase of trials and author name etc. (2).Characteristics of patients such as: median age, nonsmoker, EGFR mutation and female patients. (3). Information of study designation such as: sample size per-group, study design, randomization scheme, inclusion criteria, and type of end point used. (4). Information of treatment such as: treatment regimen, dose of chemotherapy, withdrawals, median overall survival (OS), progression-free survival (PFS), overall response rate (ORR), 1-year survival rate (1-year SR), and adverse events (AEs) and so on. Available information was extracted and recorded to a data collection form and entered into electronic database. The quantitative 5-point jadad scale was used to assess the quality of included trials based on the reporting of the studies’ methods and results (Moher et al., 1998).

Data analysis
The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. Statistical analysis of the overall hazard ratio (HR) for OS, and PFS, the risk ratio (RR) for overall response rate, 1-year SR, and grade 3 or 4 AEs was calculated using Stata version 12.0 software (Stata Corporation, College Station, Texas, USA). When OS and PFS could not be extracted from the original reports directly in several RCTs, we deciphered them from the survival curve as reported by Parmar et al. (1998). Between-study heterogeneity was estimated using the χ²-based Q statistic (Zintzaras et al., 2005). Heterogeneity was considered statistically significant when Heterogeneity < 0.05 or I² > 50%. If heterogeneity existed, data was analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. A statistical test with a p-value less than 0.05 was considered significant. HR>1 reflected more deaths or progression in EGFR-TKIs monotherapy, and RR>1 indicated more toxicities and overall response rate in EGFR-TKIs monotherapy; and vice versa. The presence of publication bias was evaluated by using the Begg and Egger tests (Begg et al., 1994; Egger et al., 1997; Vandenbroucke et al., 1998). All p-values were two-sided. All CIs had a two-sided probability coverage of 95%.

Results

Study identification and eligibility
After the selection procedure (Figure 1), eight trials were considered eligible. The characteristics of these studies were listed in Table 1. Of these eight trials, two
Table 1. Overview of Studies in the Pooled Analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Phase</th>
<th>Country</th>
<th>Patients</th>
<th>Patient Analyzed per arm</th>
<th>Regimen</th>
<th>Age, median (years)</th>
<th>Female %</th>
<th>EGFR Mutation, %</th>
<th>Nonsmoker, %</th>
<th>Adeno/BAC, MS (mo)</th>
<th>PFS/TTP (mo)</th>
<th>1-year SR, %</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>II</td>
<td>International</td>
<td>141</td>
<td>68</td>
<td>Gefitinib: 250mg/d</td>
<td>68</td>
<td>31</td>
<td>NA</td>
<td>26.5</td>
<td>NA</td>
<td>7.5</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXT: 75mg/m² iv.q.3.w.</td>
<td>73</td>
<td>27</td>
<td>24.7</td>
<td>7.1</td>
<td>3.4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2008</td>
<td>III</td>
<td>International</td>
<td>1466</td>
<td>733</td>
<td>Gefitinib: 250mg/d</td>
<td>61</td>
<td>36.4</td>
<td>11.8</td>
<td>36.6</td>
<td>11.5</td>
<td>7.6</td>
<td>2.2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXT: 75mg/m² iv.q.3.w.</td>
<td>733</td>
<td>33.4</td>
<td>12.5</td>
<td>67.1</td>
<td>24.7</td>
<td>5.7</td>
<td>8</td>
<td>2.7</td>
</tr>
<tr>
<td>2008</td>
<td>III</td>
<td>Japan</td>
<td>140</td>
<td>245</td>
<td>Gefitinib: 250mg/d</td>
<td>79</td>
<td>38.4</td>
<td>NA</td>
<td>45.6</td>
<td>NA</td>
<td>12.2</td>
<td>3.4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXT: 75mg/m² iv.q.3.w.</td>
<td>73</td>
<td>27</td>
<td>NA</td>
<td>69.6</td>
<td>NA</td>
<td>2.2</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>2008</td>
<td>III</td>
<td>Japan</td>
<td>490</td>
<td>244</td>
<td>Gefitinib: 250mg/d</td>
<td>100</td>
<td>33.4</td>
<td>12.5</td>
<td>45.6</td>
<td>NA</td>
<td>8.9</td>
<td>2.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXT: 75mg/m² iv.q.3.w.</td>
<td>60</td>
<td>33.4</td>
<td>12.5</td>
<td>57</td>
<td>69.6</td>
<td>2.7</td>
<td>9</td>
<td>NA</td>
</tr>
<tr>
<td>2010</td>
<td>III</td>
<td>Korea</td>
<td>490</td>
<td>245</td>
<td>Gefitinib: 250mg/d</td>
<td>47</td>
<td>38.4</td>
<td>NA</td>
<td>29.8</td>
<td>NA</td>
<td>78.4</td>
<td>11.5</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXT: 60mg/m² iv.q.3.w.</td>
<td>244</td>
<td>38.4</td>
<td>NA</td>
<td>35.7</td>
<td>NA</td>
<td>14.1</td>
<td>3.4</td>
<td>3.6</td>
</tr>
<tr>
<td>2010</td>
<td>III</td>
<td>Korea</td>
<td>161</td>
<td>82</td>
<td>Gefitinib: 250mg/d. Po.</td>
<td>57</td>
<td>32.9</td>
<td>NA</td>
<td>36.6</td>
<td>20.2</td>
<td>7.5</td>
<td>3.4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXT: 75mg/m² iv.q.3.w.</td>
<td>79</td>
<td>43</td>
<td>NA</td>
<td>67.1</td>
<td>NA</td>
<td>3.1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2010</td>
<td>III</td>
<td>Greece</td>
<td>297</td>
<td>150</td>
<td>Erlotinib 150mg/d. po.</td>
<td>58</td>
<td>43</td>
<td>NA</td>
<td>45.6</td>
<td>NA</td>
<td>12.2</td>
<td>3.4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pemetrexed 500mg/m². iv.q.3.w.</td>
<td>147</td>
<td>39.6</td>
<td>NA</td>
<td>69.6</td>
<td>NA</td>
<td>8.9</td>
<td>2.9</td>
<td>5</td>
</tr>
<tr>
<td>2010</td>
<td>II</td>
<td>China</td>
<td>98</td>
<td>50</td>
<td>Erlotinib 150mg/d. Po.</td>
<td>50</td>
<td>38.4</td>
<td>NA</td>
<td>77</td>
<td>NA</td>
<td>47.8</td>
<td>3.4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pemetrexed 500mg/m². iv.q.3.w.</td>
<td>48</td>
<td>39.6</td>
<td>NA</td>
<td>35.7</td>
<td>NA</td>
<td>7.7</td>
<td>3.6</td>
<td>6</td>
</tr>
<tr>
<td>2012</td>
<td>III</td>
<td>Korea</td>
<td>141</td>
<td>71</td>
<td>Gefitinib: 250mg/d. Po.</td>
<td>58</td>
<td>85.3</td>
<td>23.5</td>
<td>100</td>
<td>73.6</td>
<td>22.2</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pemetrexed 500mg/m². iv.q.3.w.</td>
<td>70</td>
<td>85.1</td>
<td>25.4</td>
<td>18.9</td>
<td>70.5</td>
<td>9</td>
<td>7.3</td>
<td>3</td>
</tr>
</tbody>
</table>

Efficacy

Overall survival: Six of the eight trials reported OS data. Taken together, the pooled hazard ratio for OS did not show significant difference between EGFR-TKIs monotherapy and standard second-line chemotherapy (HR 1.00, 95% CI: 0.92-1.10; p=0.943, Figure 2) without evidence of heterogeneity between studies (p=0.336). The pooled HR for OS was performed using fixed-effect model. Then, we did sub-group analysis according to geographical origin and found that EGFR-TKIs monotherapy was also comparable to standard second-line chemotherapy in Eastern Asian patients (HR 1.00, 95% CI: 0.84-1.20, p=0.973).

Progression-free survival: Six of the eight trials reported PFS data. The pooled hazard ratio for PFS did not show significant difference between EGFR-TKI monotherapy and standard second-line chemotherapy (HR 0.90, 95% CI: 0.75-1.08, P=0.258, Figure 3). There was significant heterogeneity between trials (p=0.003), and the pooled HR for PFS was performed using random-effect model. Sub-group analysis based on geographical origin demonstrated that EGFR-TKI was superior to standard second-line chemotherapy in Eastern Asian patients (HR 0.73, 95% CI: 0.55-0.97, p=0.03) without significant evidence of heterogeneity between studies (p=0.067). Figure 3 Random-effects model of hazard ratio (95% confidence interval) of progression free survival associated with EGFR-TKI monotherapy versus standard second-line chemotherapy.

Overall response rate: All eight trials reported ORR data. The pooled ORR for ORR did not show significant difference between EGFR-TKI monotherapy and standard second-line chemotherapy (RR 1.00, 95% CI: 0.84-1.20, p=0.973).
1-year survival rate: Five trials reported 1-year survival data, the pooled RR for 1-year SR showed that EGFR-TKI monotherapy was comparable to standard second-line chemotherapy in terms of 1-year survival rate (RR 0.97, 95%CI 0.87-1.08, P=0.619, Figure 5). There was no significant heterogeneity (p=0.928), and the pooled RR for 1-year survival rate was performed using fixed-effect model.

There were fewer incidences of grade 3 or 4 neutropenia, febrile neutropenia and neurotoxicity in EGFR-TKI monotherapy group, but more incidences of grade 3 or 4 rash were observed in EGFR-TKI monotherapy group. With regard to the risk of grade 3 or 4 diarrhea, mucositis, nausea and vomiting, equivalent frequencies were found between the two groups (Table 2).

### Table 2. Outcome of Grade 3 or 4 Toxicity Meta-analysis Comparing EGFR-TKIs with Standard Second-line Chemotherapy

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Trials</th>
<th>EGFR-TKIs Monotherapy, n (events/total)</th>
<th>Standard second-line chemotherapy, n (events/total)</th>
<th>Heterogeneity</th>
<th>RR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3–4 Neutropenia</td>
<td>4</td>
<td>36/1117</td>
<td>612/1121</td>
<td>0.003</td>
<td>0.1 (0.038-0.261)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3-4 Febrile neutropenia</td>
<td>3</td>
<td>11/1046</td>
<td>91/1051</td>
<td>0.946</td>
<td>0.136 (0.074-0.249)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3-4 Diarrhea</td>
<td>6</td>
<td>31/1402</td>
<td>27/1421</td>
<td>0.281</td>
<td>1.158 (0.702-1.912)</td>
<td>0.566</td>
</tr>
<tr>
<td>Grade 3-4 Rash</td>
<td>5</td>
<td>30/1331</td>
<td>7/1351</td>
<td>0.402</td>
<td>3.894 (1.795-8.449)</td>
<td>0.001</td>
</tr>
<tr>
<td>Grade 3-4 Mucositis</td>
<td>5</td>
<td>1/1331</td>
<td>6/1351</td>
<td>0.803</td>
<td>0.344 (0.083-1.426)</td>
<td>0.141</td>
</tr>
<tr>
<td>Grade 3-4 Vomiting</td>
<td>5</td>
<td>9/1331</td>
<td>12/1351</td>
<td>0.588</td>
<td>0.756 (0.32-1.787)</td>
<td>0.524</td>
</tr>
<tr>
<td>Grade 3-4 Nausea</td>
<td>6</td>
<td>10/1402</td>
<td>20/1421</td>
<td>0.802</td>
<td>0.511 (0.241-1.084)</td>
<td>0.08</td>
</tr>
<tr>
<td>Grade 3–4 Neurotoxicity</td>
<td>5</td>
<td>2/1157</td>
<td>19/1176</td>
<td>0.149</td>
<td>0.11 (0.026-0.465)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Publication bias: Begg’s funnel plot and Egger’s test were performed to assess the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (p=0.902 for ORR, Figure 6). Then, Egger’s test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias (p=0.239 for OS, p=0.140 for PFS, P= 0.069 for 1-year SR, p=0.538 for ORR, respectively).

**Discussion**

Our meta-analysis, with inclusion of all available randomized trials data regarding EGFR-TKIs versus standard second-line chemotherapy for advanced NSCLC, failed to demonstrate any efficacy differences in terms of OS, PFS and 1-year SR, though EGFR-TKIs monotherapy significantly improved ORR. In addition, EGFR-TKIs monotherapy was clearly more favorable than that of chemotherapy, though both treatments were well-tolerated. The results of our meta-analysis were consistent with those of a previous meta-analysis comparing gefitinib with docetaxel as second-line treatment for advanced NSCLC (Jiang et al., 2011). This former meta-analysis showed a statistically significant improvement in overall response rate with gefitinib whereas the trend for an improved overall survival and progression free survival were not significant. In addition, more grade 3...
or 4 neutropenia and fatigue were observed in docetaxel
group. But this previous meta-analysis included only 4
studies (Cufer et al., 2006; Kim et al., 2008; Maruyama
et al 2008; Lee et al., 2010) instead of 8 studies in our
meta-analysis, representing 4 additional papers (Li et al.,
2010; Vamvakas et al., 2010; Ciuleanu et al., 2012; Sun et
al., 2012). With the present sample size, we therefore had
greater statistical power to evaluate the treatment effect,
which made our results more convincing.

Previous researches had demonstrated that geographic
origin was an important factor influencing survival benefit
from EGFR-TKIs monotherapy (Yang et al., 2008; Jang et al.,
2011). Therefore, we performed subgroup-analysis according to geographic origin and found that
EGFR-TKIs monotherapy significantly improved PFS and
ORR in East Asian patients, but it did not translate
into increase in OS and 1-year SR. In addition, we also
found that the characters that well known to affect the
efficacy and survival to EGFR-TKIs therapy, such as
high proportions of female patients, never-smokers, and
patients with adenocarcinoma histology (Shepherd et
al., 2005; Thatcher et al., 2005; Uhm et al., 2009), were
not substantially different between unselected patients
receiving EGFR-TKIs and receiving single-agent therapy
in this study except for the most recent trial conducted by
Sun et al. (2012). The KCSG-LU08-01 study aimed to
come up with the efficacy of gefitinib with pemetrexed as
second-line treatment in patients with advanced NSCLC.
Results clearly favored gefitinib monotherapy therapy, the
median OS (22.2 mo versus 18.9 mo) and PFS (9.0 mo versus 3.0 mo) was significantly prolonged in gefitinib
monotherapy. Moreover, a significant improvement in
PFS was observed in 33 patients with activating EGFR
mutation (HR0.30; 95%CI 0.13-0.72). Several reasons
might partially explain these differences: Firstly, 85.2%
of included patients in this trial were female, which was
higher than other included trials; secondly, only patients
with adenocarcinoma histology were included in the trial;
finally, all included patients were Asian patients.

The Iressa NSCLC Trial Evaluating REsponseand
Survival versus Taxotere (INTEREST) was the largest
trial evaluating second-line treatment for patients with
advanced NSCLC (Kim et al., 2008). Nearly 1466 patients
were randomly assigned to single-agent docetaxel or
single-agent gefitinib. More frequencies of neutropenia,
asthenia disorders and alopecia were observed in single
docetaxel group, but both treatments were generally
well tolerated. Response rates were similar between
gefitinib and docetaxel (9.1% versus 7.6%, respectively).
Progression-free survival (HR 1.04; 95%CI: 0.93-1.18)
and Overall Survival (HR 1.02; 95%CI: 0.905-1.15) did not significantly differ between the two arms, which
led the authors to recommend gefitinib monotherapy.
In contrast, a recent trial did by Garassini et al. (2012)
found that docetaxel was superior to erlotinib in terms
of PFS in NSCLC harboring EGFR-mutations(HR0.70,
95%CI: 0.53-0.94, p=0.016), though the survival data
was immature. As a result, more trials were still needed
to identify patients who will most likely benefit from the
EGFR-TKIs therapy in the era of individualized therapy.

As the main aims of treatments in the metastatic
setting were to prolong life, provide cancer-related
symptom relief, minimize treatment-related toxicity, and
improve quality of life, toxicity was particularly relevant
for patients with advanced NSCLC. Finding of our study
indicated that there were fewer incidences of grade 3 or
4 neutropenia, febrile neutropenia and neurotoxicity in
EGFR-TKI monotherapy group, but more incidences of
grade 3 or 4 rash were observed in EGFR-TKI
monotherapy group. With regard to the risk of grade 3 or
4 diarrhea, mucositis, nausea and vomiting, equivalent
frequencies were found between the two groups. Therefore, EGFR-TKIs were associated with less toxicity
and better tolerability compared with standard second-line
chemotherapy. In view of this, we believe that erlotinib
and gefitinib could be considered as an effective option
in second-line treatment, owing to their toxicity profile.

Several limitations had to be mentioned in relation
to this meta-analysis. Firstly, this meta-analysis was
not based on individual patient data. And meta-analyses
based on published data tended to overestimate treatment
effects compared with individual patient data analyses.
In addition, it precluded a more comprehensive analysis
such as adjusting for baseline factors and other differences
that existed between the trials from which the data were
pooled. However, analyses using individual patient data
might include fewer studies if all authors did not agree to
submit their full databases to the analyzing group. Another
drawback of analyses based on individual patient data
was the time-consuming review process. Therefore, the
results must be interpreted cautiously, as an individual
patient data-based meta-analysis would give more
reliable estimation than one based on abstracted data.
Secondly, both docetaxel and pemetrexed as second-
line chemotherapy for NSCLC patients were included
in this meta-analysis, which contributed to increase the
clinical heterogeneity of the meta-analysis, but clinical
heterogeneity might improve the generalizability of the
observed heterogeneity. Thirdly, EGFR-mutation
is a major determinant of efficacy for EGFR-TKIs, but
we did not do subgroup-analysis according to EGFR-
mutation because limited data on EGFR-mutation could
be available. Finally, in the meta-analysis of published
studies, publication bias was important because trials
with positive results were more likely to be published
and with null results tend not to be published. Our paper
observed no publication bias and involved six studies
with null results.

In conclusion, our meta-analysis confirmed that the
efficacy of EGFR-TKIs monotherapy were comparable
to standard second-line chemotherapy for patients with
advanced NSCLC, and EGFR-TKIs were associated with
less toxicity and better tolerability. Moreover, our data also
demonstrated that EGFR-TKIs monotherapy tended to be
more effective in East Asian patients in terms of PFS and
ORR compared with standard second-line chemotherapy.
These results should help inform decisions about patient
management and design of future trials.

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References


