Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer

A meta-analysis

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Abstract

Background: The epidermal growth factor receptor tyrosine kinase inhibitors gefitinib and erlotinib are effective for advanced non-small cell lung cancer (NSCLC). This meta-analysis compared their effectiveness and safety.

Methods: We searched systematically in PubMed, ScienceDirect, The Cochrane Library, Scopus, Ovid MEDLINE, EMBASE, Web of Science, and Google Scholar for relevant clinical trials regarding gefitinib versus erlotinib for NSCLC. Antitumor effectiveness (overall survival [OS], progression-free survival [PFS], objective response rate [ORR] and disease control rate [DCR]) and adverse effects [AEs]) were assessed.

Results: Forty studies comprising 9376 participants were included. The results suggested that gefitinib and erlotinib are effective for advanced NSCLC with comparable PFS (95% confidence intervals [CI]: 0.98–1.11, \( P = .15 \)), OS (95% CI: 0.93–1.19, \( P = .45 \)), ORR (95% CI: 0.99–1.16, \( P = .07 \)), and DCR (95% CI: 0.92–1.03, \( P = .35 \)). For erlotinib, dose reduction was significantly more frequent (95% CI: 0.10–0.57, \( P = .001 \)) as were grade 3 to 5 AEs (95% CI: 0.36–0.79, \( P = .002 \)). In the subgroup analysis, the erlotinib group had a significantly higher rate and severity of skin rash, nausea/vomiting, fatigue, and stomatitis.

Conclusions: Gefitinib was proven to be the better choice for advanced NSCLC, with equal antitumor effectiveness and fewer AEs compared with erlotinib. Further large-scale, well-designed randomized controlled trials are warranted to confirm our validation.

Abbreviations: AEs = adverse effects, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence intervals, DCR = disease control rate, EGFR TKI = epidermal growth factor receptor tyrosine kinase, HR = hazard ratios, ILD = interstitial lung disease, NOS = Newcastle–Ottawa scale, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, QOL = quality-of-life, RCT = randomized controlled trial, RR = risk ratios.

Keywords: erlotinib, gefitinib, meta-analysis, non-small cell lung cancer, targeted therapy

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for almost 85% of all lung cancers, and has been the leading cause of cancer-related mortality globally in recent years.[1,2] The discovery and development of therapeutics targeting epidermal growth factor receptor tyrosine kinase (EGFR TKI) was an important clinical advancement for NSCLC treatment in the past decade.[3,4] As the first generation EGFR TKIs, gefitinib (iretisus) and erlotinib (tarceva) have been proved as safe and effective to treat NSCLC. Recently, both EGFR TKIs have been used widely as first line treatments of NSCLC in chemotherapy-naive/EGFR mutation-positive patients, or line 2+ treatment after failure of chemotherapy.[5-7] In clinical practice, it is still controversial whether gefitinib or erlotinib can achieve better therapeutic effectiveness. In a phase III randomized controlled trial (RCT), Urata et al[8] reported a higher incidence of grade 3–4 skin rash but less alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation in the erlotinib arm. Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were similar between the 2 groups. In another phase III RCT, Yang et al[9] reported that gefitinib and erlotinib could achieve a similar effectiveness (PFS, OS, and ORR) for NSCLC with similar toxicities. Some studies showed a better antitumor effectiveness or less toxicity in the gefitinib group for NSCLC.[8-11] However, other studies reported the opposite results and suggested that erlotinib was more effective.[12,13]

To provide the latest and most convincing evidence for the selection of targeted drugs, we conducted a meta-analysis of studies to compare the antitumor effectiveness and adverse effects (AEs) of gefitinib and erlotinib for NSCLC.
2. Materials and methods

This meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) scheme (Table S1, http://links.lww.com/MD/C206). As this meta-analysis was performed based on the published data, ethics committee and/or institutional board approval was not required.

2.1. Search strategy

We systematically searched PubMed, ScienceDirect, the Cochrane Library, Scopus, Web of Science, EMBASE, Ovid MEDLINE, and Google Scholar to identify all the relevant literature published from January 1, 1990 to October 1, 2017. The used combined text and MeSH terms as follows: “gefitinib,” “erlotinib,” and “lung cancer”. The complete search we took for PubMed went: (gefitinib [MeSH Terms] OR gefitinib [Text Word] OR irtux [Text Word] OR ZD1839 [Text Word]) AND (erlotinib [MeSH Terms] OR erlotinib [Text Word] OR tarceva [Text Word] OR OSI-774 [Text Word]) AND (lung cancer [MeSH Terms] OR lung cancer [Text Word] OR lung carcinoma [Text Word] OR lung neoplasm [Text Word] OR NSCLC [Text Word]). The reference lists of the retrieved publications were also searched for further eligible articles.

2.2. Selection criteria

Studies that met the following criteria could be included: language: published in English; population: patients with histologically or cytologically confirmed NSCLC; comparison: gefitinib versus erlotinib; outcome: PFS, OS, ORR, disease control rate (DCR), and AEs. The outcomes were directly or indirectly contained.

The most complete and novel reports could be included for data extraction and assessments if the objects were duplicated. We excluded reviews without original data, meta-analyses, animal experiments, and abstract only.

2.3. Data extraction

The following data were extracted by 2 independent investigators: first author, publication year, nation, number of participants, participant characteristics (age, sex, stage of cancer, pathological type, and treatment line), indices of antitumor effectiveness (PFS, OS, ORR, and DCR) and number of AEs (total and grade 3–5 AEs). Any disagreements were checked by a third investigator.

2.4. Quality assessment

We used the Jadad scale to assess the quality of the RCTs and the Newcastle–Ottawa scale (NOS) to assess the quality of the nonrandomized studies. The Jadad scale (5 points) contained questions for 3 main items: randomization, masking, and accountability of all patients. High quality studies scored ≥ 3 points.[14] The NOS evaluates the quality of studies by analyzing 3 items: selection, comparability, and exposure. High quality studies scored 8–9 points and medium quality studies scored 6–7 points.[15]

2.5. Statistical analysis

All statistical analyses were conducted using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 software (StataCorp LP, College Station, TX). For the analysis of PFS and OS, hazard ratios (HR) with 95% confidence intervals (CI) were used (HR > 1 favors the erlotinib group and HR < 1 favors the gefitinib group). Some studies reported relevant HR information for our outcome directly. In other studies, only Kaplan–Meier curves were provided rather than HR data. In these cases, we extracted and estimated the HR and 95% CI from the Kaplan–Meier curves according to Tierney et al.[16] For the analysis of ORR, DCR, and AEs, pooled risk ratios (RR) with 95% CIs were used (RR > 1 favors the gefitinib group and RR < 1 favors the erlotinib group). Heterogeneity across studies was evaluated using Cochran’s Q test and the I² statistic. An I² > 50% or a P value for the Q test < .1 was regarded as indicating significant heterogeneity and a random-effects model was used; otherwise, a fixed-effects model was used. A subgroup analysis of PFS, OS, and ORR was conducted to check whether the results would change in specially appointed populations according to EGFR mutation status, ethnicity, line of treatment, histology, tumor stage, and study design. Potential publication biases were assessed using Begg’s rank correlation and Egger’s linear regression tests. A P-value < .05 indicated statistical significance.

3. Results

3.1. Search results and quality assessment

We initially identified 5829 potentially eligible studies. After screening, 40 studies involving 9376 patients (5602 patients in the gefitinib group and 3774 patients in the erlotinib group) were included for the final analysis (Fig. 1).[6,8–13,17–49] Among the 40 studies, 3 were RCTs and the other 37 were retrospective studies. The results of quality assessments showed that 27 studies were of high quality (the 3 RCT scored 4–5, 6 retrospective studies scored 9 points and 18 retrospective studies scored 8 points) and 13 studies were of medium quality (9 retrospective studies scored 7 points and 4 retrospective studies scored 6 points). Table 1 summarizes the baseline characteristics and main evaluation indices of the included studies.

3.2. Antitumor effectiveness

We assessed the antitumor effectiveness in 4 aspects (PFS, OS, ORR, and DCR) between the 2 groups.

Figure 1. Flow chart of included studies.
Twenty-seven studies compared PFS (heterogeneity: \( P = 0.05, I^2 = 32\% \)). No significant difference in PFS was found between the 2 groups (95% CI: 0.98–1.11, \( P = 0.15 \); Fig. 2).

Twenty-six studies compared OS (heterogeneity: \( P = 0.001, I^2 = 52\% \)). No significant difference in OS was found between the 2 groups (95% CI: 0.93–1.19, \( P = 0.45 \); Fig. 3).

Seventeen studies compared ORR (heterogeneity: \( P = 0.31, I^2 = 12\% \)). No significant difference in ORR was found between the 2 groups (95% CI: 0.99–1.16, \( P = 0.07 \); Fig. 4A).

Fourteen studies compared DCR (heterogeneity: \( P = 0.03, I^2 = 46\% \)). No significant difference in DCR was found between the 2 groups (95% CI: 0.92–1.03, \( P = 0.35 \); Fig. 4B).

### 3.3 Toxicity

We compared the toxicity in 3 aspects (total AEs, grade 3–5 AEs, and subgroup analysis of 10 most reported AEs) between the 2 groups.

Five studies compared total AEs (heterogeneity: \( P = 0.0008, I^2 = 79\% \)). No significant difference in total AEs was found between the 2 groups (95% CI: 0.87–1.13, \( P = 0.94 \); Fig. 5A).

Nine studies compared grade 3–5 AEs (heterogeneity: \( P = 0.003, I^2 = 66\% \)). The incidence of grade 3–5 AEs was significantly lower in the gefitinib group than in the erlotinib group (95% CI: 0.36–0.79, \( P = 0.002 \); Fig. 5B). Drug discontinuations/reductions because of serious AEs occurred for some patients. Three studies compared drug discontinuations and found no significant difference between the 2 groups (95% CI: 0.59–1.62, \( P = 0.92 \); Fig. S1A, http://links.lww.com/MD/C206). Five studies compared drug reductions and found more drug reductions in the erlotinib group (95% CI: 0.10–0.57, \( P = 0.001 \); Fig. S1B, http://links.lww.com/MD/C206).

In the subgroup analysis of the 10 most reported AEs (skin rash, diarrhea, nausea/vomiting, fatigue, anorexia, interstitial lung disease (ILD), stomatitis, elevated liver enzymes, infection, and neutropenia), the results of all grade AEs showed no significant differences for diarrhea, nausea/vomiting, anorexia, ILD, elevated liver enzymes, infection, and neutropenia between the 2 groups. Erlotinib treatment induced significantly higher rates in skin rash (95% CI: 0.72–0.91, \( P = 0.0002 \), fatigue (95% CI: 0.26–0.90, \( P = 0.02 \), and stomatitis (95% CI: 0.24–0.67, \( P = 0.0004 \) (Fig. S2, http://links.lww.com/MD/C206). The results of grade 3–5 AEs showed no significant differences for anorexia, ILD, elevated liver enzymes, infection, and neutropenia between the 2 groups. Erlotinib treatment induced significantly higher rates of skin rash (95% CI: 0.14–0.44, \( P = 0.00001 \)), diarrhea (95% CI: 0.32–0.76, \( P = 0.001 \)), nausea/vomiting (95% CI: 0.11–0.47, \( P < 0.0001 \), fatigue (95% CI: 0.12–0.76, \( P = 0.01 \), stomatitis (95% CI: 0.08–0.99, \( P = 0.05 \)) and lower rate of...
elevated liver enzymes (95% CI: 1.11–3.71, \(P = .02\)) (Fig. S3, http://links.lww.com/MD/C206).

3.4. Subgroup analysis

To determine whether the antitumor effectiveness of gefitinib versus erlotinib was consistent across various subgroups, the pooled efficacies for PFS, OS, and ORR were estimated within each category of the following classification variables: region, tumor stage, histology, treatment line, EGFR mutation, and study design. The results showed that all subgroup differences were not statistically significant for PFS, OS, and ORR between the 2 treatments (Table 2).

![Figure 2](http://links.lww.com/MD/C206). Forest plot of hazard ratio (HR) of progression-free survival (PFS) associated with gefitinib versus erlotinib. HR = hazard ratio, PFS = progression-free survival.

![Figure 3](http://links.lww.com/MD/C206). Forest plot of hazard ratio (HR) of overall survival (OS) associated with gefitinib versus erlotinib. HR = hazard ratio, OS = overall survival.
Figure 4. Forest plot of risk ratios (RRs) of objective response rate (ORR, A) and disease control rate (DCR, B) associated with gefitinib versus erlotinib. ORR = objective response rate, RRs = risk ratios.

Figure 5. Forest plot of risk ratios (RRs) of all grade adverse effects (A) and grade 3–5 adverse effects (B) associated with gefitinib versus erlotinib. RRs = risk ratios.
3.5. Publication bias

There was no evidence of publication bias for PFS (Begg’s test $P = 0.632$, Egger’s test $P = 0.598$, Fig. 6A) and OS (Begg’s test $P = 0.567$; Egger’s test $P = 0.672$, Fig. 6B).

4. Discussion

Gefitinib and erlotinib have been widely used to treat advanced NSCLC during the past decade. By analyzing 40 high quality studies, we compared the antitumor effectiveness and safety of the 2 agents for NSCLC directly.$[6,8–13,17–49]$ Our meta-analysis provided the most up-to-date medical evidence and showed that the antitumor effectiveness (PFS, OS, ORR, and DCR) was comparable between the 2 agents. The results did not change after subgroup analysis according to region, tumor stage, histology, treatment line, EGFR mutation, and study design. However, the toxicity of erlotinib was significantly higher than that of gefitinib, especially in all-grade/grade 3–5 skin rash, nausea/vomiting, fatigue, and stomatitis.

| Group              | No. of studies | HR (95% CI) | $P$ | $I^2$ (%) | No. of studies | RR (95% CI) | $P$ | $I^2$ (%) | No. of studies | RR (95% CI) | $P$ |
|--------------------|----------------|-------------|-----|-----------|----------------|-------------|-----|-----------|----------------|-------------|-----|
| Total              | 27             | 1.04 (0.98–1.11) | 0.15 | 32        | 26             | 1.05 (0.93–1.19) | 0.45 | 52        | 17             | 1.13 (0.99–1.29) | 0.07 | 13 |
| Region             |                |             |     |           |                |             |     |           |                |             |     |
| Asia               | 24             | 1.04 (0.97–1.10) | 0.26 | 38        | 21             | 1.04 (0.89–1.21) | 0.61 | 58        | 13             | 1.14 (0.99–1.31) | 0.06 | 21 |
| Europe             | 2              | 1.24 (0.88–1.74) | 0.22 | 0         | 3              | 1.11 (0.81–1.51) | 0.52 | 27        | 3              | 0.14 (0.70–1.86) | 0.61 | 0  |
| North America      | 1              | 1.09 (0.84–1.42) | 0.52 | NA        | 2              | 1.08 (0.83–1.39) | 0.58 | 22        | 1              | 0.52 (0.16–1.73) | 0.28 | NA |
| Tumor stage        |                |             |     |           |                |             |     |           |                |             |     |
| IIIb–IV            | 25             | 1.04 (0.99–1.11) | 0.14 | 37        | 24             | 1.05 (0.92–1.19) | 0.47 | 56        | 16             | 1.13 (0.99–1.29) | 0.06 | 15 |
| I–IV               | 2              | 0.95 (0.54–1.64) | 0.05 | 0         | 2              | 1.06 (0.54–2.08) | 0.86 | 0         | 1              | 0.42 (0.04–4.48) | 0.47 | NA |
| Histology          |                |             |     |           |                |             |     |           |                |             |     |
| Nonsquamous        | 14             | 1.05 (0.97–1.14) | 0.24 | 48        | 13             | 1.06 (0.88–1.24) | 0.56 | 64        | 10             | 1.12 (0.98–1.28) | 0.11 | 38 |
| Squamous included  | 12             | 1.03 (0.95–1.12) | 0.05 | 0         | 12             | 1.04 (0.93–1.15) | 0.51 | 43        | 7              | 1.26 (0.81–1.96) | 0.31 | 0  |
| Unclear            | 1              | 3.05 (0.84–11.09) | 0.09 | NA        | 1              | 1.34 (0.49–3.67) | 0.57 | NA        |                 |              |     |
| Treatment line     |                |             |     |           |                |             |     |           |                |             |     |
| First line included| 15             | 1.10 (0.99–1.21) | 0.07 | 43        | 13             | 0.98 (0.76–1.27) | 0.89 | 73        | 9              | 1.10 (0.94–1.28) | 0.26 | 42 |
| Second line or later| 10             | 0.66 (0.94–1.09) | 0.73 | 7         | 10             | 1.03 (0.94–1.14) | 0.48 | 0         | 8              | 1.22 (0.96–1.55) | 0.11 | 0  |
| First line only    | 3              | 0.89 (0.32–2.49) | 0.82 | 66        | 2              | 0.24 (0.04–1.43) | 0.12 | 75        |                 |              |     |
| Second line only   | 4              | 0.95 (0.78–1.16) | 0.60 | 0         | 4              | 1.08 (0.83–1.41) | 0.58 | 19        | 3              | 1.40 (0.73–2.69) | 0.31 | 0  |
| Third line only    | 2              | 1.02 (0.58–1.82) | 0.94 | 0         | 3              | 0.94 (0.80–1.10) | 0.47 | 0         | 2              | 1.07 (0.26–4.50) | 0.92 | 5  |
| Unclear            | 2              | 1.48 (0.72–3.08) | 0.29 | 43        | 3              | 1.30 (0.91–1.88) | 0.15 | 0         |                 |              |     |
| EGFR mutation      |                |             |     |           |                |             |     |           |                |             |     |
| Partial mutation   | 12             | 1.05 (0.96–1.16) | 0.30 | 18        | 12             | 1.16 (0.94–1.44) | 0.16 | 66        | 9              | 1.17 (0.10–1.36) | 0.05 | 28 |
| All mutation       | 11             | 1.12 (0.97–1.28) | 0.12 | 46        | 9              | 1.00 (0.84–1.20) | 0.99 | 49        | 4              | 0.89 (0.63–1.25) | 0.5  | 0  |
| Unclear            | 4              | 1.01 (0.93–1.10) | 0.84 | 38        | 5              | 1.01 (0.91–1.13) | 0.83 | 0         | 4              | 1.26 (0.84–1.87) | 0.26 | 2  |
| Study design       |                |             |     |           |                |             |     |           |                |             |     |
| Retrospective study| 24             | 1.03 (0.97–1.10) | 0.37 | 34        | 23             | 1.03 (0.89–1.19) | 0.69 | 56        | 14             | 1.15 (0.99–1.34) | 0.07 | 15 |
| RCT                | 3              | 1.11 (0.96–1.27) | 0.15 | 32        | 3              | 1.11 (0.93–1.32) | 0.25 | 0         | 3              | 1.07 (0.82–1.39) | 0.62 | 30 |

HR= hazard ratio, NA = not available, ORR = objective response rate, ORR = objective response rate, PFS = progression-free survival, RCT = randomized controlled trial, RR = relative risk

Figure 6. Begg’s and Egger’s test for the comparisons of progression-free survival (PFS, A) and overall survival (OS, B). OS = overall survival, PFS = progression-free survival.
Gefitinib and erlotinib are 2 similar, but different, small molecules with different binding capabilities, pharmacokinetics, and pharmacodynamic properties related to their different molecular structures.[50–52] As first generation EGFR TKIs, whether these differences could cause different antitumor effectiveness is controversial.[53,54] In our analysis, almost all the included studies showed no differences in all indices of antitumor effectiveness, which was the basis of our results. Only one study reported an unfavorable result against erlotinib, with both lower PFS and OS, which might relate to the presence of more patients with nonadenocarcinoma in the erlotinib group.[12] Our results also showed a tendency toward prolonged median PFS (gefitinib group, 7.6 months vs 4.9 months; erlotinib group, 7.9 months vs 3.2 months) and OS (gefitinib group, 21.1 months vs 12.0 months; erlotinib group, 15.5 months vs 11.3 months) in patients with adenocarcinoma as compared with those with squamous-included NSCLC. However, no difference was found between the 2 EGFR TKIs in this subgroup.

In the subgroup of EGFR mutation, we also found no difference between the 2 EGFR TKIs in the comparison of antitumor effectiveness. However, our results proved indirectly that both gefitinib and erlotinib are more suitable for EGFR mutation-positive NSCLC. Both median PFS (gefitinib group, 10.4 months vs 4.9 months; erlotinib group, 10.0 months vs 3.5 months) and OS (gefitinib group, 22.6 months vs 16.0 months; erlotinib group, 20.9 months vs 12.0 months) were longer in all EGFR mutation-positive subgroup than in the partial mutation-positive subgroup. Thus, we observed the phenomenon that the proportion of EGFR mutations increased year by year in the treatment of EGFR TKIs (Table 1). Multiple isoforms (exon 19, exon 21 or others) of EGFR mutations were identified and which is more suitable for gefitinib or erlotinib remains unclear. A phase III RCT compared gefitinib and erlotinib in EGFR mutation-positive NSCLC and found that EGFR exon 19 mutations were associated with a significantly higher RR and longer median OS than those with exon 21 mutations treated with erlotinib or gefitinib. However, no difference was found between gefitinib and erlotinib for both mutations.[53] Similar results were reported by another RCT involving multiple mutation isoforms (exon 19, exon 21, T790M, etc.).[18] However, Kuan’s et al[19] study suggested that erlotinib treatment was associated with significantly longer progression-free survival and lower early risk of progression than gefitinib in patients with exon 19 deletions. Limited by the quantity of published studies and included patients, further larger, well-designed randomized controlled trials focusing on single EGFR mutations are warranted to select the best EGFR TKIs.

It remains a matter of debate regarding which treatment line EGFR TKIs should be used in for NSCLC. In mainstream thinking, EGFR TKIs were regarded as line 2 or later treatments after chemotherapy failure or line 1 treatment for patients unable to tolerate chemotherapy. However, Table 1 shows that more studies used gefitinib and erlotinib as the first line treatment for advanced NSCLC.[13,35,46] In our analysis, both median PFS (11.4 months vs 3.75 months) and OS (26.15 months vs 12.3 months) were longer in the first line treatment subgroup than in the subgroup of line 2 or later. This comparison was not accurate enough because of too many confounders. However, no differences were found in PFS, OS, and DCR between gefitinib and erlotinib in each subgroup according to treatment line. Wu et al. conducted a phase III RCT and suggested that first-line erlotinib could provide a significant improvement in PFS versus gemcitabine-cisplatin in patients with EGFR mutation-positive NSCLC.[54] Another phase III RCT suggested that PFS was significantly longer with gefitinib for patients with mutation-positive NSCLC as compared with carboplatin+paclitaxel.[55] Similar results were reported by several other high-quality RCTs.[56–58] Based on these positive results, gefitinib was approved by the FDA for the first-line treatment of EGFR mutation-positive NSCLC.[59] In the 2017 NCCN guidelines for NSCLC, both gefitinib and erlotinib were also suggested as first-line treatments of EGFR mutation-positive NSCLC.[60]

Drug toxicity is an important problem for erlotinib. In our analysis, high incidences of drug reactions, skin rash, diarrhea, nausea/vomitting, fatigue, and stomatitis were found in the erlotinib arm. Although the results might not affect the survival time, they greatly affected the quality-of-life (QOL) of the patients.[61,62] Two reasons might be responsible for these results: the oral dose of erlotinib (150 mg/day) was closer to its maximum tolerated dose (150 mg/day) compared with that of gefitinib (oral dose: 250 mg/d; maximum tolerated dose: 600 mg/day);[63,64] the pharmacokinetics are different between the 2 EGFR TKIs. After absorption, more gefitinib is accumulated in tumor tissue than in the plasma, which is opposite to the kinetics of erlotinib.[65] In the subgroup analysis by region, more severe AEs were found in the population of East Asia compared with those in Europe and America (gefitinib group, 18/166 [10.84%] vs 21/1020 [2.06%]; P = .003; erlotinib group, 17/91 [18.68%] vs 22/570 [3.16%], P = .011). ILD, one of the most important AEs, can lead to a worse prognosis and an increased risk of death.[66] However, the results of our analysis and of other published studies show that most ILDs were reported in the East Asia population and are rare in Western populations. The smaller physique of Asians might explain this phenomenon. Yeo reduced the dose of erlotinib down to 25 mg/day in a retrospective study and achieved a similar or even better prognosis compared with the standard dose.[67] Similar results were also reported in other retrospective studies.[110,111] Therefore, we suggest that individualized drug doses, based on weight or body surface area, might be more suitable than a fixed oral dose. Further large, well-designed RCTs are needed to confirm the best dose of gefitinib and erlotinib for each patient.

Several potential limitations should be taken into consideration when interpreting our results. First, to ensure the quality of the data, we only included high-quality studies published in English, which might result in a language bias. Second, only 3 RCTs were included, which would weaken the quality of the results. Third, significant heterogeneity existed in some comparisons (OS and total-grade 3–5 AEs), which would weaken the reliability of the results. Fourth, the type and rate of EGFR mutations were different between the included studies, which might increase the heterogeneity and weaken the quality of the results. Fifth, QOL and survival time were 2 equally important evaluating indicators for treatment. QOL could not simply be replaced by the quantity of AEs. However, no quality-of-life was compared between the 2 EGFR TKIs in all the included studies. Thus, we suggest that quality-of-life should be regarded as an essential indicator in future studies of drug evaluation.

Based on the present evidence, both gefitinib and erlotinib are effective for advanced NSCLC, with comparable PFS, OS, ORR, and DCR. Erlotinib treatment induced a significantly higher rate and severity in skin rash, nausea/vomiting, fatigue, and stomatitis, which might have caused the observed higher rate of dose reduction. Thus, we suggest that individualized drug doses, based on weight or body surface area, might be more suitable than a fixed oral dose for both agents. However, because of the inherent...
limitations of our meta-analysis, further large-scale, high-quality RCTs are warranted to confirm this conclusion.

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References
[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[3] Liu TC, Jin X, Wang Y, et al. Role of epidermal growth factor receptor in lung cancer and targeted therapies. Am J Cancer Res 2017;7:187–202.
[4] Malik PS, Jain D, Kumar L. Epidermal growth factor receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer. Oncology 2016;91:26–34.
[5] Cheng Y, Murakami H, Yang PC, et al. Randomized phase II trial of gefitinib with and without pemetrexed as first-line therapy in patients with advanced nonsquamous non-small cell lung cancer with activating epidermal growth factor receptor mutations. J Clin Oncol 2016;34:1258–66.
[6] Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Br J Cancer 2017;116:568–74.
[7] Peters S, Stathel RA, Dasu U, et al. Randomized phase III trial of erlotinib versus docetaxel in patients with advanced squamous cell non-small-cell lung cancer failing first-line platinum-based doublet chemotherapy stratified by versus with versus without. The European Thoracic Oncology Platform (ETOP) EMPHASIS-lung Trial. J Thorac Oncol 2017;12:752–62.
[8] Urata Y, Katakami N, Morita S, et al. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. J Clin Oncol 2016;34:3248–57.
[9] Shin HJ, Kim TO, Kang HW, et al. Comparison of therapeutic efficacy of gefitinib and erlotinib in patients with squamous cell lung cancer. Tuberculosis Respir Dis 2011;71:15–23.
[10] Sato S, Kurishima K, Miyazaki K, et al. Efficacy of tyrosine kinase inhibitors in non-small-cell lung cancer patients undergoing dose reduction and those with a low body surface area. Mol Clin Oncol 2014;2:604–8.
[11] Passaro A, Di Maio M, Del Signore E, et al. management of nonhematologic toxicities associated with different EGFR-TKIs in advanced NSCLC: a comparison analysis. Clin Lung Cancer 2014;15:307–12.
[12] Fan WC, Yu CJ, Tsai CM, et al. Different efficacies of erlotinib and gefitinib in Taiwanese patients with advanced non-small cell lung cancer: a retrospective multicenter study. J Thorac Oncol 2011;6:148–55.
[13] Kuan FC, Li SH, Wang CL, et al. Analysis of progression-free survival of first-line tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring leu858Arg or exon 19 deletions. Oncotarget 2017;8:143–53.
[14] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.
[15] Wells GA, Shea BJ, O’Connell D, et al. The Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Environ 2014;18:727–34.
[16] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
[17] Popat S, Barbashano Y, Ashley S, et al. Erlotinib, docetaxel, and gefitinib in sequential cohorts with relapsed non-small cell lung cancer. Lung Cancer 2008;59:227–31.
[18] Emery IF, Bartelli C, Auclair PL, et al. Response to gefitinib and erlotinib in non-small cell lung cancer: a retrospective study. BMC Cancer 2009;9:333.
[19] Kim ST, Lee J, Kim JH, et al. Comparison of gefitinib versus erlotinib in patients with non-small cell lung cancer who failed previous chemotherapy. Cancer 2010;116:3025–33.
[20] Hotta K, Kurita K, Takigawa N, et al. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese patients with non-small cell lung cancer: the Okayama Lung Cancer Study Group experience. J Thorac Oncol 2010;5:179–84.
[21] Hong J, Kyung SY, Lee SP, et al. Pemetrexed versus gefitinib or erlotinib in previously treated patients with non-small cell lung cancer. Korean J Intern Med 2010;25:294–300.
[22] Kappers I, Vollebergh MA, van Tinteren H, et al. Soluble epidermal growth factor receptor (sEGFR) and carcinoembryonic antigen (CEA) concentration in patients with non-small cell lung cancer: correlation with survival after erlotinib and gefitinib treatment. Ecanermedicals-science 2010;4:178.
[23] Wu JY, Wu SG, Yang CH, et al. Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations. Lung Cancer 2011;72:205–12.
[24] Togashi Y, Masago K, Fujita S, et al. Differences in adverse events between 250mg daily gefitinib and 150mg daily erlotinib in Japanese patients with non-small cell lung cancer. Lung Cancer 2011;74:98–102.
[25] Jung M, Kim SH, Lee YJ, et al. Prognostic and predictive value of CEA and CYFRA 21-1 levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib. Exp Ther Med 2011;2:685.
[26] Wu WS, Chen YM, Tsai CM, et al. Erlotinib has better efficacy than gefitinib in adenocarcinoma patients without EGFR-activating mutations, but similar efficacy in patients with EGFR-activating mutations. Exp Ther Med 2012;3:207–13.
[27] Kim ST, Uhlm JE, Lee J, et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. Lung Cancer 2012;75:82–8.
[28] Suzumura T, Kimura T, Kudoh S, et al. Reduced CYP2D6 function is associated with gefitinib-induced rash in patients with non-small cell lung cancer. BMC Cancer 2012;12:568.
[29] Yoshida T, Yamada K, Arumaa K, et al. Comparison of adverse events and efficacy between gefitinib and erlotinib in patients with non-small-cell lung cancer: a retrospective analysis. Med Oncol 2013;30:149.
[30] Shao YY, Shau WY, Lin ZZ, et al. Comparison of gefitinib and erlotinib efficacies as third-line therapy for advanced non-small-cell lung cancer. Eur J Cancer 2013;49:106–14.
[31] Lee E, Keam B, Kim DW, et al. Erlotinib versus gefitinib for control of leptomeningeal carcinomatosis in non-small-cell lung cancer. J Thorac Oncol 2013;8:1069–74.
[32] Yu S, Wang Y, Li J, et al. Gefitinib versus erlotinib as salvage treatment for lung adenocarcinoma patients who benefited from the initial gefitinib: a retrospective study. Thoracic Cancer 2013;4:109–16.
[33] Locatelli-Sanchez M, Couraud S, Arpin D, et al. Routine EGFR molecular analysis in non-small-cell lung cancer patients is feasible: exons 18-21 sequencing results of 753 patients and subsequent clinical outcomes. Lung 2013;191:491–9.
[34] Lim SH, Lee JY, Sun JM, et al. 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;9:506–11.
[35] Lin GN, Peng JW, Liu PP, et al. Elevated neutrophil-to-lymphocyte ratio predicts poor outcome in patients with advanced non-small-cell lung cancer receiving first-line gefitinib or erlotinib treatment. Asia Pac J Clin Oncol 2014;10:2696–703.
[36] Ren S, Su C, Wang Z, et al. Epithelial phenotype as a predictive marker for response to EGFR-TKIs in non-small cell lung cancer patients with wild-type EGFR. Int J Cancer 2014;135:2962–71.

[37] Li J, Li X, Ren S, et al. mir-200c overexpression is associated with better efficacy of EGFR-TKIs in non-small cell lung cancer patients with EGFR wild-type. Oncotarget 2014;5:7902–16.

[38] Takeda M, Okamoto I, Nakagawa K. Survival outcome assessed according to tumor response and shrinkage pattern in patients with EGFR mutation-positive non-small cell lung cancer treated with gefitinib or erlotinib. J Thorac Oncol 2014;9:220–4.

[39] Chanprapaph K, Pongcharoen P, Vachiramon V. Cutaaneous adverse events of epidermal growth factor receptor inhibitors: A retrospective review of 99 cases. Indian J Dermatol Venerol Leprol 2015;81:547.

[40] Otsuka T, Mori M, Yano Y, et al. Effectiveness of tyrosine kinase inhibitors in Japanese patients with non-small cell lung cancer harboring minor epidermal growth factor receptor mutations: results from a multicenter retrospective study (HANSHIN Oncology Group 0212). Anticancer Res 2015;35:3885–91.

[41] Song Z, Zhang Y. Efficacy of gefitinib or erlotinib in patients with squamous cell lung cancer. Arch Med Sci 2015;11:164–8.

[42] Koo DH, Kim KP, Choi CM, et al. EGFR-TKI is effective regardless of treatment timing in pulmonary adenocarcinoma with EGFR mutation. Cancer Chemother Pharmacol 2015;75:197–206.

[43] Lin JJ, Cardarelli S, Lydon CA, et al. Five-Year Survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. J Thorac Oncol 2016;11:536–65.

[44] Ruan Y, Jiang J, Guo L, et al. Genetic Association of curative and adverse reactions to tyrosine kinase inhibitors in Chinese advanced non-small cell lung cancer patients. Sci Rep 2016;6:23368.

[45] Hirano R, Uchino J, Ueno M, et al. Low-dose epidermal growth factor receptor (EGFR)-tyrosine kinase inhibition of EGFR mutation-positive lung cancer: therapeutic benefits and associations between dosage, efficacy and body surface area. Asian Pac J Cancer Prev 2016;17:785–9.

[46] Suh KJ, Keam B, Kim M, et al. Serum neuron-specific enolase levels predict the efficacy of first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Clin Lung Cancer 2016;17:245–52.

[47] Kashima J, Okuma Y, Mowa M, et al. Survival of patients with brain metastases from non-small cell lung cancer harboring EGFR mutations treated with epidermal growth factor receptor tyrosine kinase inhibitors. Med Oncol 2016;33:129.

[48] Krawczyk P, Kowalski DM, Ramlau R, et al. Comparison of the effectiveness of erlotinib, gefitinib, and afatinib for treatment of non-small cell lung cancer in patients with common and rare EGFR gene mutations. Oncol Lett 2017;13:4433–44.

[49] Li MX, He H, Ruan ZH, et al. Central nervous system progression in metastatic lung adenocarcinoma treated with EGFR-TKIs: a review of 99 cases. Indian J Dermatol Venereol Leprol 2015;81:547.

[50] Yun CH, Boggon TJ, Li Y, et al. Mechanism of activation and insights into differential inhibitor sensitivity. Cancer Cell 2007;11:217–27.

[51] Ling J, Fetterman S, Lum BL, et al. Effect of food on the pharmacokinetics of gefitinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals. Anticancer Drugs 2008;19:209–16.

[52] Cantarini MV, McFarquhar T, Smith RP, et al. Relative bioavailability and safety profile of gefitinib administered as a tablet or as a dispersion preparation via drink or nasogastric tube: results of a randomized, open-label, three-period crossover study in healthy volunteers. Clin Ther 2004;26:1630–6.

[53] Russo A, Franchina T, Riccardi GR, et al. A decade of EGFR inhibition in EGFR-mutated non small cell lung cancer (NSCLC): old successes and future perspectives. Oncotarget 2015;6:26814–25.

[54] Wu YL, Zhou C, Liem CK, et al. First-line erlotinib versus gemcitabine/ cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol 2015;26:1883–9.

[55] Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011;29:2866–74.

[56] Fiala O, Pesek M, Finek J, et al. Comparison of EGFR-TKI and chemotherapy in the first-line treatment of advanced EGFR mutation-positive NSCLC. Neoplasma 2013;60:425–31.

[57] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:733–42.

[58] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.

[59] Kazandjian D, Blumenthal GM, Yuan W, et al. FDA approval of gefitinib for the treatment of patients with metastatic EGFR-mutation-positive non-small-cell lung cancer. Clin Cancer Res 2016;22:1307–12.

[60] National Comprehensive Cancer Network. (NCCN) Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer (Version 5. 2017). Available at: https://www.nccn.org/professionals/physician_gls/pdf/scclc.pdf. Accessed March 16, 2017.

[61] Yang SC, Lai WW, Houe TR, et al. Health-related quality of life after first-line anti-cancer treatments for advanced non-small cell lung cancer in clinical practice. Qual Life Res 2016;25:1441–9.

[62] Wu YL, Fukuoka M, Mok TS, et al. Tumor response and health-related quality of life in clinically selected patients from Asia with advanced non-small-cell lung cancer treated with first-line gefitinib: post hoc analyses from the IPASS study. Lung Cancer 2013;81:280–7.

[63] Baselga J, Rischin D, Ranson M, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 2002;20:4292–302.

[64] Hidalgo M, Sui LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001;19:3267–79.

[65] Rukazenkov Y, Speake G, Marshall G, et al. Epidermal growth factor receptor tyrosine kinase inhibitors: similar but different? Anticancer Drugs 2009;20:856–66.

[66] Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 2006;24:25492556.

[67] Yeo WL, Riely GJ, Yeap BY, et al. Erlotinib at a dose of 25 mg daily for non-small cell lung cancers with EGFR mutations. J Thorac Oncol 2010;5:1048–53.

[68] Takashima N, Kimura T, Watanabe N, et al. Prognosis in patients with non-small cell lung cancer who received erlotinib treatment and subsequent dose reduction due to skin rash. Onkologie 2012;35:747–52.

[69] Sato H, Inoue A, Kobayashi K, et al. Low-dose gefitinib treatment for patients with advanced non-small cell lung cancer harboring sensitive epidermal growth factor receptor mutations. J Thorac Oncol 2011;6:1413–7.

[70] Sim SH, Keam B, Kim DW, et al. The gefitinib dose reduction on survival outcomes in epidermal growth factor receptor mutant non-small cell lung cancer. J Cancer Res Clin Oncol 2014;140:2135–42.