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Original article

# Maintenance therapy of gefitinib for non-small-cell lung cancer after first-line chemotherapy regardless of epidermal growth factor receptor mutation: a review in Chinese patients

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## Abstract

**Purpose:**
Gefitinib is a well known therapy for non-small-cell lung cancer (NSCLC). The purpose of this study was to review clinical reports of gefitinib as maintenance therapy after first-line chemotherapy regardless of epidermal growth factor receptor (EGFR) mutation, and assess its efficacy and safety in Chinese patients.

**Materials and methods:**
Systematic computerized searches of the following databases were conducted from the start of each database up to July 2012; these include Medline, EMBASE, CNKI and www.clinicaltrials.gov. Terms searched include 'non-small-cell lung cancer', 'NSCLC', 'lung cancer', 'lung tumor', 'gefitinib', 'Iressa', 'EGFR' and 'epidermal growth factor receptor tyrosine kinase inhibitors'. A total of 22 studies were reviewed.

**Results:**
In general, the overall response rate (ORR), disease control rate (DCR) and one year survival (OYS) of gefitinib maintenance therapy were 30.89%, 67.5% and 50.6% respectively, in addition, the median overall survival (OS) and median progression free survival (PFS) were 13.09 and 7.88 months respectively. Moreover, ORR, DCR, median survival time (MST) and PFS of female, nonsmoking, lung adenocarcinoma (LAC) patients and patients with rash had higher performance than male, smoking, non-LAC patients and patients without rash ($p < 0.05$). The adverse events (AEs) were mainly skin rashes and diarrhea, most of which were grades 1 or 2 and were well tolerated.

**Conclusion:**
Gefitinib produced encouraging efficacy, safety and survival when delivered as maintenance therapy for NSCLC in Chinese patients after first-line chemotherapy regardless of EGFR mutation, especially for the patients who were female, non-smokers, LAC and with rash. Key limitations of this review include limited subgroup data, small sample sizes, and the lack of EGFR/KRAS data.

## Introduction

The epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib and erlotinib both of which compete with adenosine triphosphate (ATP) for binding to the tyrosine kinase pocket of the receptor, have been extensively studied as well as applied to the treatment of non-small-cell lung cancer (NSCLC)[1–3]. They are thought to only be effective in cancers with

mutated or overactive EGFR. In Asia, the Chinese represent the largest group of people, with a population of approximately 1.7 billion at the end of 2011. In January 2003, gefitinib was introduced into the Chinese market. However, due to the lack of basic research guidance and no recommendations from the NCCN guidelines at that time, a large number of Chinese NSCLC patients were recruited to accept gefitinib treatment without being tested for the EGFR mutation, a test that would help determine which patients respond best to the drug. However, this sacrifice provided an opportunity to understand the efficacy and safety of gefitinib as a maintenance therapy regardless of EGFR mutation, and whether this kind of therapy could be accepted in medical institutions that were not qualified to test for the EGFR mutation. This study reviews the efficacy, safety, and adverse-event profile of gefitinib as a maintenance therapy after first-line chemotherapy to NSCLC regardless of EGFR mutation in Chinese patients.

## Materials and methods

### Identification and eligibility of study reports

Systematic computerized searches of the Medline databases, Chinese biomedical literature database (CNKI), and www.clinicaltrials.gov were performed using free text and the Medical Subjects Headings (MeSH) terms 'non–small-cell lung cancer', 'NSCLC', 'lung cancer', 'lung tumor', 'gefitinib', 'Iressa', 'EGFR' and 'epidermal growth factor receptor tyrosine kinase inhibitors'. The search period was from the start of each database up to July 2012 and no language restrictions were added.

### Selection criteria of study reports

The search was for studies on gefitinib as maintenance therapy in patients with advanced (inoperable stage IIIB or IV) NSCLC who have accepted standard first-line chemotherapy. The following were the selection criteria: (i) gefitinib treatment alone as maintenance therapy; (ii) studies with full text articles; (iii) studies did not concern EGFR mutation. Exclusion criteria were the following: (1) no original research (reviews, editorials, and non-research letters); (2) lost follow-up rate $\geq$20%; (3) studies where patients had received other chemotherapy than gefitinib at the same time.

### Treatment plan assessment of study reports

Patients of all studies received standard first-line chemotherapy including platinum-based doublet regimens (cis/carboplatin plus gemcitabine, taxane or navelbine respectively) and total number of cycles was no more than six. After that, patients were switched to receive gefitinib 250 mg orally per day if they completed 4–6 cycles of chemotherapy or underwent unacceptable chemotherapy associated toxicity. Gefitinib treatment was continued until intolerable toxicity, disease progression or death.

### Observation data of study reports

The following information was extracted from each article: first author, date on which the study was published, the exact data of total and practical number in case groups, smoking history and histology, patient age, sex, overall survival (OS), one year survival (OYS), median survival time (MST), overall response rate (ORR), disease control rate (DCR), progression free survival (PFS) and grade 1 to 4 adverse effects (AEs).

### Statistical analysis

Descriptive statistics were used to assess overall efficacy and safety of gefitinib as a maintenance therapy, including the mean, standard deviation and 95% confidence interval (CI). Fixed-effect and random-effect models were performed to carry out subgroup analysis. Weighted mean difference (WMD), the pooled odds ratio (OR) and 95% CI were calculated. The chi-square and Fisher's exact tests were applied to detect statistical significance and heterogeneity was also quantified with the $I^2$ statistic. Finally, publication bias was evaluated using funnel plots. The statistical analyses were performed using SPSS (SPSS Institute, version 15.0, Chicago, USA), and Stata version 12.0 (Stata Corporation, College Station, TX, USA). All $p$ values were two-sided, and $p<0.05$ was considered significant.

## Results

### Description of the studies

A database was established according to the extracted information from each selected paper. The baseline demographic factors of the patients are shown in Table 1. Initially 119 studies were identified. Twenty-two[4–25] of the 119 fulfilled the inclusion criteria (Figure 1) and the eligible studies included 1945 patients, of whom 795 (40.8%) were women and 1090 (56%) were men, aged ($60.7 \pm 12.5$) years. The sample sizes oscillated between 26 patients[13] and 286[8], and the age of the patients is mainly concentrated around 40–70 with the youngest at 24[25] and the oldest at 92[19].

 

Table 1. Patient characteristics of included clinical trials.

| Study | N | F/M | Age range | TNM stage | Smoker/non-smoker | LAC/non-LAC |
|---|---|---|---|---|---|---|
| Liu *et al.*, 2004[4] | 29 | 15/14 | 25–76 | IIIB3/IV26 | NA | 21/8 |
| Mu *et al.*, 2004[5] | 31 | 13/18 | 28–85 | IIIB5/IV26 | NA | 20/11 |
| Guan *et al.*, 2005[6] | 159 | 68/91 | 31–84 | IIIB26/IV133 | NA | 117/36 |
| Zhang *et al.*, 2005[7] | 98 | 40/58 | 28–85 | IIIB12/IV86 | 38/60 | 76/22 |
| Chang *et al.*, 2005[25] | 52 | 27/25 | 24–89 | IIIB3/IV49 | NA | 44/8 |
| Yang *et al.*, 2006[9] | 91 | 37/54 | NA | IIIB15/IV76 | 38/53 | 69/22 |
| Wang *et al.*, 2006[10] | 151 | 61/90 | NA | NA | 49/102 | 108/43 |
| Xu *et al.*, 2006[11] | 33 | 11/22 | 31–72 | IIIB10/IV23 | 14/19 | 24/9 |
| Chang *et al.*, 2006[8] | 286 | 138/148 | 20–90 | NA | 133/153 | 222/64 |
| Zhang and Yu, 2006[12] | 50 | 17/33 | NA | NA | 26/24 | 31/19 |
| Zheng *et al.*, 2007[13] | 26 | 7/19 | NA | IIIB3/IV23 | NA | 19/7 |
| Lin *et al.*, 2007[14] | 153 | 65/88 | 31–84 | IIIB27/IV127 | 66/87 | 113/40 |
| Zhang *et al.*, 2007[15] | 63 | 24/39 | NA | IIIB9/IV54 | 20/43 | 30/33 |
| Wang *et al.*, 2008[16] | 69 | 40/29 | 65–83 | IIIB13/IV56 | 15/54 | 69 |
| Kang *et al.*, 2008[17] | 28 | 11/17 | 45–72 | IIIB15/IV13 | NA | 19/9 |
| Zhong *et al.*, 2008[18] | 42 | 15/27 | NA | IIIB1/IV41 | 12/30 | 28/13 |
| Zhao *et al.*, 2009[19] | 256 | 104/152 | 23–92 | IIIB43/IV213 | NA | 197/39 |
| Lu *et al.*, 2010[20] | 75 | 48/27 | NA | NA | 12/63 | 62/13 |
| Dai *et al.*, 2010[21] | 80 | 60/20 | 40–85 | IIIB15/IV65 | NA | 69/11 |
| Guo *et al.*, 2010[22] | 88 | 40/48 | 38–84 | IIIB2/IV86 | 37/51 | 69/19 |
| Yin *et al.*, 2010[23] | 45 | 26/19 | 30–78 | IIIB14/IV31 | 17/28 | 30/15 |
| Deng *et al.*, 2011[24] | 40 | NA | 26–76 | NA | NA | 34/6 |

F, female; M, male; NA, not available; LAC, lung adenocarcinoma; TNM, tumor-node-metastasis.



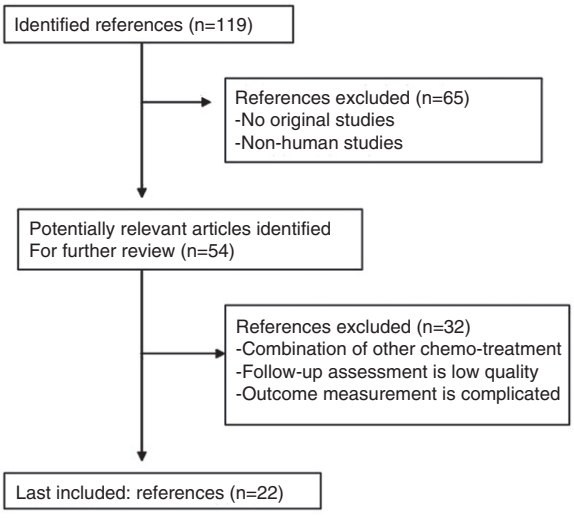


Figure 1. Study selection algorithm.

## The analysis of efficacy and survival

In total, 22 clinical reports were included in this review and the overall efficacy and survival data are shown in Table 2, including ORR, DCR, OYS, MST and PFS. After descriptive statistical analysis, the ORR was 30.89% (95% CI: 26.23% to 35.56%) and DCR was 67.5% (95% CI: 61.59% to 73.48%). The median OS provided by all 22 studies was 13.09 months (95% CI: 10.21 to 15.97); 21 of 22 studies provided the PFS data and that was 7.88 months (95% CI: 5.93 to 9.82); 17 of 22 studies provided OYS and that was 50.6% (95% CI: 43.39% to 57.82%).

## Relationship between clinical characteristics and ORR

Ten studies compared the ORR between female and male and the OR was 1.7 (95% CI 1.34 to 2.17; $Z = 4.3$, $p < 0.001$). Seven studies involving 822 patients compared non-smoker with smoker and the OR was 2.20 (95% CI 1.55 to 3.12; $Z = 4.40$, $p < 0.001$). Six trials involving 915 patients compared non-LAC with LAC and the OR was 2.27 (95% CI 1.49 to 3.47; $Z = 3.79$, $p < 0.001$). Two trials involving 407 patients compared rash with non-rash and the OR was 2.97 (95% CI 1.82 to 4.83). The ORRs in patients who were female (35%), non-smokers (34.5%), LAC patients (29.6%) and patients with rash (42.7%) were higher than male (20.4%), smokers (15.5%), non-LAC patients (13%) and patients without rash (13.2%) (Figure 2).

## Relationship between clinical characteristics and DCR

Eight studies included 1193 cases to analyze the DCR between female and male, and the OR was 1.27 (95% CI 1.03 to 1.55; $Z = 2.28$, $p = 0.023$). Seven trials involving 1010 patients compared non-smoker with smoker and the OR was 1.48 (95% CI 1.18 to 1.86; $Z = 3.39$, $p = 0.001$). Six trials involving 921 patients compared non-LAC with

Table 2. Efficacy of gefitinib for the treatment of NSCLC.

| Study | *N* | ORR | | DCR | | OYS | | Median survival | | PFS | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *N* | % | *N* | % | *N* | % | Months | 95% CI | Months | 95% CI |
| Liu *et al.*, 2004[4] | 29 | 8 | 27.59 | 20 | 68.97 | 13 | 44.83 | 5.5 | NA | 6.5 | NA |
| Mu *et al.*, 2004[5] | 31 | 11 | 35.3 | 18 | 58.1 | NA | NA | 11.5 | 5.6–17.3 | 5.5 | 1.6–9.4 |
| Guan *et al.*, 2005[6] | 159 | 43 | 27 | 86 | 54.1 | 70 | 44 | 10 | NA | 3 | 2.1–4 |
| Zhang *et al.*, 2005[7] | 98 | 31 | 31.6 | 66 | 67.3 | 52 | 53.1 | 12 | 8.33–15.61 | 7 | 5.39–8.61 |
| Chang *et al.*, 2005[25] | 52 | 13 | 25 | 24 | 46.2 | NA | NA | 9.1 | 4.8–13.5 | 2.4 | 2.1–2.8 |
| Yang *et al.*, 2006[9] | 91 | 19 | 20.9 | 58 | 63.7 | 51 | 56.4 | 7.5 | NA | 5 | 3.2–6.7 |
| Wang *et al.*, 2006[10] | 151 | 45 | 29.8 | 100 | 66.2 | 87 | 57 | 15.3 | 11.5–19.2 | 12.95 | 7.6–16.4 |
| Xu *et al.*, 2006[11] | 33 | 8 | 24.2 | 31 | 93.9 | 12 | 36.4 | 9.8 | 2.1–18 | 6.5 | 0.7–16.4 |
| Chang *et al.*, 2006[8] | 286 | 65 | 22.7 | 162 | 56.8 | 105 | 36.7 | 7.9 | NA | NA | NA |
| Zhang and Yu, 2006[12] | 50 | 8 | 16 | 30 | 60 | NA | NA | 13 | NA | 6 | NA |
| Zheng *et al.*, 2007[13] | 26 | 12 | 46.2 | 21 | 80.8 | 8 | 31.6 | 10.4 | 6.4–13.9 | 8.2 | 5.3–11.1 |
| Lin *et al.*, 2007[14] | 153 | 41 | 27 | 83 | 54.1 | 67 | 44.1 | 10.3 | 8.1–12.6 | NA | NA |
| Zhang *et al.*, 2007[15] | 63 | 16 | 25.4 | 51 | 80.9 | 33 | 53 | 15.3 | 11.8–18.8 | 12.4 | 11.2–13.6 |
| Wang *et al.*, 2008[16] | 69 | 17 | 24.6 | 61 | 88.4 | 43 | 62.2 | 15 | 2–39 | 7 | 3.8–10.2 |
| Kang *et al.*, 2008[17] | 28 | 11 | 39.3 | 18 | 64.3 | 11 | 38.7 | 9.5 | NA | 7 | NA |
| Zhong *et al.*, 2008[18] | 42 | 17 | 40.5 | 30 | 66.6 | 19 | 45 | 10.1 | 3.4–16.8 | 5.7 | 4.5–6.9 |
| Zhao *et al.*, 2009[19] | 256 | 60 | 23.4 | 140 | 54.7 | 123 | 48 | 11.4 | 8.6–14.2 | NA | NA |
| Lu *et al.*, 2010[20] | 75 | 28 | 37 | 49 | 66 | 67 | 89.3 | 26.13 | 22.77–29.49 | 17.13 | 14.74–19.53 |
| Dai *et al.*, 2010[21] | 80 | NA | NA | NA | NA | NA | NA | 34 | 25.4–42.6 | 14 | NA |
| Guo *et al.*, 2010[22] | 88 | 26 | 29.5 | 56 | 63.6 | NA | NA | 9 | 6–12 | 4.4 | 2.4–6.4 |
| Yin *et al.*, 2010[23] | 45 | 15 | 33.3 | 32 | 71.1 | 22 | 50 | 15.3 | 11.22–19.38 | 6.0 | 4.36–7.64 |
| Deng *et al.*, 2011[24] | 40 | 25 | 62.5 | 37 | 92.5 | 28 | 70 | 20 | 11.9–28 | 13 | 8–17.9 |
| Amount | 1945 | 519 | 30.89 | 1173 | 67.5 | 811 | 50.6 | 13.09 | 10.21–15.97 | 7.88 | 5.93–9.82 |

ORR, overall response rate; DCR, disease control rate; OYS, one year survival; NA, not available; 95% CI, 95% confidence interval; PFS, progression free survival.



LAC and the OR was 1.52 (95% CI 1.14 to 2.02; $Z = 2.88$, $p = 0.004$). Two trials involving 393 patients compared rash with non-rash and the OR was 1.91 (95% CI 1.32 to 2.77). The DCR in patients who were female, nonsmokers, LAC patients and patients with rash were higher than male, smokers, non-LAC patients and patients without rash (Figure 3).

## Relationship between clinical characteristics and MST/PFS

Marginally prolonged MST (from 1.16 to 2.40 months) was observed among female patients in comparison with male patients (WMD = 1.23, 95% CI −0.04 to 2.51, $p = 0.059$) in three studies. Four studies investigated smoking history and the results show a significant prolongation in MST for never smokers treated with gefitinib in comparison with smokers (WMD = 4.96, 95% CI 3.86 to 6.07, $p < 0.0001$). The MST with gefitinib in patients with LAC and rash was significantly longer than in non-LAC patients (WMD = 6.34, 95% CI 4.39 to 8.29, $p < 0.0001$) and those without rash (WMD = 7.04, 95% CI 3.97 to 10.11, $p < 0.0001$) (Figure 4). Female patients had prolonged PFS in comparison with male patients (WMD = 1.89, 95% CI 0.74 to 3.05, $p = 0.001$) and never smokers also showed a prolonged PFS compared with smokers (WMD = 4.65, 95% CI 2.77 to 6.53, $p < 0.0001$).The PFS of patients with LAC and rash was significantly longer than non-LAC patients (WMD = 3.83, 95% CI −0.28 to 7.94, $p < 0.0001$) and those without rash (WMD = 3.41, 95% CI 2.39 to 4.43, $p < 0.0001$) (Figure 5).

## Publication bias

In the funnel plot analysis of publication biases, the shape of the funnel plot appeared to be approximately symmetrical, suggesting that publication biases did not have a significant influence on the results. The results of Egger's test was as ($t = 0.06$, $p = 0.408$) and the results of Begg's test was (SD of score = 8.08, $p = 0.386$). Therefore, both Egger's test and Begg's test suggest that publication biases did not have a significant influence on the results (Figure 6).

## Tolerability of gefitinib maintenance therapy

The most common AEs were gastrointestinal and skin-related AEs. Figure 7 showed the overall incidence rates of all adverse effects. The overall rash frequency of Grade 1–2 was 43.6%, and Grade 3–4 was 14.33%. The overall frequency of diarrhea for Grade 1–2 and Grade 3–4 were 27.4% and 2.37% respectively. In addition, 3.65% (38 patients) and 2.56% (23 patients) showed hepatic toxicity of Grade 1–2 and Grade 3–4. The overall frequency of vomiting and nausea for Grade 1–2 was 6.72% and Grade 3–4 was 0.61%. Out of all study reports, nine patients showed ILD (interstitial lung disease), and 8 of

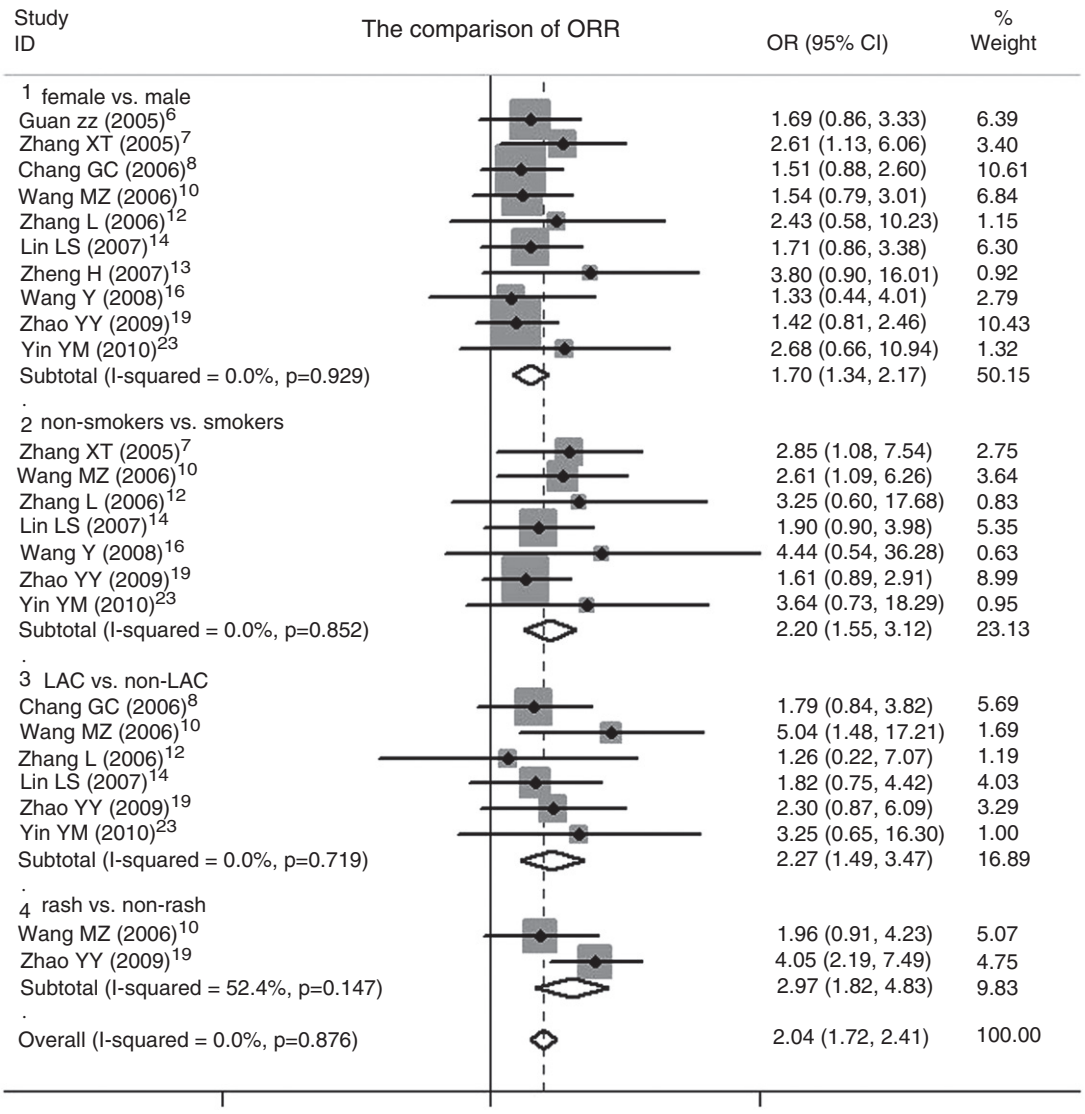


Figure 2. Meta-analysis of comparison: relationship between clinical characteristics and ORR with gefitinib. The ORRs in patients who were female (35%), non-smokers (34.5%), LAC patients (29.6%) and patients with rash (42.7%) were higher than male (20.4%), smokers (15.5%), non-LAC patients (13%) and patients without rash (13.2%). LAC, lung adenocarcinoma; ORR, overall response rate.



9 patients displayed relatively severe ILD. All in all, most of the toxicity was grade 1–2, and remitted after treatment.

## Discussion

Epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKI) have been developed as validated targeted anticancer agents and approved for clinical use. Gefitinib is the representative agent which has demonstrated identical efficacy and lower toxicity compared with cellular toxicity agents and has therefore been extensively used in clinical practice[26]. This present work discusses the efficacy and safety of gefitinib as a maintenance therapy after first-line chemotherapy in NSCLC regardless of EGFR mutation and also tries to evaluate apparent differences in efficacy outcomes between different clinical characteristics. Previous studies have suggested a benefit of maintenance chemotherapy for patients with NSCLC following front-line chemotherapy[27,28]. Hida *et al.* also reported that gefitinib used in a maintenance setting following induction chemotherapy improved PFS by 0.33 months ($p<0.001$) and OS by 1.09 months ($p=0.03$) compared with patients treat with continuous chemotherapy[28]. In the present review, a total of 22 studies were included in the final systemic evaluation and a total of 1945 eligible patients were enrolled into these studies. Overall RR and DCR were 30.89% and 67.5%,

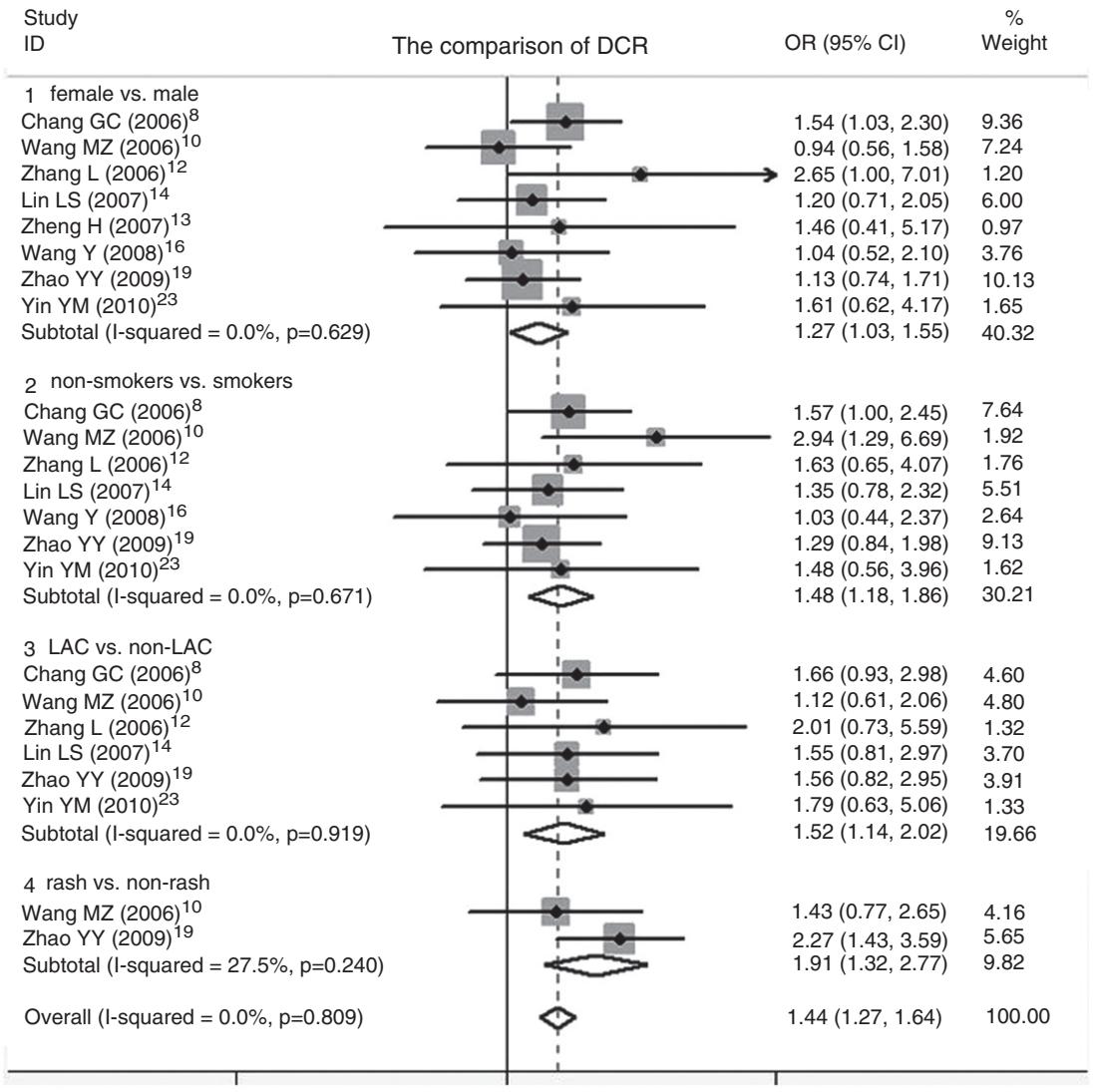


Figure 3. Meta-analysis of comparison: relationship between clinical characteristics and DCR with gefitinib. The DCRs in patients who were female, nonsmokers, LAC patients and patients with rash were higher than male, smokers, non-LAC patients and patients without rash ($p < 0.05$). LAC, lung adenocarcinoma; DCR, disease control rate.

respectively, higher than those of 18.4% and 54.4% in the IDEAL-1 study, and 11.8% and 42.0% in the IDEAL-2 study[1,3]. The results suggested that there might be ethnic differences in gefitinib efficacy. In the IDEAL-1 study, response rate was higher for Japanese patients than non-Japanese patients (27.5% vs. 10.4%, $p = 0.0023$), but became non-significant after multivariate model analysis. Although ethnicity was not a significant factor in the IDEAL-1 study, there is a trend for the Chinese patients to respond better to gefitinib[3]. Recently, Lee *et al.*[29] demonstrated that, as second-line therapy, gefitinib has superior PFS and better tolerability. Maemondo *et al.*[30] also reported that the gefitinib group had a significantly longer median PFS (10.8 months vs. 5.4 months; $p < 0.001$), as well as a higher response rate (73.7% vs. 30.7%, $p < 0.001$) than the standard chemotherapy group. In this review of gefitinib maintenance treatment in Chinese patients with advanced NSCLC, the median overall survival for the whole population was 13.09 months (95% CI: 10.21 to 15.97) and the 1-year survival rate was 50.6%. An overall median PFS of 7.88 months (95% CI: 5.93 to 9.82) was also observed, which was compatible with the reports aforementioned.

In this review, histology type, sex, or smoking status had differences in ORR, DCR, MST and PFS, which was consistent with some phase II trials. Adenocarcinoma, never smokers and female patients had a better response rate[1], and the ORR, DCR, MST and PFS of those who were female, nonsmokers and LAC patients were better than male, smokers and non-LAC patients. The skin rash induced with gefitinib was significantly associated with ORR, DCR, MST and PFS, and can be used as indicators

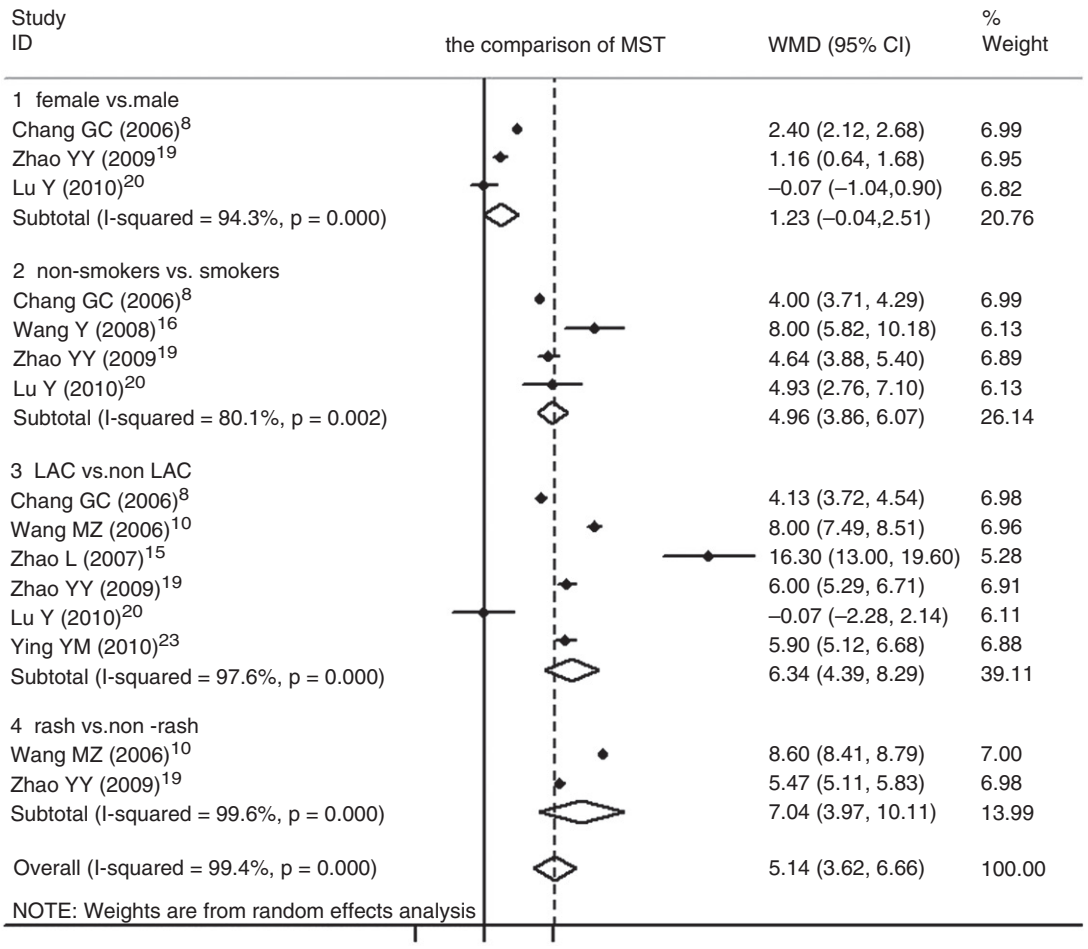


Figure 4. Meta-analysis of comparison: relationship between clinical characteristics and MST with gefitinib. The MSTs in patients who were nonsmokers, LAC patients and patients with rash were longer than smokers, non-LAC patients and patients without rash ($p < 0.05$). LAC, lung adenocarcinoma; MST, median survival time.

for treatment efficacy. Previous studies have indicated that second-line gefitinib therapy for advanced NSCLC patients who failed with first-line standard chemotherapy had less toxicities and better quality of life compared with second-line chemotherapy[31]. In this investigation, a daily oral 250 mg dose of gefitinib was well tolerated in Chinese patients with advanced NSCLC, who received gefitinib as maintenance therapy. The AEs seen in this review were mainly skin rashes and diarrhea, most of which were grades 1–2 and were well tolerated. The most common grades 1–2 toxicities included skin rash (43.6%), diarrhea (27.4%), hepatic toxicity (3.65%) and nausea/vomiting (6.72%), but grade 3–4 skin rash (14.33%), diarrhea (2.37%) and hepatic toxicity (2.56%) were observed in our study, at a lower incidence rate. The authors found that 9 of 1249 patients (0.7%) had acute interstitial pneumonia with gefitinib treatment, but no one died and this remitted after treatment. The incidence was similar to other places in the world. The worldwide frequency of interstitial lung disease to date in ~92,750 patients who received gefitinib is <1.0%[32]. No hematological or neural toxicity was observed in any of the studies in our review; however, 36 of 1249 patients developed grade 1–2 stomatitis during treatment, which has previously been associated with gefitinib treatment in 7.8% of patients in IDEAL-1 but was not reported in IDEAL-2[1]. In these studies, patients older than 70 years were included and these patients were able to continue gefitinib treatment, except for four who stopped treatment due to hemoptysis. Therefore, one advantage of gefitinib is that it appears well tolerated in patients with advanced age.

However, some deficiencies in the present meta-analysis were found. First, the quality of subgroup analysis was low because some subgroup data were limited. Second, the reports are single-arm trials and some reports comprise a small sample size. In addition, most of the included studies were published in Chinese and some different analysis methods were used (e.g., different scored scales were used to assess quality of life), with heterogeneous data. Hence, the validity of the results

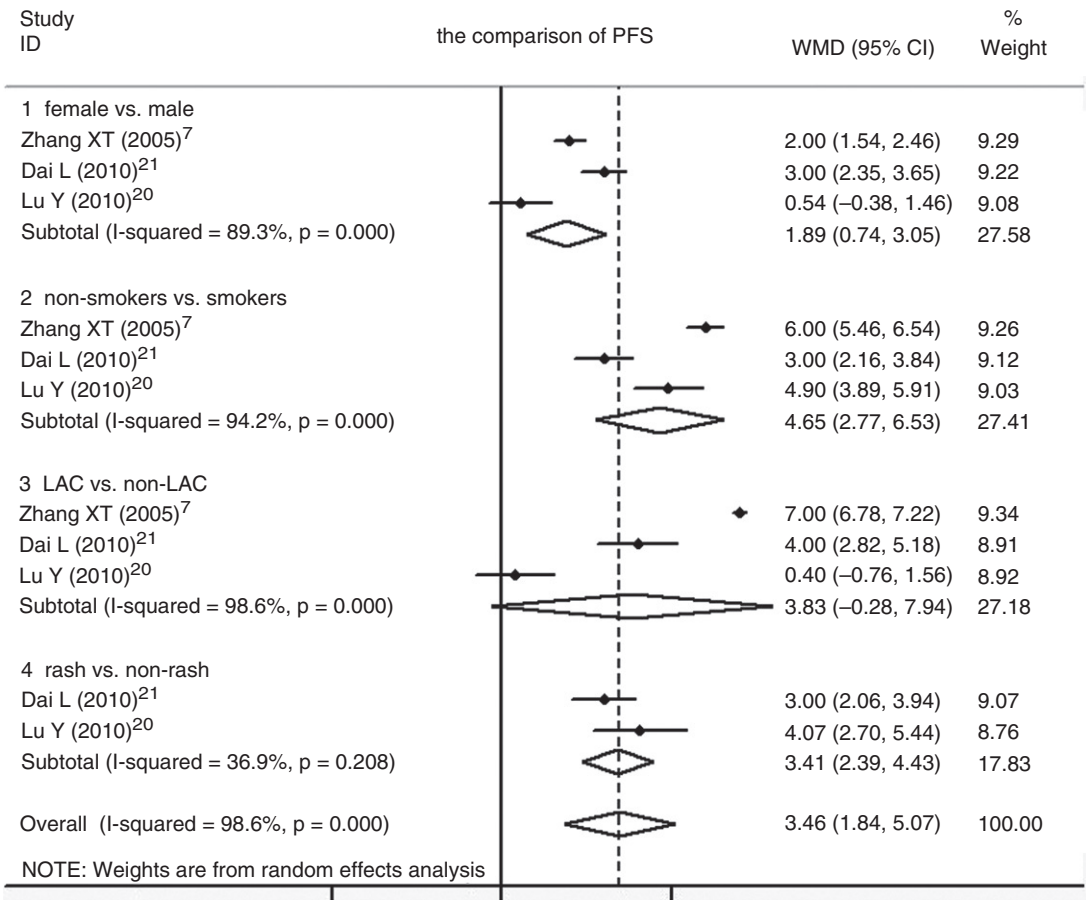


Figure 5. Meta-analysis of comparison: relationship between clinical characteristics and PFS with gefitinib. The PFS in patients who were female, nonsmokers, LAC patients and patients with rash were better than male, smokers, non-LAC patients and patients without rash ($p < 0.05$). LAC, lung adenocarcinoma; PFS, progression free survival.



may be compromised. Activating EGFR mutations have been reported in many patients responding to EGFR-TKIs, and seem to correlate with clinical response to EGFR-TKIs. However, some patients without an EGFR mutation responded to EGFR-TKIs and some with an EGFR mutation failed to respond[33–35]. To date, the association between EGFR mutations and survival has not been demonstrated clearly. KRAS mutations have also been associated with resistance to gefitinib and erlotinib, although EGFR and KRAS mutations seem mutually exclusive[36]. The limitation regarding the lack of EGFR/KRAS data existed in this study even though part of the aim was to disclose whether gefitinib therapy regardless of EGFR mutation would be efficacious and safe as a maintenance therapy for NSCLC, because this kind of limitation was still a natural risk regarding gefitinib therapy. Although some deficiencies existed in the studies reviewed, they still contain credible evidence pointing toward such controversial points showing that patients with NSCLC can benefit from gefitinib as maintenance therapy after first-line chemotherapy even if there are difficulties testing for EGFR mutation.

## Conclusion

Regardless of EGFR mutation, gefitinib produced encouraging survival when delivered as maintenance therapy for NSCLC patients after first-line chemotherapy in Chinese patients, especially for patients who were female, nonsmokers, LAC and with rash. Although gefitinib has been indicated for and commonly prescribed as a second-line therapy for lung cancer, some small-scale medical institutions still cannot make EGFR mutation examinations because of limited research conditions and unwillingness of patients. In this situation, whether gefitinib could be recommended remains controversial. These research results may provide information that NSCLC patients can benefit from gefitinib therapy as maintenance therapy after first-line chemotherapy even if there are difficulties in examining for EGFR mutation.

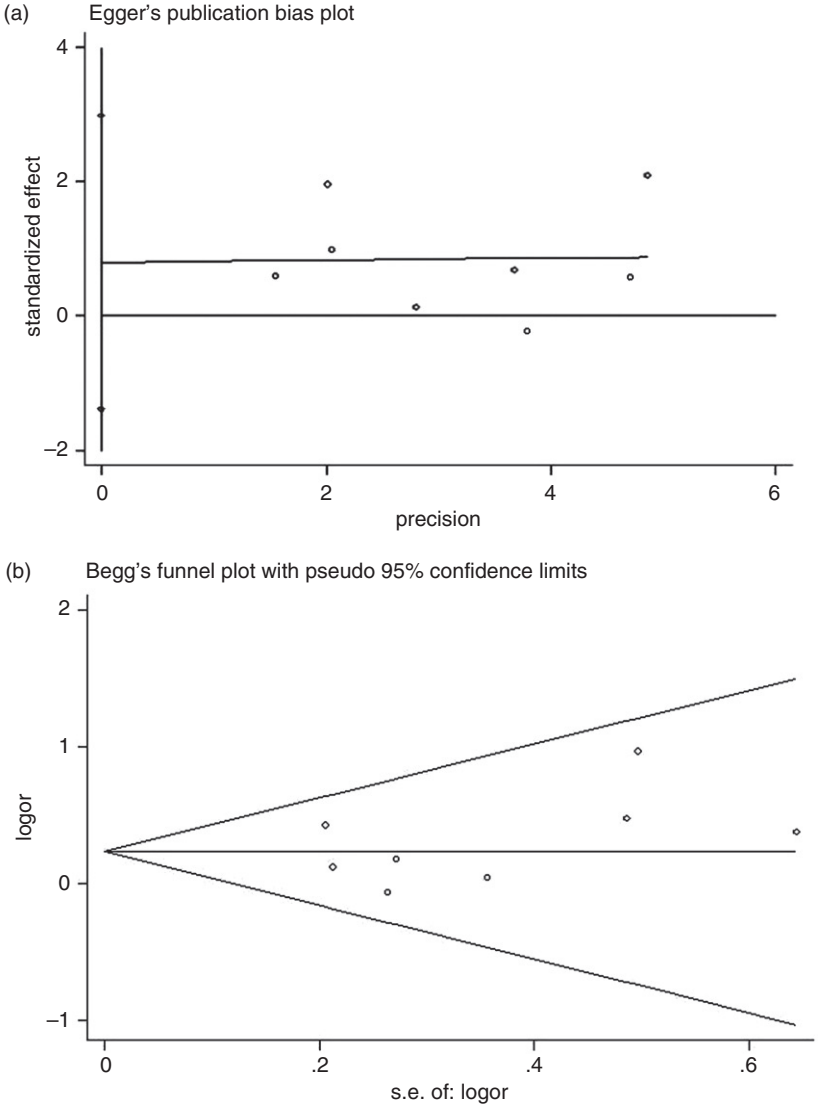


Figure 6. Funnel plot of comparison: relationship between clinical characteristics and efficacy with gefitinib. Egger's publication bias plot (A) and Begg's publication bias plot (B).

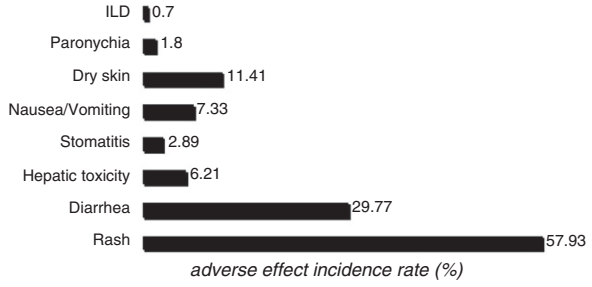


Figure 7. The incidence rate of adverse effects with gefitinib therapies. ILD, interstitial lung disease.

## Transparency

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**Declaration of financial/other interests**

R.B., Y.S., L.W., Z.W., and M.Z. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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