A meta-analysis of the therapeutic effect of gefitinib combined with chemotherapy and chemotherapy alone in treating non-small cell lung cancer

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Abstract

**Background:** Whether the combination of gefitinib and chemotherapy is beneficial for advanced non-small cell lung cancer (NSCLC) remains controversial. This study aimed to summarize the currently available evidence and compare the efficacy and safety of gefitinib combined with chemotherapy versus chemotherapy alone for treating advanced NSCLC.

**Methods:** Literature on comparing the effects of gefitinib combined with chemotherapy and chemotherapy alone in treating NSCLC was retrieved from the PubMed, EMBASE and Cochrane Database. The primary outcome measures included progression-free survival (PFS) and overall survival (OS). Revman 5.3 was used for data processing.

**Results:** Seven randomized controlled trials were included, involving a total of 1418 patients. There appeared a significant improvement in PFS (hazard ratio (HR) = 0.60 [95% CI 0.43, 0.82], \(P = .001\)) after treatment with gefitinib combined with chemotherapy when compared with chemotherapy alone. The subgroup analysis showed a significant advantage of sequential administration (HR = 0.67 [95% CI 0.57, 0.79], \(P < .00001\)). There was no significant improvement in OS (HR = 0.92 [95% CI 0.71, 1.20], \(P = .54\)), and no significant improvement in overall response rate (ORR) (HR = 0.98 [95% CI 0.67, 1.44], \(P = .93\)). The risks of rash and diarrhea (odds ratios) were higher in gefitinib combined with chemotherapy group when compared with chemotherapy alone, and there were significant differences on grade 3/4 rash and thrombocytopenia between 2 groups.

**Conclusion:** Gefitinib combined with chemotherapy is superior to chemotherapy alone in PFS, sequential administration prolongs the patients’ PFS, however, a survival advantage is not shown in OS or ORR. Gefitinib combined with chemotherapy aggravates rash, diarrhea and thrombocytopenia.

**Abbreviations:** EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, HR = hazard ratio, MPFS = Median progression-free survival, MST = median survival time, NSCLC = non-small cell lung cancer, OR = odds ratios, ORR = overall response rate, OS = overall survival, PFS = progression-free survival.

**Keywords:** chemotherapy, gefitinib, meta-analysis, mode of administration, non-small cell lung cancer (NSCLC)

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Not applicable. Because this article is a meta-analysis of the literature on gefitinib and gefitinib chemotherapy, it does not directly involve human studies, so no ethics committee approval is required.

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1. Introduction

Lung cancer is one of the malignant tumors with the highest mortality rate in the world,\(^1\) especially NSCLC contributes to 85% of mortalities,\(^2\) and brain metastases occur in 25% to 40% patients with NSCLC. NSCLC is usually asymptomatic at the early stage, whereas 70% to 80% patients are diagnosed with NSCLC at the advanced stage. Currently, the treatment of advanced lung cancer does not produce a satisfactory therapeutic response. Therefore, clinically, other programs have been sought to achieve the purpose of improving the therapeutic effect and improving the prognosis of patients. Existing studies have proven that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are standard first-line therapeutic drugs, and gefitinib or erlotinib is used alone to treat patients with EGFR mutations.\(^3\) However, with the treatment prolonged, especially after over 9 months, gefitinib or erlotinib resistance was developed, reducing the effect.\(^4\) The most common cause of acquired resistance to EGFR-TKIs is the exists of EGFR gene mutation in exon 20-T790M mutations. On the other hand, treatments with platinum drugs combined with pemetrexed, gemcitabine and paclitaxel were the common chemotherapy regimen used in patients with advanced NSCLC. Platinum-based chemotherapy can prolong the median survival time (MST) by 6 to 12 weeks, which is a doubling of 1-year survival.\(^5\) Based on
this, some researchers added gefitinib or erlotinib to a standard chemotherapy regimen to enhance the therapeutic effect,[6] and compared the efficacy with the pure chemotherapeutic effect. The addition types were divided into synchronous therapy and sequential therapy, while the synchronous therapy were divided into intercalation therapy and continuous therapy. Some studies showed that the survival advantage was enhanced if EGFR-TKIs were added to the chemotherapy regimen. The results of a meta-analysis showed that erlotinib combined with chemotherapy could effectively delay the development of drug resistance in patients, with long-term treatment still able to achieve a considerable curative effect.[7] In the FASTACT-2 study, treatment with EGFR-TKIs and chemotherapy were performed alternately, significantly prolonging the PFS and OS of patients with EGFR mutation. The therapeutic regimen consisted of gemcitabine plus carboplatin or alternative application of cisplatin chemotherapy and erlotinib.[8] However, survival advantages were not found in INTACT I, II or TRIBUTE studies.[9–11] This meta-analysis compared the survival advantages of gefitinib combined with chemotherapy and chemothera-
py alone for NSCLC. The sub-group analyzed the survival advantages of concurrent and sequential chemotherapy compared with chemotherapy alone, and the adverse reactions of chemotherapy combined with gefitinib and chemotherapy alone.

2. Materials and methods

2.1. Search strategies

Two authors searched the PubMed, EMBASE and Cochrane Database (2019:6) for English only articles published from January 2000 to June 2019. The 2 authors resolved all differences by discussing with a third party. Search method: PubMed: (Randomized Controlled Trial AND (“NSCLC” OR Non-small cell lung cancer) AND (“Gefitinib” OR Iressa [Title/Abstract]). EMBASE: (“gefitinib”:ab,ti OR “irressa”:ab,ti) AND randomized AND controlled AND trial AND (“non-small cell lung cancer”:ab,ti OR “nscl”:ab,ti); Cochrane Database (2019:6): Gefitinib or Iressa in Title Abstract Keyword AND Randomized controlled trial in Title Abstract Keyword AND Non-small cell lung cancer or NSCLC in Title Abstract Keyword.

2.2. Inclusion and exclusion criteria

Literature selection was performed by 2 people, with all differences resolved by discussing with a third party. Inclusion criteria: (i) randomized controlled trials; (ii) patients confirmed with advanced NSCLC in pathological/cytologic examinations; (iii) a comparative study of gefitinib with standard chemotherapeutics and single use of standard chemotherapeutics; (iv) 2 outcomes (PFS, OS) were reported. Exclusion criteria: (i) observational cohort studies; (ii) repetition of the study population.

2.3. Literature quality assessment

The Bias Risk Toolbar in Cochrane Collaboration was used to assess the risk of bias of various randomized controlled trials. The following was the assessment content: (1) randomized allocation method; (2) allocation concealment; (3) whether blind methods were used for research subjects, implementers of treatment scheme, and measurers of research results; (4) data integrity; (5) selective reporting of study results; (6) other biases. The 2 researchers made an assessment independently. When the results of 2 researchers were inconsistent, the 2 researchers discussed with each other or consulted a third party.

2.4. Data acquisition

The 2 authors independently extracted data, including the first author’s information, publication year, study area, treatment comparison, mode of administration, number of patients and age. The outcome indicators include PFS and OS, ORR and adverse reactions.

2.5. Statistical analysis and publication bias

The 2 authors made a statistical analysis. They calculated the combined HR for both PFS and OS, the OR of adverse reactions, and calculated the 95% CI. The authors used Q-statistics to assess the statistical heterogeneity existing in the study, and used I²-statistics to assess the magnitude of heterogeneity. If statistical heterogeneity is detected, the test results of statistical heterogeneity included in the study are: P < .1, I² > 50%, and a random-effect model was adopted. Otherwise, a fixed-effect model would be adopted. After the subgroup analysis, the following came under discussion: intercalation therapy (chemotherapy intercalated with gefitinib) or continuous treatment (continuous gefitinib chemotherapy), sequential therapy, patients with EGFR mutations and race. The results of the meta-analysis appeared as a forest plot. Review Manager 5.3 was used for all calculations. Funnel plots were drawn to evaluate the publication bias (Supplemental Digital Content (Fig. S1, http://links.lww.com/MD/E633), Supplemental Digital Content (Fig. S2, http://links.lww.com/MD/E634).

3. Results

3.1. Literature search results

A total of 754 articles were selected in the preliminary search strategy. Unrelated clinical trials, meta-analyses, reviews, notes, studies, conference abstracts, RCTs with insufficient data, observational studies and case reports were excluded. Finally, 7 trials were chosen for the meta-analysis, including 1418 patients (Table 1 basic information of the 7 literature documents). See the flow chart in Figure 1 for the selection procedures. Two of the 7 trials were placebo-controlled double blind trials,[12,13] standard chemotherapeutic drugs included carboplatin and paclitaxel, cisplatin/carboplatin and pemetrexed, carboplatin and gemcitabine. Three trials used intercalation of gefitinib combined with chemotherapy as the drug delivery method,[14–16] while continuous gefitinib combined with chemothera-
y

ty was performed in 2 trials[12,17]; the sequential therapeutic test was conducted in 2 trials.[15,18] The NSCLC patients in these 7 clinical trials include non-smokers and smoking patients, as well as patients with EGFR mutations, EGFR wild-type patients and unknown EGFR mutation status.

3.2. Risk of bias and publication bias evaluation

The Bias Risk Toolbar of Cochrane Collaboration was used to assess the risk of bias of various randomized controlled trials. The results were listed in Table 2. A significant publication bias was
Table 1
Basic information of the literature included.

| Study   | Area         | Median age | Total/female | Disease stage | Treatment comparison | Drug delivery | End point     | Non-smoker | Smoker | EGFRm-mutation status |
|---------|--------------|------------|--------------|--------------|----------------------|---------------|---------------|------------|--------|----------------------|
| Ahn 2012 | China, Korea | 56         | 25/19        | IIIB/IV      | 4 cycles of Pem (500 mg/m²) + Cisp (75 mg/m²) every 3 wk + gefitinib (250 mg/d) every 3 wk and ≤2 optional cycles of Cisp | Sequential    | PFS, OS, CR    | 25         | 0      | Unknown              |
|         |              | 55.5       | 24/18        |              |                      |               |               |            |        |                      |
| Choi 2015 | USA         | 60         | 44/9         | IIIB/IV      | Pac (175 mg/m²) + Carb (AUC 5) + G (250 mg) orally on days 2 through 15 every 3 wk, 4 cycles | Intercalated  | PFS, OS, toxicity, ORR, CR, PR | 7          | 37     | 38 patients with unknown EGFR mutation status, 6 patients with EGFR-wild-type |
|         |              | 59         | 46/4         |              |                      |               |               |            |        | 43 patients with unknown EGFR mutation status, 3 patients with EGFR-wild-type |
| Jian 2017 | China       | 56         | 109/88       | IIIB/IV      | Gem (1250 mg/m²) + Carb (5 AUC) intercalating G (250 mg/d on days 15–25 of each cycle) | Intercalated  | PFS, OS, ORR, adverse events | 109        | 0      | Unknown              |
|         |              | 58         | 110/83       |              |                      |               |               |            |        |                      |
| Soria 2015 | Europe, Asia | 60         | 133/85      | IIIB/IV      | Gsp (75 mg/m²) + Pem (500 mg/m²) on the first day of each cycle, G (250 mg) | Continuous    | PFS, OR, OS, safety, tolerability | 110        | 0      | Unknown              |
|         |              | 58         | 132/84       |              |                      |               |               |            |        | 133 mutation (Exon 19 deletion), No EGFR-wild-type patient |
| Takeda 2009 | Japanese | 63         | 300/108      | IIIB/IV      | Platinum-doublet chemotherapy + G (250 mg, 3 cycles) | Sequential    | PFS, OS, ORR | 90         | 210    | Unknown              |
|         |              | 62         | 298/107      |              |                      |               |               |            |        |                      |
| Tham 2009 | Singapore    | 60         | 51/36        | IIIB/IV      | Gem (1000 mg/m²) and Carb (100 mg/m²) on days 1, 8, and 15 every 28 d + G (250 mg, 6 cycles) | Continuous    | PFS, OS, RR    | 51         | 0      | Unknown              |
|         |              | 54         | 29/21        |              |                      |               |               |            |        |                      |
| Yu 2014  | China        | 55.3       | 58/25        | IIIB/IV      | Pem (500 mg/m² d1) and either Cisp (75 mg/m² d1) or Carb (aUC = 5 d1) + G (250 mg/d on days 3–16 of a 3-wk cycle) | Intercalated  | PFS, OS, NPR, ORR, biosafety | 29         | 29     | 16 patients with unknown EGFR mutation status, 16 patients with EGFR mutation, 26 patients with EGFR-wild-type |
|         |              | 54.9       | 59/34        |              |                      |               |               |            |        | 12 patients with unknown EGFR mutation status, 19 patients with EGFR mutation 28 patients with EGFR-wild-type |

Carb = carboplatin, Cisp = cisplatin, CR = complete response, G = gefitinib, Gem = Gemcitabine, NA = Not available, NPR = non-progression rate, OR = objective response, ORR = overall response rate, OS = overall survival, Pac = paclitaxel, Pem = Pemetrexed, PFS = progression-free survival, PR = partial response, RR = response rate.
3.3. Median progression-free survival (MPFS)

The HR in PFS data was available from the 7 trials. The meta-analysis showed that there was a statistically significant difference in PFS in the patients treated with gefitinib plus chemotherapy (HR = 0.60 [95% CI 0.43, 0.82], P = .001). There was significant heterogeneity among the trials ($\chi^2 = 34.42, df = 6 (P < .00001); I^2 = 83\%$) (Fig. 2). In the subgroup analysis, the results of 2 trials suggested no improvement in PFS for adenocarcinoma patients (HR = 0.79 [95% CI 0.41, 1.53], P = .48), the results of 2 trials suggested no improvement in PFS in the patients with EGFR mutations (HR = 0.49 [95% CI 0.12, 1.96], P = .31), 5 trials were conducted with Asians as the subjects, result showing a significant improvement in PFS (HR = 0.50 [95% CI 0.33, 0.75], P = .001). The aggregate HR meta-analysis of chemotherapy intercalated with gefitinib failed to show improvement in PFS (HR = 0.68 [95% CI 0.38, 1.22], P = .20) (Fig. 3). Moreover, continued therapy with gefitinib and chemotherapy did not show an improvement in PFS (HR = 0.41 [95% CI 0.09, 1.82], P = .24) (Fig. 3). After chemotherapy, gefitinib sequential therapy was given, leading to an improvement in PFS (HR = 0.67 [95% CI 0.57, 0.79], P < .00001).

3.4. Overall survival (OS)

The HR in OS data was available from the 7 trials. There was no statistically significant improvement in OS (HR = 0.92 [95% CI 0.71, 1.20], P = .54) (Fig. 4), there was heterogeneity among the trials ($\chi^2 = 15.49, df = 6 (P = .02); I^2 = 61\%$). In the subgroup analysis, 2 trials showed a significant improvement in OS in the patients with adenocarcinoma (HR = 0.80 [95% CI 0.66, 0.98]), and 5 trials were conducted with Asians as the subjects, showing no improvement in OS (HR = 0.80 [95% CI 0.62, 1.03], P = .09). When the chemotherapy treatment was combined with gefitinib, chemotherapy plus intercalation of gefitinib did not show an improvement in OS (HR = 0.78 [95% CI 0.60, 1.00], P = .05). Continuous treatment with gefitinib and chemotherapy did not show an improvement in OS (HR = 0.97 [95% CI 0.34, 2.74], P = .95) (Fig. 5). After chemotherapy, sequential treatment with gefitinib did not show an improvement in OS (HR = 1.20 [95% CI 0.51, 2.85], P = .68).

3.5. Objective response rate (ORR)

The ORR was not significant improvement in the group treated with gefitinib plus chemotherapy (HR = 0.98 [95% CI 0.67, 1.44], P = .93). There was no heterogeneity between the groups ($\chi^2 = 0.17, df = 2 (P = .92); I^2 = 0\%$) (Fig. 6).

3.6. Adverse reactions

All grade of adverse reactions and the adverse reactions at grade 3 and above were evaluated. Common adverse reactions were roughly the same between the group treated with gefitinib combined with chemotherapy and the group treated with chemotherapy alone, such as leukopenia (OR = 1.05 [95% CI 0.69, 1.61], P = .81), nausea (OR = 1.29 [95% CI 0.92, 1.81], P = .14), fatigue (OR = 1.33 [95% CI 0.85, 2.06], P = .21), constipation (OR = 0.90 [95% CI 0.59, 1.37], anemia (OR = 1.08 [95% CI 0.75, 1.54], P = .69), neutropenia (OR = 1.03 [95% CI 0.70, 1.50], P = .90). While there were differences on rash (OR = 3.82 [95% CI 2.31, 6.31], P < .00001) and diarrhea (OR = 2.83...
Table 2
Assessment results of risk of bias.

| Study       | Generation of random sequences | Allocation concealment | Performance bias | Measurement bias | Follow-up bias | Reporting bias | Other biases |
|-------------|-------------------------------|------------------------|------------------|------------------|----------------|----------------|-------------|
| Ahn 2012    | Low risk                      | Unclear                | High risk        | High risk        | Low risk       | Low risk       | Low risk     |
| Choi 2015   | Low risk                      | Unclear                | High risk        | High risk        | Low risk       | Low risk       | Low risk     |
| Jan 2017    | Low risk                      | Unclear                | Unclear          | Unclear          | Low risk       | Low risk       | Low risk     |
| Soria 2015  | Low risk                      | Low risk               | High risk        | High risk        | Low risk       | Low risk       | Low risk     |
| Takeda 2009 | High risk                     | Unclear                | High risk        | Low risk         | Low risk       | Low risk       | Low risk     |
| Tham 2009   | Unclear                       | Unclear                | Unclear          | Unclear          | Low risk       | Low risk       | Low risk     |
| Yu 2014     | High risk                     | Unclear                | High risk        | High risk        | Low risk       | Low risk       | Low risk     |

There were significant differences in grade 3/4 rash (OR = 7.45 [95% CI 1.70, 32.59], P = .008) and thrombocytopenia (OR = 1.75 [95% CI 1.17, 2.63], P = .007) between the group treated with gefitinib combined with chemotherapy and the group treated with chemotherapy alone. There was no significant difference between the 2 groups in other adverse reactions above grade 3: leukopenia (OR = 1.01 [95% CI 0.75, 1.34], P = .97), nausea (OR = 1.18 [95% CI 0.75, 1.84], P = .48), diarrhea (OR = 1.39 [95% CI 0.56, 3.48], P = .37), neutropenia (OR = 1.20 [95% CI 0.90, 1.60], P = .21), vomiting (OR = 1.56 [95% CI 0.62, 3.94], P = .35), dyspepsia (OR = 0.77 [95% CI 0.37, 1.60], P = .48), stomatitis (OR = 2.05 [95% CI 0.37, 11.37], P = .41). See Supplemental Digital Content (Fig. S4, http://links.lww.com/MD/E635) for the forest plot.

4. Discussion
Researchers are concerned about the resistance to gefitinib and the adverse effects of platinum-based chemotherapeutic drugs. However, EGFR mutation testing is not attainable in approximately 20% of patients, particularly in the Asia-Pacific region and other less developed regions of the world. For this subset of patients, the combination of chemotherapy and gefitinib maybe provide some benefits. In standard chemotherapy, combined or sequential administration of gefitinib has been performed many times in clinical trials, but it remains unknown whether gefitinib can significantly improve the survival advantage of chemotherapy and reduce the adverse reactions of chemotherapy. Existing meta-analysis results showed that intercalation of gefitinib or erlotinib in a therapeutic regimen could improve the chemotherapeutic efficacy. There were comparative studies on the therapeutic effects of chemotherapy with gefitinib and administration of gefitinib alone, and there were also studies on whether administration of gefitinib had effects on survival. However, there is no meta-analysis of the therapeutic effects of gefitinib with chemotherapy and chemotherapy alone, nor the comparaison between the differences in various modes of administration, that is, intercalation, continuous or sequential treatment.

This meta-analysis showed an improvement in PFS in the patients receiving gefitinib combined with chemotherapy, and there was a statistically significant difference (HR = 0.60 [95% CI 0.43, 0.82], P = .001), but there was no improvement in OS (HR = 0.92 [95% CI 0.71, 1.20], P = .54). This was consistent with the previous 2 systematic evaluations, suggesting that EGFR-TKIs can be applied with chemotherapy to improve PFS, but OS cannot be improved. The subgroup analysis results showed no improvement in PFS in the patients with EGFR mutations or the patients with adenocarcinoma; compared with chemotherapy alone, gefitinib combined with chemotherapy prolonged Asian patients’ PFS, but OS was not improved.

Compared with chemotherapy alone, chemotherapy combined with gefitinib did not show a survival advantage, and intercalation or continued administration of gefitinib did not show an improvement in PFS and OS. The reason why concurrent chemotherapy combined with gefitinib did not show survival advantage compared with single chemotherapy maybe the potential antagonism of such drug combinations.

![Figure 2. Forest plot of meta-analysis for PFS.](http://links.lww.com/MD/E636)
studies show that EGFR-TKIs can induce cell cycle arrest at G1, which is consistent with the theory that an EGFR-TKIs can cause cell cycle arrest in G1 phase. This may protect tumor cells from the cytotoxicity of cell cycle-dependent chemotherapeutic drugs. However, chemotherapy with sequential administration of gefitinib significantly improved PFS compared with chemotherapy alone.

Common adverse reactions were roughly the same between gefitinib combined chemotherapy group and single chemotherapy group, while the risks of rash and diarrhea were higher in gefitinib combined with chemotherapy group when compared with chemotherapy alone. There were significant differences in grade 3/4 rash (OR=7.45 [95% CI 1.70, 32.59], P=0.008) and thrombocytopenia (OR=1.75 [95% CI 1.17, 2.63], P=0.007).

![Forest plot of subgroup analysis for PFS.](image3.png)
Figure 4. Forest plot of meta-analysis for OS.

Figure 5. Forest plot of subgroup analysis for OS.
between gefitinib combined chemotherapy group and single chemotherapy group.

This systematic review has some limitations. Although some clinical studies show that gefitinib has a good therapeutic effect on Asians, non-smokers, women and patients with adenocarcinomas, due to the limitations of the included studies, we did not make a subgroup analysis of the subjects by gender, smoking habit, pathological classification of cancer and different dosage. Advantages of the present study should be taken in the future clinical trials. However, it is important to note that exploratory subgroup analysis should not be overexplained. There are still some challenges. First of all, the sample size of the subgroup should be increased. The smoking patients and non-smokers should be analyzed as subgroups, while their sizes are relatively small. Secondly, it is hard to measure the status of EGFR mutation. Using molecular biomarkers to assess the relationship between EGFR TKIs treatment response and results is full of difficulties. Similarly, a large sample size would be needed to design a study which aims at evaluating predictive biomarkers, because the significant decline of the final number which is suitable for analyzing should be considered. In conclusion, the combination of chemotherapy and gefitinib is a more feasible therapeutic regimen for Asian patients with NSCLC than chemotherapy alone, and sequential administration is an effective combination strategy.

Author contributions
Le Cai and Qingda Zhao designed the study. Qingda Zhao and Kai Sun collected and evaluated the data. Xuemei Lei and Le Cai conducted statistical analysis. Qingda Zhao wrote the initial draft. Le Cai contributed to reviewing and approving the final version.

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