Systematic Review and Meta-Analysis

Medicine®

OPEN

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

Qingda Zhao, Master[a], Kai Sun, Bachelor[b], Xuemei Lei, Bachelor[c], Le Cai, Master[d,*]

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)

Editor: Undurti N. Das.

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.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Traditional Chinese Medicine, First Medical Center, Chinese PLA General Hospital, Beijing, [b] Penglai Traditional Chinese Medicine Hospital, Penglai, [c] Laibin Traditional Chinese Medicine Hospital, Laibin, [d] Department of Pharmacy, Medical Supplies Center, Chinese PLA General Hospital, Beijing, China.

[*] Correspondence: Le Cai, Department of Pharmacy, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China (e-mail: caile15009@163.com).

How to cite this article: Zhao Q, Sun K, Lei X, Cai L. A meta-analysis of the therapeutic effect of gefitinib combined with chemotherapy and chemotherapy alone in treating non-small cell lung cancer. Medicine 2020;99:31(e21490).

Received: 3 February 2020 / Received in final form: 10 May 2020 / Accepted: 27 June 2020

http://dx.doi.org/10.1097/MD.0000000000021490

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 chemotherapy 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" [Title/Abstract] OR Non-small cell lung cancer) AND ("Gefitinib" OR Iressa [Title/Abstract]). EMBASE: ("gefitinib":ab,ti OR "iressa":ab,ti) AND randomized AND controlled AND trial AND ("non-small cell lung cancer":ab,ti OR "nsclc":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 I^2-statistics to assess the magnitude of heterogeneity. If statistical heterogeneity is detected, the test results of statistical heterogeneity included in the study are: $P < .1$, $I^2 > 50\%$, 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 chemotherapy was performed in 2 trials[12,17]; the sequential therapeutic test was conducted in 2 trials.[13,18] The NSCLC patients in these 7 clinical trials include non-smokers and smoking patients, as well as patients with EFGR mutations, EFGR 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/m^2) + Cisp (75 mg/m^2) every 3 wk + gefitinib (250 mg/d) every 3 wk and ≤2 optional cycles of Cisp	Sequential	PFS, OS	25	0	Unknown
		55.5	24/18		4 cycles of Pem (500 mg/m^2) + Cisp (75 mg/m^2) every 3 wk			24	0	Unknown
Choi 2015	USA	60	44/9	IIIB/IV	Pac (175 mg/m^2) + 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		Pac (175 mg/m^2) + Carb (AUC 5), 4 cycles			2	44	43 patients with unknown EGFR mutation status, 3 patients with EGFR-wild-type
Jian 2017	China	56	109/88	IIIB/IV	Gem (1250 mg/m^2) + 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		Gem (1250 mg/m^2) + Carb (5 AUC)			110	0	Unknown
Soria 2015	Europe, Asia	60	133/85	IIIB/IV	Cisp (75 mg/m^2) + Pem (500 mg/m^2) on the first day of each cycle, G (250 mg)	Continuous	PFS, OR, OS, safety, tolerability	88	45	133 mutation (Exon 19 deletion), No EGFR-wild-type patient
		58	132/84		Cisp (75 mg/m^2) + Pem (500 mg/m^2) + placebo			91	41	132 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		Platinum-doublet chemotherapy + placebo (6 cycles)			96	202	Unknown
Tham 2009	Singapore	60	51/36	IIIB/IV	Gem (1000 mg/m^2) and Carb (100 mg/m^2) on days 1, 8, and 15 every 28 d + G (250 mg, 6 cycles)	Continuous	PFS, OS, RR	51	0	Unknown
		54	29/21		Gem (1000 mg/m^2) + Carb (100 mg/m^2) on days 1, 8, and 15 every 28 d			29	0	Unknown
Yu 2014	China	55.3	58/25	IIIB/IV	Pem (500 mg/m^2 d1) and either Cisp (75 mg/m^2 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		Pem (500 mg/m^2 d1) and either Cisp (75 mg/m^2 d1)			39	20	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 ratex, OS = overall survival, Pac = paclitaxel, Pem = Pemetrexed, PFS = progression-free survival, PR = partial response, RR = response rate.

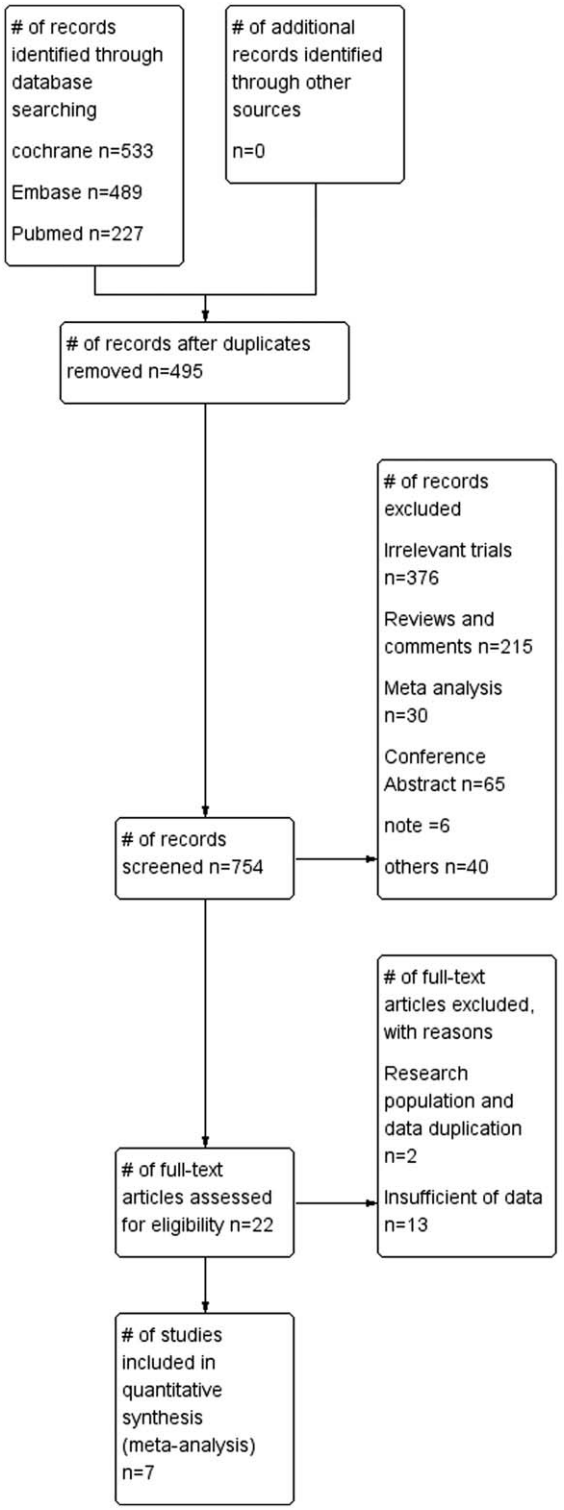

Figure 1. Flow chart of inclusion and exclusion.

not detected by the funnel plot in the primary outcomes. Of the 7 randomized controlled trials included, 2 were performed by the central randomized method[12,18]; 1 was performed by the envelope distribution method,[12] while follow-up loss was found in 3 trial cases.[14–16]

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 ($P < 0.00001$); $I^2 = 83\%$] (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	High risk	Unclear	High risk	Unclear	High risk	Low risk	Low risk
Jian 2017	Unclear	Unclear	Unclear	Unclear	High risk	Low risk	Low risk
Soria 2015	Low risk	Low risk	High risk	Unclear	Low risk	Low risk	Low risk
Takeda 2009	High risk	Unclear	High risk	Unclear	Low risk	Low risk	Low risk
Tham 2009	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	Low risk
Yu 2014	High risk	Unclear	High risk	Unclear	High risk	Low risk	Low risk

[95% CI 1.77, 4.52], $P < .00001$) between the 2 groups. See Supplemental Digital Content (Fig. S3, http://links.lww.com/MD/E635) for the forest plot.

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/E636) 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.[19] There were comparative studies on the therapeutic effects of chemotherapy with gefitinib and administration of gefitinib alone,[20] and there were also studies on whether administration of gefitinib had effects on survival.[21] However, there is no meta-analysis of the therapeutic effects of gefitinib with chemotherapy and chemotherapy alone, nor the comparation 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.[22,23]

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. Preclinical

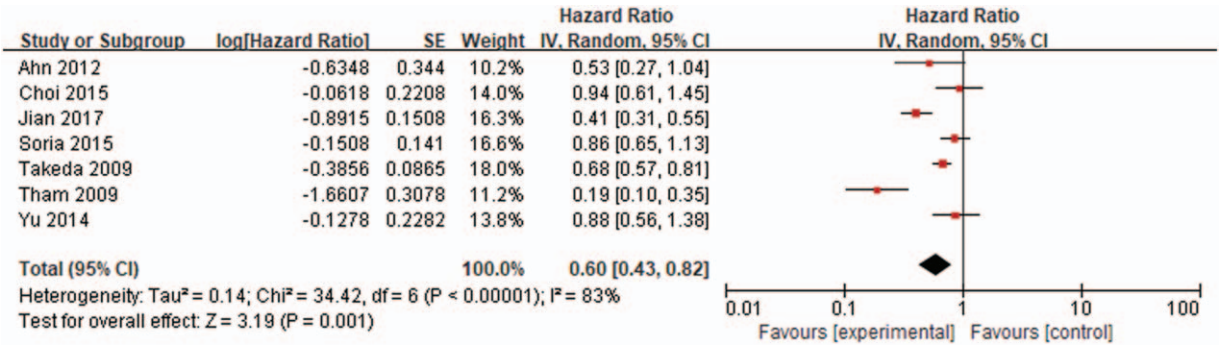

Figure 2. Forest plot of meta-analysis for PFS.

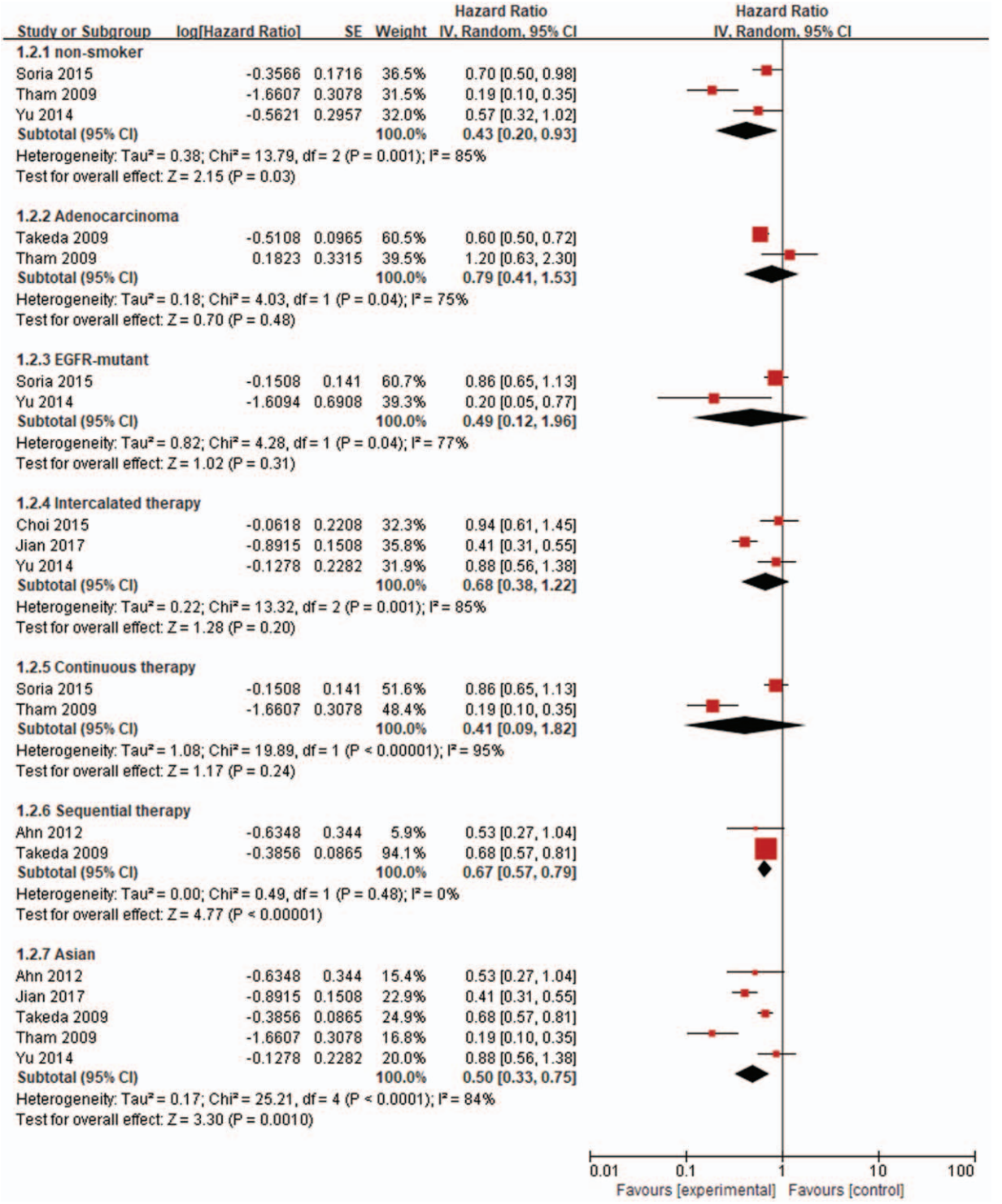

Figure 3. Forest plot of subgroup analysis for PFS.

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], $P = .008$) and thrombocytopenia (OR = 1.75 [95% CI 1.17, 2.63], $P = .007$)

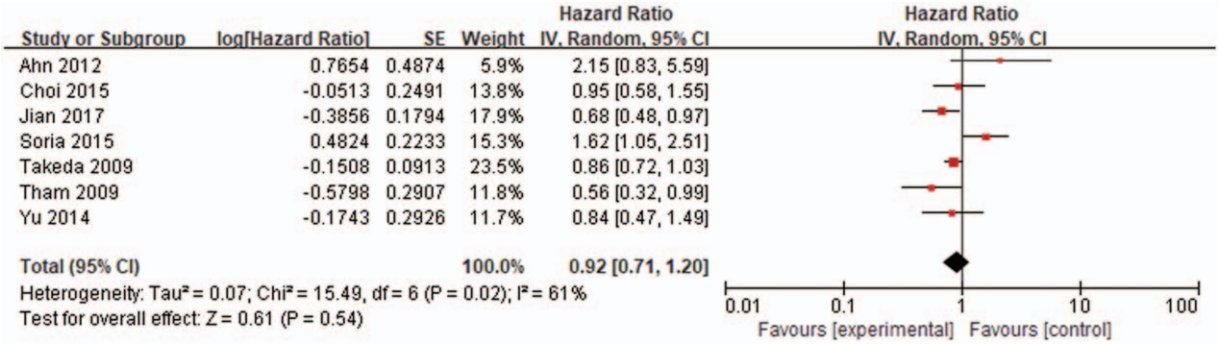

Figure 4. Forest plot of meta-analysis for OS.

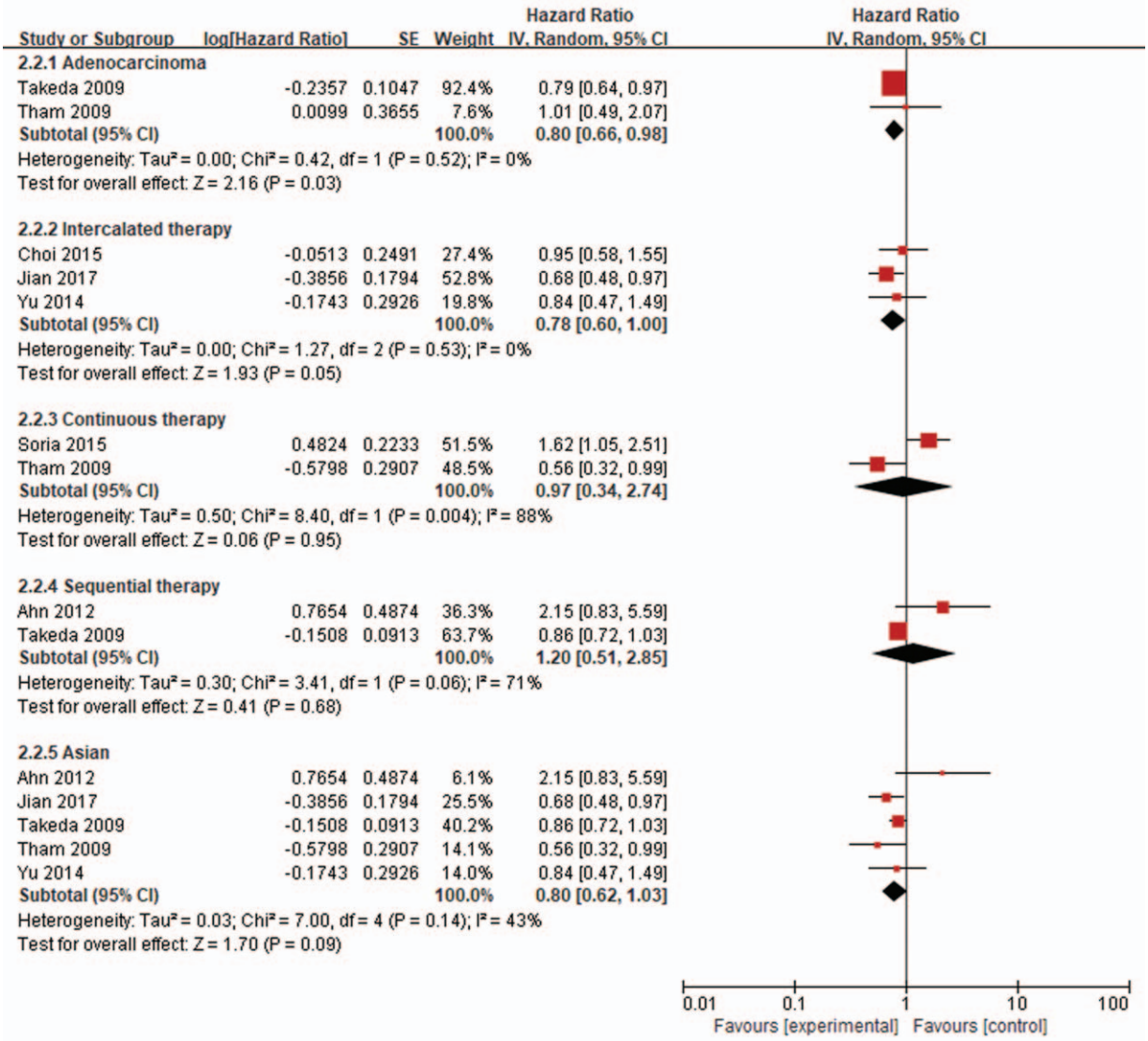

Figure 5. Forest plot of subgroup analysis for OS.

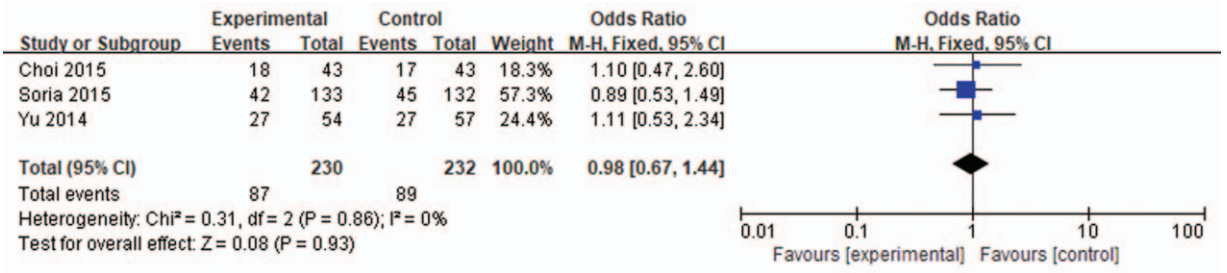

Figure 6. Forest plot of subgroup analysis for ORR.

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,[24] 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 second revision of the article. All authors contributed to reviewing and approving the final version.

References

[1] Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49:33–64.
[2] Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
[3] Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
[4] Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 2010;28:357–60.
[5] Non-small Cell Lung Cancer Collaborative GroupChemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;31:899–909.
[6] Ciardiello F, Caputo R, Bianco R, et al. Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. Clin Cancer Res 2000;6:2053–63.
[7] Xu JL, Jin B, Ren ZH, et al. Chemotherapy plus erlotinib versus chemotherapy alone for treating advanced non-small cell lung cancer: a meta-analysis. PLoS One 2015;10:e0131278.
[8] Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol 2013;14:777–86.
[9] Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1. J Clin Oncol 2004;22:777–84.
[10] Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2. J Clin Oncol 2004;22:785–94.
[11] Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;23:5892–9.
[12] Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 2015;16:990–8.
[13] Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203). J Clin Oncol 2010;28:753–60.
[14] Choi YJ, Lee DH, Choi CM, et al. Randomized phase II study of paclitaxel/carboplatin intercalated with gefitinib compared to paclitaxel/carboplatin alone for chemotherapy-naïve non-small cell lung cancer in a clinically selected population excluding patients with non-smoking adenocarcinoma or mutated EGFR. BMC Cancer 2015;15:763.
[15] Jian H, Li W, Ma Z, et al. Intercalating and maintenance gefitinib plus chemotherapy versus chemotherapy alone in selected advanced non-small cell lung cancer with unknown EGFR status. Sci Rep 2017;7:8483.
[16] Yu H, Zhang J, Wu X, et al. A phase II randomized trial evaluating gefitinib intercalated with pemetrexed/platinum chemotherapy or pemetrexed/platinum chemotherapy alone in unselected patients with advanced non-squamous non-small cell lung cancer. Cancer Biol Ther 2014;15:832–9.
[17] Tham CK, Choo SP, Lim WT, et al. Gefitinib in combination with gemcitabine and carboplatin in never smokers with non-small cell lung carcinoma: a retrospective analysis. J Thorac Oncol 2009;4:988–93.
[18] Ahn MJ, Yang JC, Liang J, et al. Randomized phase II trial of first-line treatment with pemetrexed-cisplatin, followed sequentially by gefitinib or pemetrexed, in East Asian, never-smoker patients with advanced non-small cell lung cancer. Lung Cancer 2012;77:346–52.
[19] Rossi A, La Salvia A, Galetta D, et al. Intercalated combination of chemotherapy and epidermal growth factor receptor inhibitors for patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis. Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 2016;27.
[20] Sheng Z, Zhang Y. EGFR-TKIs combined with chemotherapy versus EGFR-TKIs single agent as first-line treatment for molecularly selected patients with non-small cell lung cancer. Med Oncol 2015;32:420.

[21] Zhou H, Zeng C, Wang LY, et al. Chemotherapy with or without gefitinib in patients with advanced non-small-cell lung cancer: a meta-analysis of 6,844 patients. Chin Med J 2013;126:3348–55.
[22] Zhou JG, Tian X, Wang X, et al. Treatment on advanced NSCLC: platinum-based chemotherapy plus erlotinib or platinum-based chemotherapy alone? A systematic review and meta-analysis of randomised controlled trials. Med Oncol 2015;32:471.
[23] Qi WX, Shen Z, Lin F, et al. Comparison of the efficacy and safety of EFGR tyrosine kinase inhibitor monotherapy with standard second-line chemotherapy in previously treated advanced non-small-cell lung cancer: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2012; 13:5177–82.
[24] Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809–18.