Systematic Review and Meta-Analysis

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Combination of traditional Chinese medicine and epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of non-small cell lung cancer

A systematic review and meta-analysis

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Abstract

Background: In China, traditional Chinese medicine (TCM) is an increasingly important part of the treatment of non-small cell lung cancer (NSCLC), which usually includes a combination of prescription and syndrome differentiation. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been proven to be the first-line drugs for the treatment of advanced EGFR mutation-positive NSCLC. In China, EGFR-TKIs are used in combination with traditional Chinese medicines to reduce side effects and/or enhance effectiveness. Nevertheless, the relationship between TCMs and EGFR-TKIs remain unclear. This meta-review aimed to explore the clinical evidence of TCMs combined with EGFR-TKIs in the treatment of NSCLC.

Methods: Related studies were found by searching the databases of EMBASE, PubMed, Web of Science, MEDLINE, Cochrane library database, China Academic Journals (CNKI), Wanfang and Weipu. This study included 57 randomized controlled trials, all of these were processed by Stata software (version 12.0). In the study, all the materials are published articles, patient anonymity and informed consent and ethics Approval/Institutional review board are not necessary.

Results: This study demonstrated that the objective response rate was higher in the group of TCMs plus EGFR-TKIs than in the group of EGFR-TKIs alone (risk ratios 1.39, 95% confidence intervals [1.29, 1.50]). Further research of specific herbal medicines showed that Huangqi, Baishu, Fuling, Gancao, Maidong, Baihuashecao, Shashen, Dangshen and Renshen, had significant higher contributions to results.

Conclusion: TCMs may improve the efficacy of EGFR-TKIs in the treatment of NSCLC.

Abbreviations: CI = confidence intervals, CR = complete response, EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer, ORR = objective response rate, RR = risk ratios, TCM = traditional Chinese medicine.

Keywords: meta-analysis, non-small cell lung cancer, traditional Chinese medicine, tyrosine kinase inhibitors

Editor: YX Sun.

XS, MZ, and XH contributed equally to this work.

This study was funded by grants from National Natural Science Foundation of China (grant No. 81672932, 81730108, 81874380 and 81973635), and the Natural Science Foundation for Distinguished Young Scholars of Zhejiang Province (grant No. LR18H160001), Zhejiang Provincial Science and Technology Project of Traditional Chinese Medicine (grant No. 2019ZZ016).

Nothing in this manuscript has been published previously and has not been considered elsewhere. All authors read and approved the final version of the manuscript before submission.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Sui X, Zhang M, Han X, Zhang R, Chen L, Liu Y, Xiang Y, Xie T. Combination of traditional Chinese medicine and epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of non-small cell lung cancer: a systematic review and meta-analysis. Medicine 2020;99:32(e20683).

Received: 18 February 2020 / Received in final form: 5 May 2020 / Accepted: 11 May 2020

http://dx.doi.org/10.1097/MD.0000000000020683

1. Introduction

Lung cancer remains the most common cancer worldwide and the leading cause of cancer-related deaths.[1] There are 2 main types of lung cancer: small cell lung cancer and non-small cell lung cancer (NSCLC). While NSCLC accounts for approximately 85% of all lung cancer cases.[2] If patients are NSCLC, they are often diagnosed at an advanced stage and some new oncogene-targeted drugs and treatment regimens have been applied in clinical practice of NSCLC and achieved remarkable results. Epidermal growth factor receptor mutated NSCLC patients are sensitive to small molecule receptor tyrosine kinase inhibitors (TKIs), which occur in 60% to 70% of patients.[3,4] However, unfortunately, acquired drug resistance inevitably develops, leading to disease progression. Therefore, how to augment the efficacy and/or prevent the resistance of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are an imperative issue.

Natural product-based traditional Chinese medicine (TCMs) are widely used in China and have long been combined with traditional therapies to treat cancer patients.[5] Currently, the treatment of lung cancer by combination of TCMs and traditional therapy has become 1 of the most important means recognized in China. This treatment may assist in reducing the side effects, enhancing cytotoxic effects, preventing or overcoming resistance to anticancer drugs, and/or improving the quality of life of patients.[6–8] However, the relationship between TCMs and EGFR-TKIs remain less well elucidated.

In this article, we compared the objective tumor response rate (ORR) between EGFR-TKIs alone and EGFR-TKIs combined with TCMs in NSCLC. As a result, data of our study showed that the ORR was significantly higher in the TCM plus EGFR-TKIs group than in the EGFR-TKIs alone group. Further research of specific plant-based TCMs showed that Huangqi, Baishu, Fuling, Gancao, Maidong, Baihuashecao, Shashen, Dangshen and Renshen, had significant higher contributions to results. Taken together, our meta-analysis provides evidence that TCMs have the potential to enhance the efficacy of EGFR-TKIs in the treatment of NSCLC.

2. Materials and Methods

2.1. Search methods

From July 2009 to February 2019, related studies were found by searching the databases of EMBASE, PubMed, Web of Science, MEDLINE, and Cochrane library database, meanwhile, we also consulted some Chinese periodicals, such as China Academic Journals (CNKI), Wanfang and Weipu. The key words are as follows:

(1) Disorder: NSCLC and related terms;
(2) Intervention: traditional Chinese medicine, Chinese herbal medicine and related terms;
(3) Study type: randomized controlled trial and related terms.

The experimental and control groups included in this analysis were the intervention and EGFR-TKIs groups, respectively. All NSCLC cases were confirmed by histopathological examination. Two independent reviewers independently searched the literature and extracted the data.

2.2. The type of results measured

According to Response Evaluation Criteria in Solid Tumors (RECIST), the objective efficacy evaluation standard for solid tumors, it can be divided into: complete response (CR): all measurable tumor lesions disappear completely and maintain for more than 4 weeks; Partial response: the sum of the products of the largest diameter and the largest perpendicular diameter of each lesion was reduced by no less than 50% and maintained for more than 4 weeks without the appearance of new lesions. Stable disease: 50% decrease or more than 25% increase in the sum of the products of the largest diameter and the largest perpendicular diameter of each lesion; Progressive disease: at least 25% increase in the product of the largest diameter and the largest perpendicular diameter in at least 1 lesion or new lesion. ORR was the primary clinical outcome. CR plus partial response were combined into the data pool as ORR.

2.3. Types of research

All studies comparing RCT of TCMs plus EGFR-TKIs with EGFR-TKIs alone were selected and assessed for inclusion in our study.

2.4. Eligibility criteria

Patients in this study should meet the following criteria: Pathological diagnosis of NSCLC stage III/IV; One or more 2-dimensional measurable lesions; $18 < \text{age} < 80$; Karnofsky performance status (KPS) score ≥ 60 or Zubrod-ECOG-WHO (ZPS) score ≤ 2; Average life expectancy ≥ 3 months; normal heart, bone marrow, lung, liver and kidney function.

2.5. Data extraction

The Stata software application (version 12.0; StataCorp, College Station, TX) was used for data synthesis and analysis. Risk ratios (RR) and 95% confidence intervals (CI) were calculated; pooled RR and 95% CI were calculated using a fixed-effects model if the homogeneity assumption was not rejected ($P > .1$, $I^2 < 50\%$). If not, used the random effects model. Chi-square-based Q statistic was used for subgroup analysis based on between-trial heterogeneity, and statistical significance was considered when the P-value was less than .05 or I^2 was greater than 50%.

2.6. Bias detection

All statistics were analyzed using Stata 12.0 version (Stata Corporation, College Station, TX). Funnel plot is a method to identify the existence of publication bias by visual observation. This method takes the effect size as the abscissa and the y-coordinate is the standard error. The dispersion of small samples is large, so it is often at the bottom of the funnel plot, while that of large samples is small, so it is at the top.

3. Results

3.1. Literature search

As shown in Figure 1, these were the detailed steps for our literature retrieval. According to the retrieval method, 11,676 potential related citations were retrieved. After screening, this meta-analysis included 57 studies.[9–65] All studies conformed to the requirements of EGFR-TKIs regimen combined with TCMs intervention *versus* EGFR-TKIs regimen solely. ORR was provided in a similar manner. The 57 studies were classified as capsules (7 studies), granule group (2 studies), decoction group

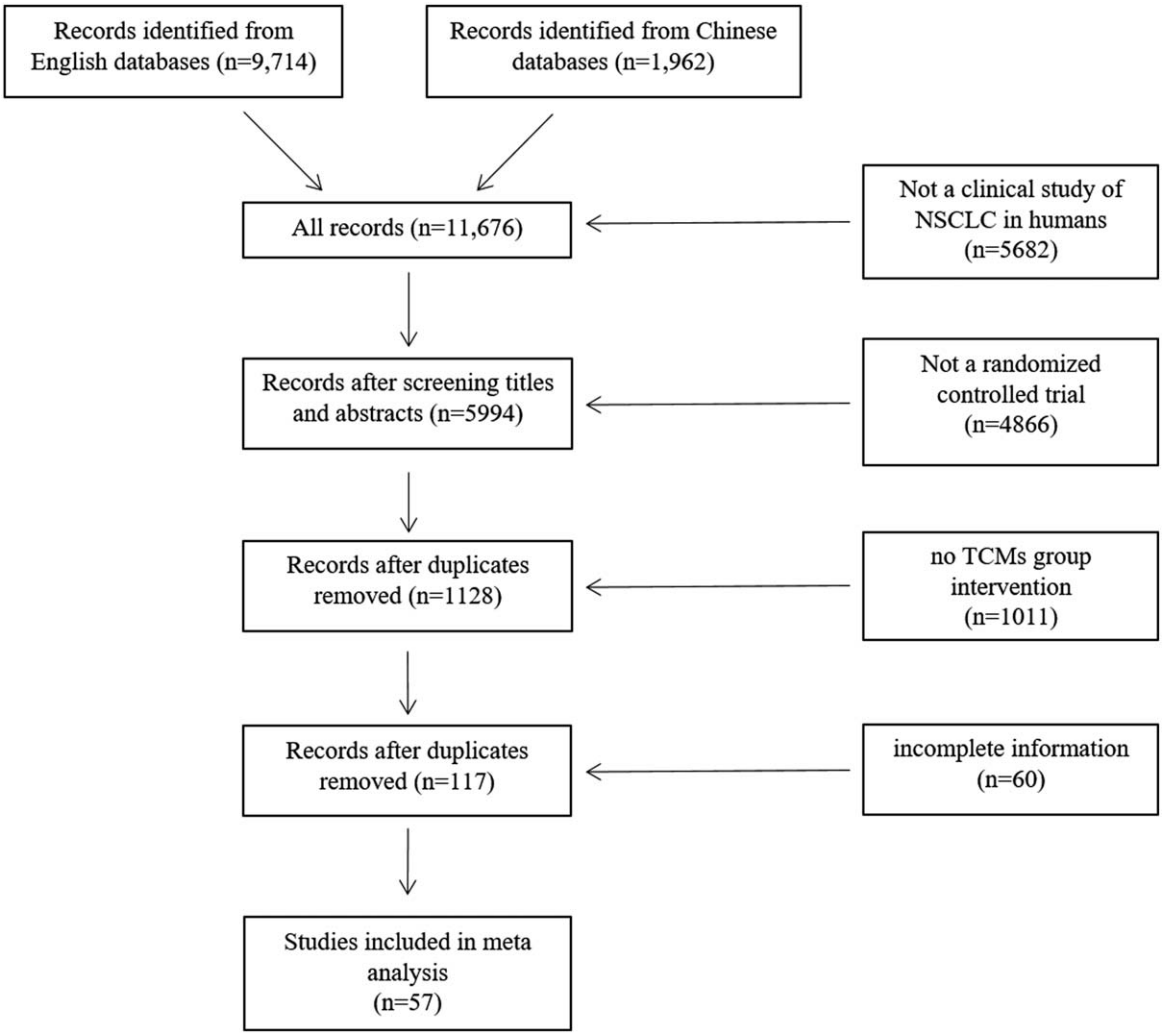

Figure 1. Flow diagram of the search and selection process of randomized controlled trials (RCTs) of EGFR-TKIs regimens combined with TCM for NSCLC.

(22 studies), TCM differentiation group (5 studies) and injection group (21 studies), there were a total of 4266 individuals, 2161 in the experimental group and 2105 in the control group. Table 1 summarizes the clinical characteristics of all participants, including TCM intervention dose, sample size, duration, dose, and cycle of EGFR-TKIs regimen.

3.2. Risk of bias assessment

We used RoB2.0 to assess the risk of bias in these articles. Except 2 articles (Kang X, et al; Lu S, et al), other studies have shown that with randomization, so the risk of deviation (SG) from sequence generation was assessed as "low". The experimental groups in the 2 studies were not randomized, so the risk of SG bias in this group was assessed as "high". Three studies (Zhang L, et al; Hou J, et al; Li Y, et al) described allocation concealment (AC), participant blindness (BPt), and these were decided "low risk". The other 54 studies did not describe the treatment course of AC and were therefore considered to be at "unclear risk". In cancer trials, it is difficult to blind participants. For selective outcome reporting (SOR), the study was assessed as "low-risk" only if the objectives and outcome measures described in the methods section are in the results section. Our results show TRR symmetry in funnel plots of the 57 studies, indicating a lower risk of publication bias.

3.3. Tumor response according to RECIST criteria

Fifty-seven studies used RECIST criteria to assess TRR. A meta-analysis of CR and TRR was performed. RR ≥ 1 (IV model, fixed, 95% confidence interval), it is beneficial for the test group. Based on the different dosage forms of medicine, they were divided into 6 groups for meta-analysis: total (57 studies); capsule group (7 studies); granule group (2 studies); decoction group (22 studies); TCM syndrome group (5 studies); injection group (21 studies).

Total group. In 57 studies (n = 4266, Table 1), ORR improved significantly in the experimental arm (RR 1.39, 95% CI [1.30, 1.50]); $P = .621 > .05$, $I^2 = 0\%$), indicating low heterogeneity, the fixed effect model was used for calculating OR value of combined effect size (Fig. 2).

Capsule group. Seven studies were included in the capsule group (n = 547, Table 1). TRR improved significantly (RR 1.30 [1.05–1.63], $I^2 = 0\%$). Moreover, the TRR funnel plot is symmetric. Two studies were included in the granule group

Table 1

Characteristics of randomized controlled trial of EGFR-TKI combined with traditional Chinese medicine in the treatment of non-cellular lung cancer (NSCLC).

First Author (Year)	Sample Size T/C; Gender (M) T/C; Age T/C	TNM (T/C); KPS/ZPS	TCM intervention; dosage and duration	EGFR-TKI regimen; dose and duration	Risk of Bias (SG, AC, BPt, BOA (obj.), IOD, SOR)
Feng Y (2013)	30/30;18/42 (all);62.6 (all)	III b – IV; KPS≥60	Matrine Injection;20 mL and 250 ml NS, IV, qd, 14 d/course, until the disease progresses	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Yang X (2018)	27/32;8/8;65.6/63.6	III b – IV; ZPS < 2	Yiqi Yangyin Sanjie Decotion;200 mL, po, bid, until the disease progresses	Gefitinib; 250 mg, po, qd; or Erlotinib;150 mg, po, qd; or Icotinib;125 mg, po, tid, until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Qian J (2014)	12/13;15/10 (all);58 (all)	III b – IV; NS	Kanglaite Injection; 200 mL, IV, qd, 28 d/cycle, until the disease progresses	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Li X (2017)	103/103;34/31;61.45±21.15/62.21±22.36	III b – IV; KPS > 60	Traditional Chinese medicine combination program; 200 mL, po, bid, until the disease progresses	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD:U, SOR: L
Kang X (2012)	18/22;6/8;NS	III b – IV; ZPS < 2	FeiYan NingFang; 150 mL, po, bid, until the disease progresses	Gefitinib; 250 mg, po, qd; or Erlotinib;150 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Liu D (2018)	40/40;32/31;62.15±11.38/61.96±11.04	III – IV; KPS > 60	Astragalus polysaccharide injection; 250 mg, IV, qd, 21 d/cycle, NS	Gefitinib; 250 mg, po, qd, 21 days/cycle, NS	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Zhang H (2014)	30/30;16/17;64.60±11.34/65.83±11.45	NS; KPS≥60	YiQi TongLuo JieDu Decoction; 200 mL, po, bid, until the disease progresses	Gefitinib; 250 mg, po, qd; or Erlotinib;150 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Gong J (2017)	31/29;20/18;55.70±9.08/53.80±6.08	NS; KPS≥60	Sweetened with ginseng soup; 200 mL, po, bid, for 2 mo	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Zhang Q (2016)	15/15;6/7;64.6±2.2/63.2±1.7	III b – IV; ZPS < 2	Elemene injection; 500 mg, IV, qd, 21 d/course, until the disease progresses	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Fu D (2013)	19/19;28/10 (all);65 (all)	III – IV; KPS > 60	Renshen Erling Decoction; NS, po, bid, 1mo/cycle, 3 cycle	Erlotinib; 150 mg, po, qd, ac1h or pc2h, po, qd, 1month/cycle,3 cycle	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Yuan L (2017)	30/30;15/13;63.27±7.47/59.57±9.59	III b ~ IV; KPS≥60	Yi Fei prescription; 200 mL, po, bid, 4 wk/cycle, 2 cycles	Gefitinib; 250 mg, po, qd, 4 weeks/cycle, 2 cycles	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Zhang M (2017)	27/23;13/12;64.96±12.89/68.13±9.83	III b – IV; NS	Yangyin Jiedu Decoction; 200 mL, po, bid, until the disease progresses	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Yang C (2016)	50/50;26/27;58.7±2.1/57.4±2.4	III b – IV; NS	Fuzheng Kangai Fang; NS, po, bid, for 21 d	Gefitinib; 250 mg, po, qd, for 21 d	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Huang Y (2011)	38/38;8/68 (all); 56±2.5 (all)	NS;NS	Bufeidingchuan Prescription; 1 dose, qd, for 30 d	Gefitinib; 250 mg, po, qd, 30 d/cycle, more than 1 cycle	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Zhu S (2016)	38/38;22/20;67.38±5.53/68.52±5.63	III – IV; KPS≥60	Java brucea oil emulsion injection;30 mL and 250 mL 0.9% NS, IV, qd, 15d/course, for 2 mo	Gefitinib; 250 mg, po, qd, 30 d/cycle, for 2 mo	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Li B (2016)	25/25;37/13 (all);68.65±5.82 (all)	III – IV; KPS≥60	Baihegujin Decoction; NS, po, tid, pc1h, for 20 consecutive days a mo	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Li Y (2018)	30/30;15/16;61.80±9.11/60.03±8.98	III b – IV; KPS > 70	Supplementing qi and nourishing yin soup; po, qd, for 1 mo	Erlotinib; 150 mg, po, qd, ac1h or pc2h, for 1 mo	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Zhao Y (2015)	50/50;27/24;70/69	III b – IV; KPS≥60	Tongyang fuzheng soup; po, bid, for 2 mo	Gefitinib; 250 mg, po, qd, until the disease progresses	SG: L, AC: U, BPt: H, BOA: U, IOD: U, SOR: L
Yu Y (2016)	39/28;22/16;65.4±6.7/65.1±6.8	III – IV; NS	Astragalus polysaccharide injection;250 mg and 500 mL 0.9%NS,28d/cycle, NS	Gefitinib; 250 mg, po, qd, 28 d/cycle, NS	SG: H, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Zhao Y (2017)		III – IV; NS			SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L

(*continued*)

Table 1

(continued).

First Author (Year)	Sample Size T/C; Gender (M) T/C; Age T/C	TNM (T/C); KPS/ZPS	TCM intervention; dosage and duration	EGFR-TKI regimen; dose and duration	Risk of Bias (SG, AC, BPt, BOA (obj.), IOD, SOR)
	30/30;14/15;56. 7±6.9/57.3.3±7.6		Feiliu Decoction; 150 ml, po, qid, 30 d/cycle, 2 cycles	Icotinib; 125 mg, po, tid; 30 d/cyccle, 2 cycles	
Tang C (2017)	34/31;22/19;56.3±8.1/60.4±8.6	III b – IV; ZPS≤2	Gong ai san jie fang; 200 mL, po, tid, for 8 wk	Icotinib; 125 mg, po, tid, until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Sun P (2019)	30/30;21/20;64.32±5.24/64.36±5.25	NS;NS	Gastric Control and Renal Centronine; Gastric Control1, 50 mL, po, bid, 3 d, Gastric Control 2, 25 mL, po, tid or qid, 3 days, Renal Centronine1,50 mL,po,bid,3 d,for 4∼8 mo	Gefitinib;250 mg,po,qd,for 2∼3 mo	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Zhang S (2014)	55/55;24/26;51.9±3.4/52.5±3.5	III – IV; KPS≥60	Kanglaite Injection;100 mL,IV,bid,21d/cycle,3 cycles	Gefitnib;250 mg,po,qd,21days/cycle,3 cycles	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Tu X (2011)	20/20;11/13;61±18.03/58±16.74	IV; KPS > 60	zi Yinfuzheng fang;250 mL,po,bid,until the disease progresses	Gefitinib;250 mg,po,qd,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Jia Y (2009)	30/28;21/20;64.1 (all)	III – IV; KPS≥60	Xiaoyantang plus-minus prescriptions;150 mL, po,bid,30d/cycle,for 2mo	Erlotinib;150 mg,po,qd,30days/cycle,for 2months	SG: L, AC: U, BPt: U, BOA: U, IOD: U, SOR: L
Lu S (2015)	59/60;34/33;64.59±9.08/65.46±7.56	III b – IV; NS	TCM syndrome differentiation; NS,until the disease progresses	Icotinib;125 mg,po,tid,until the disease progresses	SG: H, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
LI J (2010)	35/35;20/21;58.65/57.90	III – IV; ZPS < 2	Feiyiliuheji;30 mL,po,bid,for 8 wk	Erlotinib;150 mg,po,qd,for 8 weeks	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Yang W (2016)	43/43;24/23;65.46±7.86/65.47±7.88	III b – IV; KPS > 60	Kanglaite Injection;200 mL,IV,bid,21d/cycle,3 cycles	Icotinib;125 mg,po,tid,21days/cycle,3 cycles	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Guo Q (2016)	30/30;16/18;57.47±9.57/58.63±11.11	III b – IV; KPS≥60	Guben Xiaozheng Decoction; 300 mL,po,bid, NS	Gefitinib;250 mg,po,qd,NS	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Feng Y (2016)	60/20;59/21 (all);62.58±6.46 (all)	III b – IV; ZPS < 2	Bufei Huayu Tang;200 mL,po,bid,30 d/cycle,3 cycles	Gefitinib;250 mg,po,qd,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD:L, SOR: L
Zhang P (2010)	30/30;0/60 (all);55.47±11.2/56.41±12.7	NS;NS	The Powder for Removing Rashes;1 dose,po, qd,5doses/wk,for 2 wk	Gefitinib;250 mg,po,qd,30days/cycle,more than 1 cycle	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Qi J (2017)	30/30;37/23 (all);68.12±9.76 (all)	NS;NS	Compound Kushen injection; 2∼4 mL,IM,bid, or 12 ml,IV, 200mL/cycle,for 1 mo	Gefitnib;250 mg,po,qd,NS	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Zhang J (2018)	38/38;20/21;57.82±8.41/56.28±10.02	III b – IV; NS	Xiao aiping Injection;80 mL and 500 mL 5% GS,IV,qd,for 4 wk	Icotinib;125 mg,po,tid,for 4 weeks	SG: L, AC: U, BPt: H, BOA:L, IOD: L, SOR: L
Cao Y (2014)	29/29;36/22 (all);68.4±6.5 (all)	III b – IV; ZPS < 2	Java brucea oil emulsion injection;30 mL and 250 mL 0.9%NS,IV,qd,30 d/course,until the disease progresses	Gefitinib;250 mg,po,qd,30days/course,until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Yang W (2016)	32/32;17/16;63.0±0.46/64.0±0.32	IV; KPS≥60	Xiaoaiping Injection;60 mL,IV,qd,4 wk/cycle,2 cycles, After that 2 cycles pre 4 mo,until the disease progresses	Gefitnib;250 mg,po,qd,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Guo J (2013)	32/31;35/28 (all);57.4 (all)	III – IV; KPS > 60	Kanglaite Injection;100 ml,IV,bid,21d/cycle,3 cycles	Erlotinib;150 mg,po,qd,ac1h or pc2h,21days/cycle,3 cycles	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: U
Wei W (2018)	37/37;26/25;55.31±7.12/54.62±6.25	NS;NS	Aidi Injection;80ml0.9%NS,IV,qd,15days/course,NS	Gefitnib;250 mg,po,qd,15days/course,NS	SG: H, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Zhang L (2018)	31/31;19/17;44.5±6.540.6±8.5	III – IV; KPS≥60	Aidi Injection;100 mL,IV,qd,30 d/cycle,q10d,2 cycles	Gefitnib;250 mg,po,qd,30 days/cycle,q10d,2 cycles	SG: L, AC: L, BPt: L, BOA: L, IOD: L, SOR: L

(*continued*)

Table 1

(continued).

First Author (Year)	Sample Size T/C; Gender (M) T/C; Age T/C	TNM (T/C); KPS/ZPS	TCM intervention; dosage and duration	EGFR-TKI regimen; dose and duration	Risk of Bias (SG, AC, BPt, BOA (obj.), IOD, SOR)
Hou J (2017)	54/54;22/21;73.65±13. 14/ 74.47±12.52	III – IV; KPS > 70	Aidi injection;60 mL and 450 mL 0.9%NS,IV, qd,for 10 d	Gefitnib;250 mg,po,qd,for 10 days	SG: L, AC: L, BPt: L, BOA: L, IOD: L, SOR: L
Wang X (2016)	59/57;70/46 (all);59.5±10.6 (all)	NS;NS	Xiaoaiping injection;80 mL,IV,qd,28days/cycle; NS	Gefitnib;250 mg,po,qd,28days/cycle;NS	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Liang J (2014)	40/40;22/21;64.60±0.23/ 66.24±0.36	III – IV; KPS > 60	Aidi Injection;100 mL and 500 mL 0.9%NS,IV, qd,15d/cycle,until the disease progresses	Gefitnib;250 mg,po,qd,ac1h,until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD:L, SOR: L
Zhang Q (2011)	39/39;18/18;52.4±4.0/56.3± 5.1	III – IV; KPS≥60	Kanglaite Injection;100 mL,IV,qd,21d/ cycle,3cycles	Gefitnib;250 mg,po,qd,21days/cycle,3cycles	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Wang T (2018)	52/51;30/27;54.34±7.18/ 56.09±7.25	NS; KPS > 65	Aidi Injection;80mL0.9%NS,IV,qd,15d/course, NS	Gefitnib;250 mg,po,qd,15days/course,NS	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Zhou Y (2017)	60/60;72/48 (all);73.0±2.5 (all)	IV; KPS > 60	elemene injection;600 mg and 5%GS,IV,qd,for 10 d	Gefitnib;250 mg,po,qd,for 10 days	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Wang Y (2015)	20/20;25/15 (all);56.3±5.1 (all)	III – IV; KPS≥60	Shenlingbaizhu granule;6g,po,tid,21 d/cycle,3 cycles	Gefitnib;250 mg,po,qd,21 days/cycle,3 cycles	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Zhang X (2014)	21/20;19/22 (all);NS	III b – IV; 60 < KPS < 90	Shenlingbaizhu granule;3g,po,tid,until the disease progresses	Gefitinib;250 mg,po,qd;or Erlotinib;150 mg,po, qd,until the disease progresses	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Zhao S (2018)	40/40;28/24;60.23±8.75/ 62.42±9.84	III b – IV; ZPS < 2	Compound Banmao Capsules; 3 grains/time, po, bid, for 9 wk	Gefitnib;250 mg,po,qd,for 9 weeks	SG: L, AC: U, BPt: H, BOA: U, IOD: L, SOR: U
Liu L (2017)	47/47;49/45 (all);63.48±3.33/ 63.37±3.21	III – IV; NS	Cidan Capsules;1.35g,po,qid,for 2 mo	Erlotinib;150 mg,po,qd,for 2 months	SG: L, AC: U, BPt: H, BOA: U, IOD: U, SOR: U
Wang J (2017)	40/40;16/17;53.60±10.96/ 53.65±10.94	III b – IV; ZPS≤2	Kanglaite capsules; 2.7g,po,bid,until the disease progresses	Gefitnib;250 mg,po,qd,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Hou J (2018)	45/45;23/21;67.4±5.8/68.2± 6.1	III b – IV; ZPS < 2	Yangzheng Xiaoji Capsules;1.56g,po,tid,for 8 wk	Erlotinib;150 mg,po,qd,for 8 weeks	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Wang X (2017)	35/35;21/22;51.6±12.3/52.1± 12.8	III b – IV; KPS≥70	Pingxiao capsule;2.6g,po,tid,until the disease progresses	Gefitnib;250 mg,po,qd,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Liu H (2012)	50/50;14/16;62/65	III b – IV; KPS≥60	Shenyi capsule;20 mg,po,bid,until the disease progresses	Gefitnib;250 mg,po,qd,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L
Gong Z (2017)	80/40,80/40;20/42,19/42;41± 7/40±6,39±5/40±6	III b – IV; KPS > 60	Aiyu Capsules or Fufang Banmao Capsules; Aiyu Capsules,0.35g,po,tid,for 8 wk,or Fufang Banmao Capsules,1g,po,tid,for 8 weeks	Gefitnib;250 mg,po,qd,for 8 weeks	SG: L, AC: U, BPt: U, BOA: L, IOD: L, SOR: L
Liu Y (2014)	56/56;64 (all);51.53±4.83 (all)	III b – IV; KPS≥70	TCM syndrome differentiation; NS,po,bid,until the disease progresses	Gefitnib;250 mg,po,qd,pc 30 min,until the disease progresses	SG: L, AC: U, BPt: H, BOA: U, IOD: U, SOR: L
Liu W (2016)	32/32;17/19;61.12±12.37/ 61.35±11.35	III b – IV; KPS > 60	TCM syndrome differentiation; 200 mL,po,bid, until the disease progresses	Gefitnib;250 mg,po,qd,pc30 min,until the disease progresses	SG: L, AC: U BPt: H, BOA: L, IOD: L, SOR: L
Li Y (2016)	24/24;16/13;NS	III b – IV; KPS > 60	TCM syndrome differentiation; NS,po,bid,for 3 mo	Gefitnib;250 mg,po,qd,for 3 months	SG: L, AC: L, BPt: L, BOA: L, IOD: L, SOR: L
Wu Q (2017)	30/30;8/15;NS	III b – IV; ZPS≤2	TCM syndrome differentiation; 300 mL,po, bid,4wk/cycle,until the disease progresses	Icotinib;125 mg,po,tid,until the disease progresses	SG: L, AC: U, BPt: H, BOA: L, IOD: L, SOR: L

AC = allocation concealment, ac = ante cibum, bid = twice per day, BOA (obj) = blinding of outcome assessment (objective outcome measure, ie, TRR), BPt = blinding of participants/personnel, C = control group, ECOG = Eastern Cooperative Oncology Group Performance Status, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitors, H = high risk, ID = intravenous drip, IOD = incomplete outcome data, KPS = Karnofsky Performance Status, L = low risk, M = male, NS = not stated, pc = post cibum, po = per os, q.10 d = every ten days, Risk of Bias Categories, qd = once per day, SG = sequence generation, SOR = selective outcome reporting. Risk of Bias Judgements, T = treatment group, TCM = traditional chinese medicine, tid = thrice per day, TNM = cancer staging system ("T" for tumor, denotes the extent of the intestinal wall; "N" for lymphatic node, the amount of lymphatic node involvement; and "M" for the metastasis), TRR = tumor response rate, U = unclear risk, ZPS = Zubrod-ECOG-WHO.

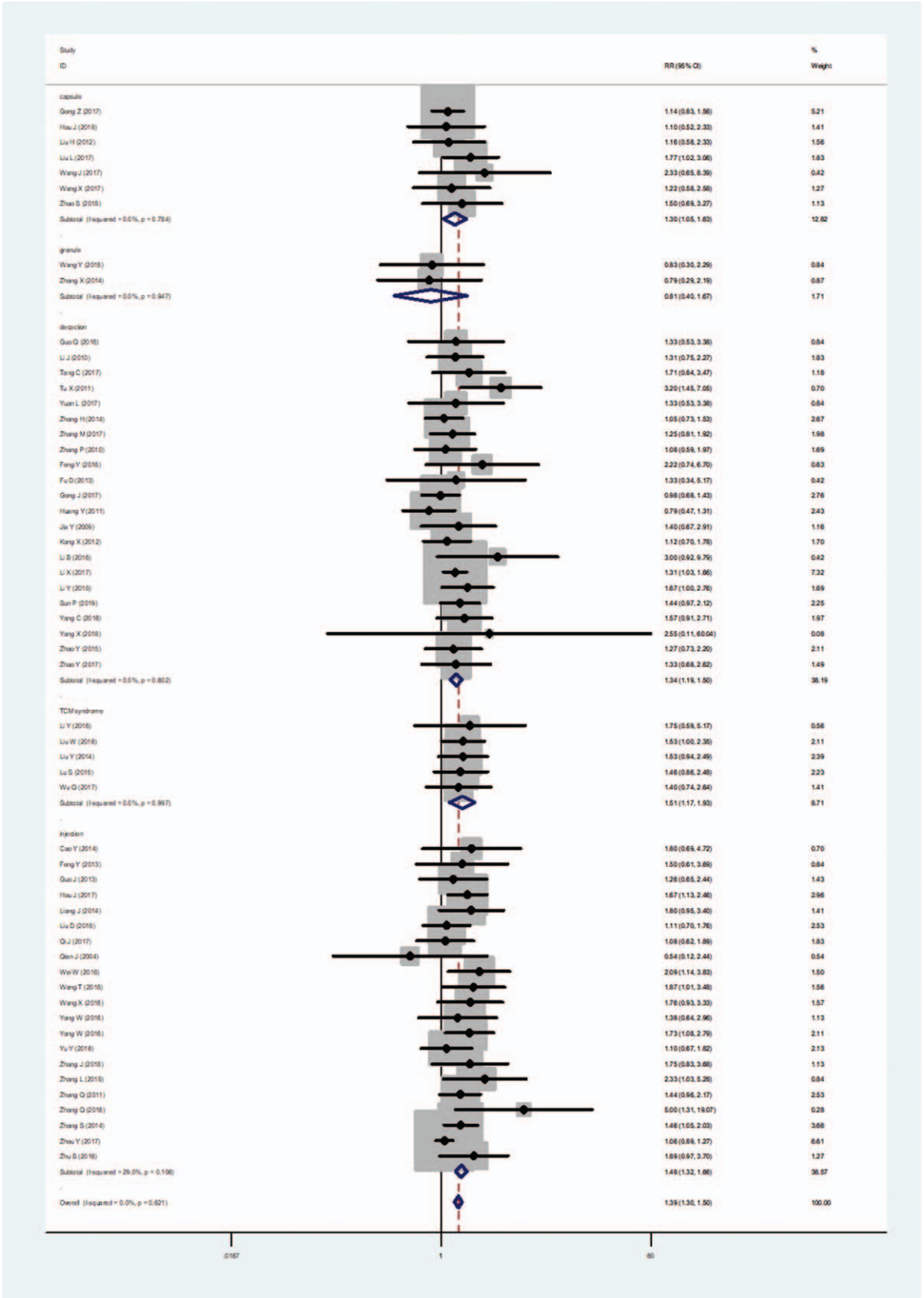

Figure 2. Forest plot of meta-analysis of tumor response rate (TRR) of TCM plus EGFR-TKIs-based regimens versus EGFR-TKIs alone.

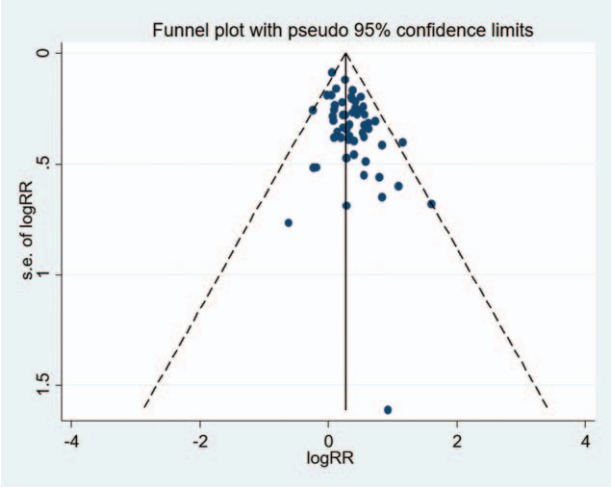

Figure 3. Funnel plot with pseudo 95% confidence limits.

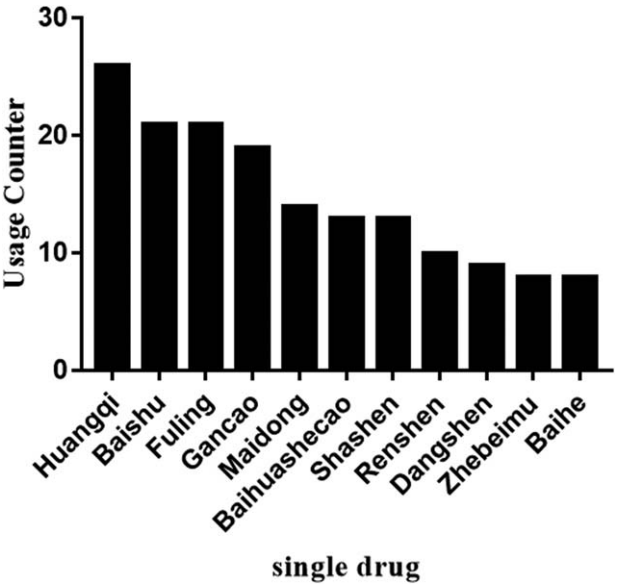

Figure 4. Single TCM has the anticancer potential.

(n = 73, Table 1). There may be effective improvements for TRR (RR 0.81 [0.40–1.67], $I^2 = 0\%$). TRR funnel plot is slightly asymmetric; maybe the sample size is too small.

Decoction group. Twenty-two studies were included in the decoction group (n = 1629, Table 1). Significant improvement in TRR (RR 1.34 [1.19–1.50], $I^2 = 0\%$). The TRR funnel plot is obviously symmetrical.

TCM syndrome group. Five studies were included in the TCM syndrome group (n = 372, Table 1). There was also a significant improvement in TRR (RR 1.51 [1.17–1.93], $I^2 = 0\%$). The TRR funnel plot is symmetric.

Injection group. Twenty-one studies were included in the injection group (n = 1645, Table 1). TRR improved significantly (RR 1.48 [1.32–1.66], $I^2 = 0\%$). The TRR funnel plot is symmetric.

To put it briefly, the curative effect of adjuvant treatment of lung cancer with traditional Chinese medicine was observed in the order: TCM syndrome group > injection group > decoction group > capsule group > granule group.

3.4. Bias in meta-analysis

In Funnel plot (Fig. 3), we can clearly see that our sample studies are large (57 studies) and the estimated effect size varies less. Therefore, the estimated effect size points are scattered at the top of the funnel plot, and funnel plots can be roughly symmetrical. Therefore, the bias of our studies is relatively small.

3.5. The effects of multi-ingredient TCM

In the 57 studies with 46 prescriptions, we made an analysis on the use of single and multiple traditional Chinese medicine (Fig. 4 and Table 2).

Level 1: Single TCMs. One hundred fifty-one ingredients in the formulation have been included in this study. Of these, 27 ingredients were used in 5 or more formulations. The name of each ingredient was displayed in pin yin. According to their frequency of use in prescription, here is a list of TCMs: Huangqi (n = 26), baishu (n = 21), fuling (n = 21), gancao (n = 19), maidong (n = 14), baihuashecao (n = 13), shashen (n = 13), and renshen (n = 10) (Fig. 4).

Level 2: Combinations of 2 TCMs. In this level, a total of 22 pairs of TCMs were used more than 7 times, including huangqi + baishu (n = 18), huangqi + fuling (n = 14), huangqi + gancao (n = 12), baishu + fuling (n = 17), baishu + gancao (n = 13), huangqi + baihuashecao (n = 12), huangqi+ maidong (n = 11), huangqi + shashen (n = 11), baishu + maidong (n = 11), fuling + gancao (n = 11), fuling + baihuashecao (n = 11), baishu + baihuashecao (n = 10), fuling + maidong (n = 10), maidong + shashen (n = 10) (Table 2).

Other levels: Combinations of 3 and more TCMs. These combinations of TCMs are used no less than 5 times in 46 prescriptions and they were shown in Table 2.

3.6. Potential synergistic effects selection for TCMs

TCMs were divided into qi-tonifying herbals (Huangqi, Baishu, Gancao, Dangshen, Renshen, Shanyao), Yin-nourishing berbals (Shashen, Tiandong, Maidong, Baihe, Nvzhenzi), heat-clearing phlegm-transforming herbals (Zhebeimu, Gualou, Jiegeng) in turn from high frequency to low frequency (Table 2). Moreover, when 2 drugs are combined, 2 qi-tonifying drugs are the most; the second are qi-tonifying drugs + clearing damp herbals. For more combinations, the combination of qi-tonifying and clearing damp berbals is the most common.

4. Discussion

At present, western medicine is the main treatment for lung cancer. Western medicine plays a role in directly fighting against cancer cells. While, traditional Chinese medicines (TCMs) for cancer treatment often plays a multi-target or multi-effect therapeutic role.[66] There are many aspects in the treatment of cancer with TCMs, such as enhancing the inhibitory effect on cancer cells, inhibiting the angiogenesis of tumors, and reversing the effect of drug resistance targeting. Shu Q et al[67] found that aqueous extract of Taxus chinensis in combination with erlotinib inhibits the proliferation of cancer cells by inhibiting the expression of P-EGFR, P-ERK, and P-JNK proteins in the

Table 2

The usage of single and multiple traditional Chinese medicines.

Level	Combination	Number of prescription	Weight (%)
1	Huangqi	26	56.52
1	Baishu	21	45.65
1	Fuling	21	45.65
1	Gancao	19	41.30
1	Maidong	14	30.43
1	Baihuashecao	13	28.26
1	Shashen	13	28.26
1	Renshen	10	21.47
1	Dangshen	9	19.57
1	Zhebeimu	8	17.39
1	Baihe	8	17.39
2	Huangqi + Baishu	18	39.13
2	Baishu + Fuling	17	36.96
2	Huangqi + Fuling	14	30.43
2	Baishu + Gancao	13	28.26
2	Huangqi + Gancao	12	26.09
2	Huangqi + Baihuashecao	12	26.09
2	Fuling + Gancao	11	23.91
2	Fuling + Baihuashecao	11	23.91
2	Baishu + Maidong	11	23.91
2	Huangqi + Shashen	11	23.91
2	Huangqi + Maidong	11	23.91
2	Fuling + Maidong	10	21.74
2	Baishu + Baihuashecao	10	21.74
2	Maidong + Shashen	10	21.74
3	Huangqi + Baishu+Fuling	14	30.43
3	Huangqi + Baishu+Gancao	10	21.74
3	Huangqi + Baishu+Maidong	10	21.74
3	Huangqi + Baishu+Baihuashecao	10	21.74
3	Baishu + Fuling + Gancao	10	21.74
3	Huangqi + Fuling + Baihuashecao	10	21.74
3	Baishu + Fuling + Maidong	9	19.57
3	Baishu + Fuling+ Baihuashecao	9	19.57
4	Huangqi + Baishu + Fuling + Maidong	9	19.57
4	Huangqi + Baishu + Fuling + Baihuashecao	9	19.57
4	Huangqi + Baishu + Fuling+Gancao	7	15.22
4	Huangqi + Baishu + Fuling + Shashen	7	15.22
4	Huangqi + Baishu+ Maidong + Baihuashecao	7	15.22
4	Huangqi + Baishu + Maidong + Shashen	7	15.22
4	Baishu + Fuling + Maidong + Shashen	7	15.22
5	h +b+f+m+Baihuashecao	6	13.04
5	h+b+f+m+Shashen	6	13.04
5	h+b+m+bh+Shashen	5	10.87
5	h+b+f+g+Maidong	5	10.87
5	h+b+m+bh+Shashen	5	10.87

b = Baishu, bh = Baihuas hecao, f = Fuling, g = Gancao, h = Huangqi, m = Maidong.

EGFR/MAPK signaling pathway. Kou J et al[68] found that Xiaoaiping combined with hyperthermia could inhibit the proliferation of gefitinib-resistant human lung adenocarcinoma A549 cell line by reducing the expression of vascular endothelial growth factor and mediating angiogenesis. Gao F et al[69] found that β-elemene can reverse PC9/ZD resistance, which probably is related with its down-regulation of p-Erk and p-Akt protein expression.

Molecular targeted therapy has been recognized as 1 of the effective methods to treat some cancer types. The Food and Drug Administration has tested and approved EGFR-TKIs as molecularly targeted agents for the treatment of NSCLC, mainly including the First-generation drug gefitinib (Iressa, 2003) and Erlotinib (Tarceva, 2004); The Second generation drug Afatinib (Afatinib, Gilotrif, 2013), and the third generation of drugs for Osimertinib (Osimertinib, Tagrisso, 2015). At present, thousands of studies have demonstrated the effectiveness of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as molecular targeted agents.[70,71] Many studies have now shown that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have multidrug resistance mechanisms in EGFR-mutated NSCLC. Nevertheless, relapsed drug resistance in EGFR-TKIs remains a major clinical challenge due to heterogeneous mechanisms.[72] Because of the high cost of treatment and the lack of relevant clinical research results, in particular, there are few research cases of combined application of TCM. To explore the clinical basis of adding TCMs to EGFR-TKIs in the treatment of NSCLC, our study evaluated 57 studies that were classified as capsule group (7studies), granule group (2 studies), decoction group (22 studies), TCM differentiation group (5 studies) and injection group (21 studies), which had 4266 experimental subjects, 2161 in the experimental group and 2105 in the control group. In this study, TCM or TCM plus EGFR-TKIs in the treatment of NSCLC get the better of EGFR-TKIs solely in terms of short-term efficiency and long-term survival rate, reflecting the synergistic effect of TCM-assisted EGFR-TKIs treatment. The principle of treatment is to strengthen the body and remove pathogenic factors. The diseases of zang-fu organs are mainly located in the lung, spleen and stomach, and heart and kidney. The treatment mostly adopts flexible compatibility and cutting methods, which can be roughly divided into the following categories:

(1) Tonifying qi and yin: shashen, maidong, huangqi, renshen and so on;
(2) Heat-clearing and detoxifying: baihuashecao, daqingye, shancigu, lianqiao and so on;
(3) Dispelling wind and arresting itching: fangfeng, jiangcan, chantui, baixianpi, difuzi and so on;
(4) Promoting circulation and removing stasis: danshen, chishao, yujin, taoren, honghua, eshu and so on;
(5) Clearing damp phlegm: chenpi, banxia, fuling, baishu and so on.

Taken together, we have demonstrated that particular combinations of TCMs with EGFR-TKIs have a greater effect on TRR than EGFR-TKIs alone. Among them, it is worth noticing combination of Maidong, Baihuashecao, Shashen, Renshen and Dangshen. Therefore, TCM may have the potential to improve the efficacy of EGFR-TKI in the treatment of lung cancer. However, the limitations of this study are also obvious, such as almost all the selected studies are in Chinese literature, the lack of rigorous design and implementation, and the low quality of research, which affect the accuracy and reliability of the conclusions of this study to a certain extent.

Author contributions

XS and TX conceived the idea and designed the study. MZ collected all materials, analyzed the data, and wrote the paper. XmH, RnZ, LxC, YL and YX provided technical support. All the authors read and approved the final version of the manuscript prior to submission.

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