Comparison of effectiveness and adverse effects of gefitinib, erlotinib and icotinib among patients with non-small cell lung cancer: A network meta-analysis

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Abstract. The present network meta-analysis aimed to compare the effectiveness and adverse effects of gefitinib, erlotinib and icotinib in the treatment of patients with non-small cell lung cancer (NSCLC). Two reviewers searched the Cochrane, PubMed, Embase, ScienceDirect, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals and Wanfang databases for relevant studies. Studies were then screened and evaluated, and data was extracted. End-points evaluated for NSCLC included complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), median survival time (MST) and adverse effects, including rash, diarrhea, nausea and vomiting, fatigue and abnormal liver function. For the analysis of incorporated studies, RevMan, SPSS, R and Stata software were used. A total of 43 studies with 7,168 patients were included in the network meta-analysis. No significant differences were observed in CR, PR, SD, PD, ORR or DCR between gefitinib, erlotinib and icotinib by using network meta analysis. Compared with gefitinib, erlotinib resulted in a higher rate of nausea and vomiting [adjusted odds ratio (OR)=2.0; 95% credible interval, 1.1-3.7]. However, no significant differences were observed in the rates of rash, diarrhea, fatigue or abnormal liver function using network meta-analysis. Compared with erlotinib, gefitinib resulted in a lower SD rate [OR=0.86; 95% confidence interval (CI): 0.75-0.99; P=0.04], and lower rates of rash (OR=0.45; 95% CI, 0.36-0.55; P<0.00001), diarrhea (OR=0.75; 95% CI, 0.61-0.92; P=0.005), nausea and vomiting (OR=0.47; 95% CI, 0.27-0.84; P=0.01) and fatigue (OR=0.43; 95% CI, 0.24-0.76; P=0.004) through meta-analysis of two congruent drugs. However, gefitinib resulted in a higher rate of rash compared with icotinib (OR=1.57; 95% CI, 1.18-2.09; P=0.002). Otherwise, no significant differences were observed in CR, PR, PD, ORR, DCR and abnormal liver function between gefitinib, erlotinib and icotinib through meta-analysis of two congruent drugs. The PFS rate for gefitinib, erlotinib and icotinib was 5.48, 5.15 and 5.81 months, respectively. The MST was 13.26, 13.52, 12.58 months for gefitinib, erlotinib and icotinib, respectively. Gefitinib and icotinib resulted in significantly higher PFS rates compared with erlotinib (P<0.05). Erlotinib resulted in a significantly longer MST compared with gefitinib and icotinib (P<0.05). In conclusion, gefitinib, erlotinib and icotinib had similar effectiveness for the treatment of patients with advanced NSCLC. However, gefitinib resulted in a lower frequency of fatigue, and nausea and vomiting, compared with the other two drugs. Icotinib resulted in a lower frequency of rash. Erlotinib resulted in a longer MST, but was also associated with a higher frequency of rash, and nausea and vomiting.

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Introduction

Lung cancer is the one of the leading causes of cancer-associated mortality worldwide (1). The majority (~80-85%) of patients with lung cancer patients have non-small cell lung cancer (NSCLC) and 70% of patients with NSCLC are at an advanced stage by the time of diagnosis (1). In China, lung cancer was a common type of cancer (48.32/100,000) and cause of cancer-associated mortality (39.27/100,000) in 2011 (2). The burden created by elderly Chinese patients with lung cancer is high (3). For patients with NSCLC who cannot undergo surgery due to having an advanced stage of the disease, platinum-based combination chemotherapy has become the primary treatment (4,5). However, in the majority of patients with NSCLC, the disease will eventually progress

despite combination therapy (4). Therefore, drugs with better efficacies for the treatment of advanced NSCLC are required.

During the last decade, the development of molecular targeted drugs has increased the effectiveness of NSCLC therapy (5). Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib, erlotinib and icotinib, have been demonstrated to be effective for the treatment of advanced NSCLC with few adverse effects, particularly in patients with NSCLC harboring EGFR mutations (5,6). A multi-institutional randomized phase II trial demonstrated that gefitinib had effective clinical antitumor activity and provided symptomatic relief in patients with NSCLC (7). However, the ISEL study reported that treatment with gefitinib did not significantly improve the survival of patients with NSCLC (8). The BR.21 clinical trial reported that erlotinib, another EGFR-TKI, could prolong survival in patients with NSCLC (9). Although the gefitinib and erlotinib have similar molecular and chemical structures, studies have reported different effects of the two drugs on the survival of patients with NSCLC (8,9). Furthermore, other studies have reported that, compared with gefitinib, erlotinib possesses an improved disease control rate and prolongs progression-free survival with increased median survival time, but has more adverse effects, in patients with NSCLC (1,10,11). The WJOG5108L clinical trial reported that gefitinib and erlotinib have similar efficacies (12). Xia *et al* (13) reported that icotinib exhibited a similar effectiveness and toxicity compared with gefitinib for the treatment of advanced NSCLC, but icotinib exhibited better disease control rate (DCR) and improved rate of diet and sleep period (13). In addition, the ICOGEN clinical trial demonstrated that icotinib and gefitinib achieved similar clinical cure rates in patients with NSCLC (14).

As demonstrated by the findings discussed above, the effectiveness of gefitinib, erlotinib and icotinib for the treatment of patients with advanced NSCLC remains controversial. To the best of our knowledge, no clinical trials comparing the success rate of gefitinib, erlotinib and icotinib have been reported. In the current study, a network meta-analysis was performed to compare the effectiveness and adverse effects of gefitinib, erlotinib and icotinib for the treatment of patients with advanced NSCLC.

Materials and methods

Search strategy. According to the patient, intervention, control, outcome (PICO) principle (15), the Cochrane (www.cochranelibrary.com), PubMed (www.ncbi.nlm.nih.gov/pmc), Embase (www.embase.com), ScienceDirect (http://www.sciencedirect.com/), China National Knowledge Infrastructure (www.cnki.net), VIP Database for Chinese Technical Periodicals (http://qikan.cqvip.com/) and Wanfang (http://g.wanfangdata.com.cn/) databases were searched using the following key words gefitinib, erlotinib, icotinib and non-small cell lung cancer. Search strategies were as follows: 'gefitinib' AND 'erlotinib' AND 'non-small cell lung cancer OR non-small cell lung carcinoma OR NSCLC'; 'gefitinib' AND 'icotinib' AND 'non-small cell lung cancer OR non-small cell lung carcinoma OR NSCLC'; 'erlotinib' AND 'icotinib' AND 'non-small cell lung cancer OR non-small cell lung carcinoma OR NSCLC'.

Eligibility criteria. Studies were selected based on primary screening of the identified abstracts or titles, followed by a secondary screening of the full text. According to the PICO principle, the following eligibility criteria were established: i) Research includes a randomized controlled trial, case-control study or cohort study; ii) subjects are patients with advanced NSCLC confirmed by pathological investigation; iii) intervention measures were gefitinib, erlotinib or icotinib; and iv) end-points included complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall response rate (ORR), DCR, progression-free survival (PFS), median survival time (MST) or adverse effects. Exclusion criteria were as follows: i) Patients having tumors other than NSCLC; ii) initial treatment contained drugs that function via the same molecular mechanism as EGFR-TKIs; and iii) study design devoid of control group. Reviews and case reports were also excluded.

Data extraction and quality assessment. Two reviewers independently evaluated the quality of the studies to be included and then extracted the data. The following information was extracted from eligible studies: First author, date of publication, country of affiliations, type of study, number of patients analyzed, interventions, CR, PR, SD, PD, ORR, DCR, PFS, MST and adverse events.

The quality of randomized controlled trials from the Cochrane network was evaluated in terms of the presence or absence of a randomized patient grouping method, concealed assignment, blinding method, incomplete data reporting, selective reporting and other bias (16). Incomplete data reporting (16) was defined as describing the completeness of outcome data for each main outcome. This includes the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported and any re-inclusions in analyses performed by the review authors. Selective reporting (16) was defined as stating how the possibility of selective outcome reporting was examined by the review authors, and what was found. This includes the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified. All included studies met the following criteria: Randomized, blinding, incomplete data and selective outcome reporting. Allocation concealment and other sources of bias were unclear in all randomized controlled trials.

The Newcastle-Ottawa Scale questionnaire was used to evaluate the quality of case-control and cohort studies (17). The methods of assessment primarily focused on the following three areas: Choice of subjects, comparability and exposure (outcome). The results of the quality assessment are shown in Tables I and II. The included studies were indicated to be of a good quality (18).

Response assessment. Patient response was assessed according to the Response Evaluation Criteria in Solid Tumors (19), which included CR, PR, SD, PD, ORR, DCR, PFS and MST. CR and PR were added together to calculate the ORR, while disease control rate was defined by CR, PR and SD. Toxicities

Table I. Quality assessment of the case control studies.

Study (author, year)	Selection				Comparability	Exposure			Total score	(Refs.)
	Case definition	Representative cases	Selection of controls	Definition of controls		Ascertainment of exposure	Consistency of exposure	Non-response rate		
Song *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(23)
Wu *et al*, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(24)
Wang, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(27)
Weng, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(30)
Zhang *et al*, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(31)
Zhang, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(32)
Zhang *et al*, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(34)
Zhang *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(35)
Li *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(36)
Bai *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(37)
Li, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(38)
Zhang *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(39)
Ma *et al*, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(40)
Lim *et al*, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(42)
Fan *et al*, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(11)
Yoshida *et al*, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(43)
Hong *et al*, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(44)
Emery *et al*, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(45)
Togashi *et al*, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(10)
Wu *et al*, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(46)
Wu *et al*, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(47)
Kim *et al*, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	(48)
Cui *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(52)
Liu and Liu, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(53)
Xia *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(13)
Sun *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(57)
Zhang *et al*, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7	(58)

Quality was assessed using the Newcastle-Ottawa scale. A higher overall score (out of 9) corresponds to a lower risk of bias; a score of ≤5 indicates a high risk of bias.

Table II. Quality assessment of the cohort study.

	Selection				Outcome				
Study (author, year)	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest	Comparability	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total score (Refs.)
Shao *et al*, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8 (41)

Quality was assessed using the Newcastle-Ottawa scale. A higher overall score (out of 9) corresponds to a lower risk of bias; a score of ≤5 indicates a high risk of bias.

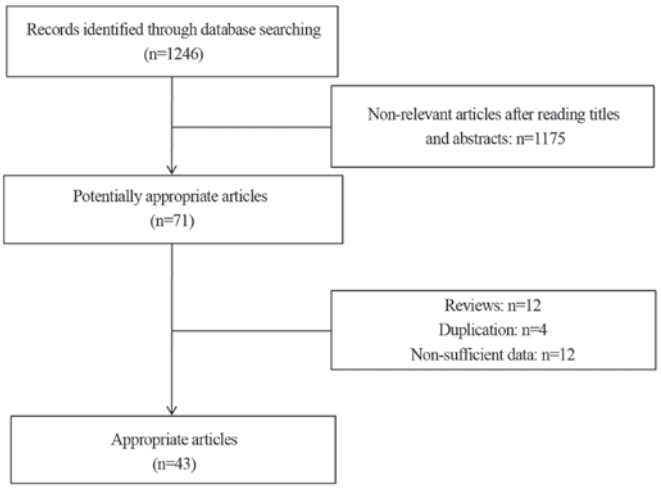

Figure 1. Flow chart illustrating the selection process for articles to be included in the network meta-analysis.

were determined according to the Common Terminology Criteria for Adverse Events version 3.0 (20).

Statistical analysis. Statistical analyses were conducted using RevMan (version 5.2; Cochrane Collaboration, Copenhagen, Denmark), SPSS (version 20.0; IBM Corp., Armonk, NY, USA), R (version 3.3.0; http://mirror.bjtu.edu.cn/cran/) and Stata (version 13.0; StataCorp LLC, College Station, TX, USA) software. R and Stata software were used to perform node-splitting analysis of inconsistencies, network meta-analysis and ranking for drug efficacy. The model for R software is considered a good indicator when potential scale reduction factor (PSRF) is close to 1 (21). A pooled analysis was performed using RevMan software in order to evaluate indicators (CR, PR, SD, PD, ORR, DCR, rash, diarrhea, nausea and vomiting, fatigue and abnormal liver function) among drugs. The adjusted odds ratio (OR) and 95% confidence interval (CI) or 95% credible interval (CrI) were used as measures of response for enumeration data. The fixed-effects model (Mantel-Haenszel method) was used for cases with no significant heterogeneity ($P>0.1$ and $I^2<50\%$). Otherwise, the random-effects model was used. PFS and MST were calculated by the weighted average method using SPSS. The non-parametric Kruskal-Wallis test was used to compare differences in the PFS and MST between groups. Funnel plots were used to assess possible publication bias amongst the included studies. Stata software was used to analyze publication bias with the 'metabias' command and to evaluate sensitivity with the 'metaninf' command. All tests were two-tailed. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature search. As illustrated in Fig. 1, 1,246 potentially relevant articles were identified through database searching. According to the aforementioned selection criteria, 43 articles (4,10-14,22-58) containing data on 7,168 patients were selected for the network meta-analysis. The characteristics of the eligible studies are described in Table III.

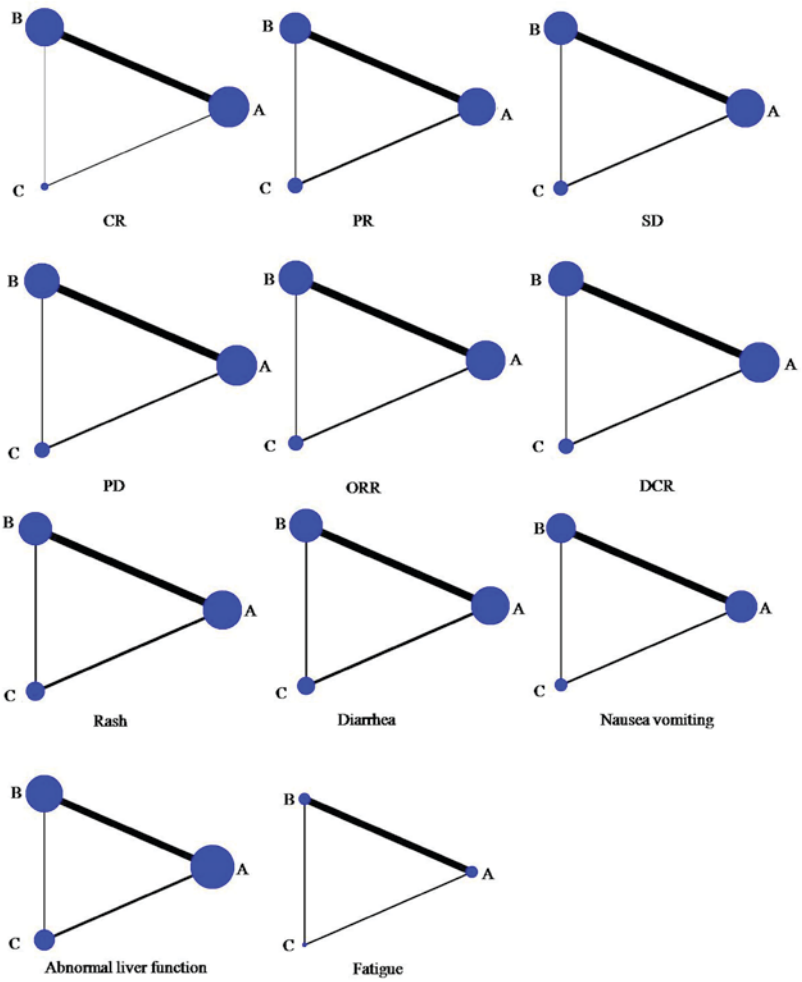

Figure 2. Network map of the clinical efficacies and adverse events of A, B and C. Node size and line width are based on the number of intervention studies included in the meta-analysis. Larger nodes and thicker lines indicate a higher frequency of intervention with the indicated drug. A, gefitinib; B, erlotinib; C, icotinib; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

Network meta-analysis for the clinical effectiveness and adverse effects of gefitinib, erlotinib and icotinib. Network maps (Fig. 2) and network forest plots (Fig. 3) were produced for all indicators. Compared with gefitinib, the network meta-analysis indicated that erlotinib had no significant differences in OR. The ORs for erlotinib were as follows: CR, 1.1 (95% CrI, 0.65-1.9); PR, 0.97 (95% CrI, 0.82-1.1); SD, 1.1 (95% CrI, 0.95-1.3); PD, 0.93 (95% CrI, 0.77-1.1); ORR, 0.96 (95% CrI, 0.82-1.1); and DCR, 1.1 (95% CrI, 0.86-1.3). Icotinib also had no significant differences in OR compared with gefitinib. The ORs for icotinib were as follows: CR, 0.84 (95% CrI, 0.26-2.4); PR, 1.2 (95% CrI, 0.89-1.6); SD, 1.1 (95% CrI, 0.79-1.4); PD, 0.92 (95% CrI, 0.65-1.3); ORR, 1.2 (95% CrI, 0.90-1.6); and DCR, 1.3 (95% CrI, 0.91-1.7).

In terms of adverse events, compared with gefitinib, erlotinib resulted in higher rates of nausea and vomiting (OR=2.0; 95% CrI, 1.1-3.7) during network meta-analysis. However, there were no significant differences in OR for rash (OR=1.1; 95% CrI, 0.95-1.3), diarrhea (OR=1.3; 95% CrI, 0.96-1.8), fatigue (OR=2.2; 95% CrI, 0.84-5.4) or abnormal liver function (OR=1.3; 95% CrI, 0.85-2.1). Compared with gefitinib, icotinib also had no significant differences in OR for rash (OR=1.0; 95% CrI, 0.79-1.4), diarrhea (OR=0.80; 95% CrI, 0.50-1.3), nausea and vomiting (OR=1.2; 95% CrI, 0.44-3.8), fatigue (OR=3.3; 95% CrI, 0.26-39.0) or abnormal liver function (OR=0.84; 95% CrI, 0.46-1.6).

Meta-analysis of two congruent drugs. In the meta-analysis, compared with erlotinib, gefitinib produced lower rates of SD (OR=0.86; 95% CI, 0.75-0.99; P=0.04; Fig. 4), rash (OR=0.45; 95% CI, 0.36-0.55; P<0.00001; Fig. 5), diarrhea (OR=0.75; 95% CI, 0.61-0.92; P=0.005; Fig. 6), nausea and vomiting (OR=0.47; 95% CI, 0.0.27-0.84; P=0.01; Fig. 7) and fatigue (OR=0.43; 95% CI, 0.24-0.76; P=0.004; Fig. 8). However, gefitinib produced a higher incidence of rash compared with icotinib (OR=1.57; 95% CI, 1.18-2.09; P=0.002; Fig. 9). No significant differences were observed between gefitinib and icotinib for CR, PR, PD, ORR, DCR, diarrhea or abnormal liver function (Table IV).

Ranking of interventions. Interventions were ranked by how often they caused certain adverse effects (Table V). Erlotinib was observed to produce the highest rate of SD, followed by icotinib. However, erlotinib was also associated with highest risk of rash, followed by gefitinib (data not shown). Icotinib was associated with the highest risk of diarrhea, followed by gefitinib. Erlotinib was associated with the highest risk of nausea and vomiting, followed by icotinib. Icotinib was associated with the highest risk of fatigue, followed by erlotinib.

Analysis of inconsistency and convergence. Using the consistency model, the PSRF for all indicators of clinical efficacies

Table III. Characteristics of the studies included in the network meta-analysis.

Study (author, year)	Country	Type of study	Intervention	n	CR (n)	PR (n)	SD (n)	PD (n)	ORR (%)	DCR (%)	PFS (months)	MST (months)	Rash (n)	Diarrhea (n)	Nausea and vomiting (n)	Abnormal liver function (n)	Fatigue (n)	(Refs.)
Wang and Zhang, 2012	China	Randomized	Gefitinib	41	2	13	17	9	36.69	78.05	-	13	-	-	-	-	-	(22)
			Erlotinib	42	1	13	23	5	33.33	88.10	-	12	-	-	-	-	-	
Song *et al*, 2015	China	Case-control	Gefitinib	67	0	18	27	22	26.8	67.2	6	-	9	-	-	5	-	(23)
			Erlotinib	14	0	3	3	8	21.4	42.9	2	-	9	-	-	2	-	
			Icotinib	28	0	5	12	11	17.9	60.7	3	-	15	-	-	3	-	
Wu *et al*, 2011	China	Case-control	Gefitinib	24	0	7	13	4	29.2	83.3	7.6	-	10	3	-	2	-	(24)
			Erlotinib	20	0	5	8	7	25	75	6.2	-	12	4	-	3	-	
Yuan, 2015	China	Randomized	Gefitinib	9	6		2	1	66.67	88.89	-	-	-	-	-	-	-	(25)
			Erlotinib	9	5		3	1	55.56	88.89	-	-	-	-	-	-	-	
Qu, 2015	China	Randomized	Gefitinib	50	2	11	25	12	26	76	-	-	-	-	-	-	-	(26)
			Erlotinib	50	8	21	18	3	58	94	-	-	-	-	-	-	-	
Wang, 2014	China	Case-control	Gefitinib	30	4	12	4	10	53.33	66.67	-	-	7	8	4	5	-	(27)
			Erlotinib	30	3	15	4	8	60	73.33	-	-	12	5	7	8	-	
Xie *et al*, 2015	China	Randomized	Gefitinib	27	1	14	8	4	55.6	85.2	8	-	17	4	-	-	-	(28)
			Erlotinib	23	2	12	6	3	60.9	87.0	8.5	-	16	3	-	-	-	
Xie, 2014	China	Randomized	Gefitinib	34	5	13	10	6	52.94	82.35	-	-	-	-	-	-	-	(29)
			Erlotinib	34	2	10	10	12	35.29	64.7	-	-	-	-	-	-	-	
Weng, 2015	China	Case-control	Gefitinib	38	2	13	11	12	39.47	68.42	6.12	-	29	-	-	-	-	(30)
			Erlotinib	34	2	10	8	14	35.29	58.82	6.14	-	26	-	-	-	-	
Zhang *et al*, 2012	China	Case-control	Gefitinib	40	0	9	12	19	22.5	52.5	3.5	-	29	18	2	4	-	(31)
			Erlotinib	40	0	8	18	14	20.0	65.0	3.5	-	32	17	0	5	-	
Zhang, 2014	China	Case-control	Gefitinib	71	3	12	36	20	21.13	71.83	-	-	-	-	-	5	-	(32)
			Erlotinib	54	2	9	29	14	20.37	74.07	-	-	-	-	-	4	-	
Chen *et al*, 2009	China	Case-control	Gefitinib	25	0	13	5	7	52	72	6.8	9.8	15	-	-	1	-	(33)
			Erlotinib	24	0	16	4	4	66.67	83.33	7.3	10.3	20	-	-	2	-	
Zhang *et al*, 2009	China	Case-control	Gefitinib	50	2	17	15	16	38	68	-	-	38	33	-	-	-	(34)
			Erlotinib	50	3	15	12	20	36	60	-	-	38	35	-	-	-	
Zhang *et al*, 2015	China	Case-control	Gefitinib	41	1	9	13	18	24.3	56.1	-	13.5	5	3	1	2	5	(35)
			Erlotinib	45	0	12	15	18	26.7	60	-	13.2	6	5	0	2	5	
Li *et al*, 2015	China	Case-control	Gefitinib	37	3	13	18	3	42.11	91.89	-	-	20	16	15	2	-	(36)
			Erlotinib	36	3	13	17	3	44.44	91.67	-	-	32	28	26	11	-	
Bai *et al*, 2015	China	Case-control	Gefitinib	38	0	16	19	3	42.1	92.1	10.6	14.8	24	13	3	4	-	(37)
			Erlotinib	29	0	14	13	2	48.3	93.1	11.7	15.7	22	9	2	3	-	

Table III. Continued.

Study (author, year)	Country	Type of study	Intervention	n	CR (n)	PR (n)	SD (n)	PD (n)	ORR (%)	DCR (%)	PFS (months)	MST (months)	Rash (n)	Diarrhea (n)	Nausea and vomiting (n)	Abnormal liver function (n)	Fatigue (n)	(Refs.)
Li, 2013	China	Case-control	Gefitinib	20	0	6	8	6	30.0	70.0	6.2	-	11	-	3	-	-	(38)
			Erlotinib	11	0	5	3	3	45.5	72.7	6.5	-	6	-	1	-	-	
Zhang *et al*, 2015	China	Case-control	Gefitinib	39	6	12	17	4	46.15	89.74	9.5	-	-	-	-	-	-	(39)
			Erlotinib	42	4	15	19	4	45.24	90.48	9.0	-	-	-	-	-	-	
Ma *et al*, 2013	China	Case-control	Gefitinib	49	0	25	20	4	51.0	91.1	17.5	-	31	12	-	13	-	(40)
			Erlotinib	17	0	7	8	2	41.2	86.7	13.0	-	16	12	-	2	-	
Shao *et al*, 2013	China	Cohort	Gefitinib	655	-	-	-	-	-	-	5.5	10.2	-	-	-	-	-	(41)
			Erlotinib	329	-	-	-	-	-	-	3.4	9.9	-	-	-	-	-	
Lim *et al*, 2014	Korea	Case-control	Gefitinib	121	0	93	16	12	76.9	90.1	11.7	-	-	-	-	-	-	(42)
			Erlotinib	121	0	90	15	16	74.4	86.8	9.6	-	-	-	-	-	-	
Kim *et al*, 2012	Korea	Randomized	Gefitinib	48	1	22	12	12	47.9	72.9	4.9	-	30	16	4	-	0	(4)
			Erlotinib	48	1	18	13	15	39.6	66.7	3.1	-	35	17	2	-	8	
Fan *et al*, 2011	China	Case-control	Gefitinib	715	246	175	294	34.4	58.9	3.6	9.6	-	-	-	-	-		(11)
			Erlotinib	407	145	123	139	35.6	65.8	4.6	10.7	-	-	-	-	-		
Yoshida *et al*, 2013	Japan	Case-control	Gefitinib	107	-	-	-	-	-	-	-	-	67	39	8	14	32	(43)
			Erlotinib	35	-	-	-	-	-	-	-	-	33	6	5	2	21	
Hong *et al*, 2010	Korea	Case-control	Gefitinib	20	5	3	12	25.0	40.0	3.5	21.8	7	3	2	0	0		(44)
			Erlotinib	17	2	7	8	12.5	50.0	4.4	21.5	10	5	0	3	2		
Emery *et al*, 2009	USA	Case-control	Gefitinib	115	3	3	30	75	5.2	31.3	2.4	-	46	43	8	-	7	(45)
			Erlotinib	45	2	2	21	18	8.9	55.6	2.8	-	26	17	8	-	5	
Togashi *et al*, 2011	Japan	Case-control	Gefitinib	85	44	17	21	51.7	71.8	-	-	53	28	10	22	-		(10)
			Erlotinib	69	25	17	19	36.2	60.9	-	-	54	36	36	24	-		
Urata *et al*, 2016	Japan	Randomized	Gefitinib	244	1	111	61	61	45.9	70.9	6.5	22.8	207	118	82	-	-	(12)
			Erlotinib	227	3	97	71	46	44.1	75.3	7.5	24.5	255	141	96	-	-	
Wu *et al*, 2012	China	Case-control	Gefitinib	124	0	52	46	26	41.9	79.0	7.6	-	-	-	-	-	-	(46)
			Erlotinib	100	0	42	27	31	42.0	69.0	7.9	-	-	-	-	-	-	
Wu *et al*, 2011	China	Case-control	Gefitinib	440	-	-	-	-	-	-	5.0	18.0	-	-	-	-	-	(47)
			Erlotinib	276	-	-	-	-	-	-	2.9	11.6	-	-	-	-	-	
Kim *et al*, 2010	Korea	Case-control	Gefitinib	171	0	65	43	61	38.0	63.2	4.6	12.6	-	-	-	-	-	(48)
			Erlotinib	171	1	54	56	57	32.2	64.9	2.7	12.1	-	-	-	-	-	
Chen *et al*, 2012	China	Randomized	Gefitinib	14	0	1	7	2	7.1	57.1	-	3.8	3	1	-	-	-	(49)
			Icotinib	14	0	3	5	4	21.4	57.1	-	11	1	0	-	-	-	
Chen *et al*, 2011	China	Randomized	Gefitinib	6	0	1	3	2	16.7	66.6	3.2	4.8	-	-	-	-	-	(50)
			Icotinib	6	0	2	2	2	33.3	66.6	3.6	6	-	-	-	-	-	

Table III. Continued.

Study (author, year)	Country	Type of study	Intervention	n	CR (n)	PR (n)	SD (n)	PD (n)	ORR (%)	DCR (%)	PFS (months)	MST (months)	Rash (n)	Diarrhea (n)	Nausea and vomiting (n)	Abnormal liver function (n)	Fatigue (n)	(Refs.)
Cui *et al*, 2015	China	Randomized	Gefitinib	28	0	7	8	13	25.0	53.6	-	-	8	5	-	-	-	(51)
			Icotinib	28	0	11	7	10	39.3	64.3	-	-	3	1	-	-	-	
Cui *et al*, 2015	China	Case-control	Gefitinib	21	0	12	5	4	57	81	-	-	13	7	4	2	-	(52)
			Icotinib	49	1	28	12	8	59	84	-	-	31	16	10	6	-	
Liu and Liu, 2014	China	Case-control	Gefitinib	12	3	5	2	2	66.7	83.3	-	-	4	5	4	3	1	(53)
			Erlotinib	10	2	5	1	2	70.0	80.0	-	-	6	4	6	4	2	
			Icotinib	8	1	4	1	2	62.5	75.0	-	-	2	3	5	3	2	
Lin and Zhang, 2014	China	Randomized	Gefitinib	24	0	2	12	3	8.3	58.3	6.5	8.8	11	9	-	-	-	(54)
			Icotinib	24	0	5	9	7	20.8	58.3	6.8	9.2	10	7	-	-	-	
Xia *et al*, 2015	China	Case-control	Gefitinib	93	11	31	27	17	45.2	74.2	-	-	85	7	-	1	-	(13)
			Icotinib	126	14	44	51	17	46.0	86.5	-	-	112	11	-	3	-	
Xu *et al*, 2015	China	Randomized	Gefitinib	40	0	9	14	13	22.2	55.6	9	-	10	4	-	4	-	(55)
			Icotinib	40	0	10	13	12	27.7	61.1	11	-	6	6	-	1	-	
Shi *et al*, 2013	China	Randomized	Gefitinib	196	0	53	93	40	27.2	74.9	3.4	13.9	98	58	14	25	-	(14)
			Icotinib	199	1	54	95	42	27.6	75.4	4.6	13.3	81	43	11	16	-	
Huang, 2014	China	Randomized	Erlotinib	13	0	2	7	4	15.4	69.2	-	-	7	1	1	-	-	(56)
			Icotinib	13	0	3	5	5	23.1	61.6	-	-	5	2	1	-	-	
Sun *et al*, 2015	China	Case-control	Erlotinib	41	8	13	20	19.5	48.8	4	-	13	3	-	2	-		(57)
			Icotinib	43	12	15	16	27.9	62.8	6	-	17	1	-	0	-		
Zhang *et al*, 2015	China	Case-control	Erlotinib	34	1	6	19	8	20.6	76.5	6.86	-	17	5	-	3	-	(58)
			Icotinib	34	0	12	17	5	35.3	85.3	8.53	-	12	3	-	2	-	

A dash indicated no data. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; MST, median survival time; n, number of patients.

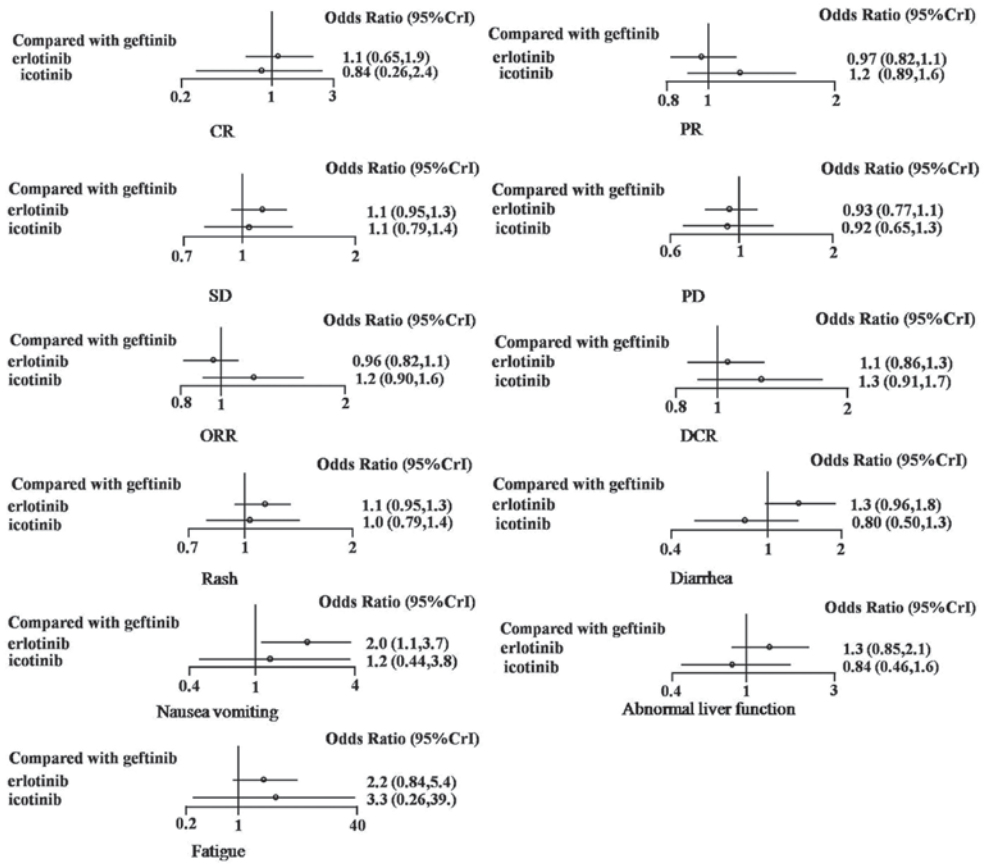

Figure 3. Forest plot of the clinical efficacies and adverse events in the network meta-analysis. CrI, credible intervals; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

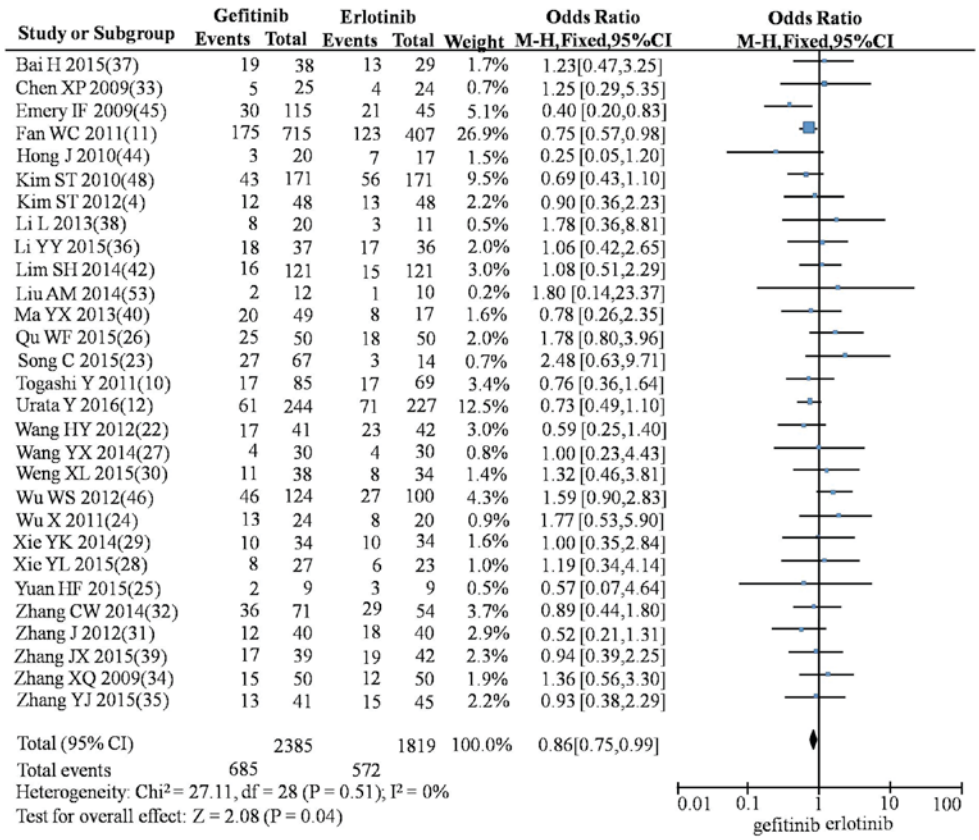

Figure 4. Forest plot comparing the rate of stable disease following gefitinib and erlotinib treatment for patients with advanced non-small cell lung cancer. M-H, Mantel-Haenszel; CI, confidence interval.

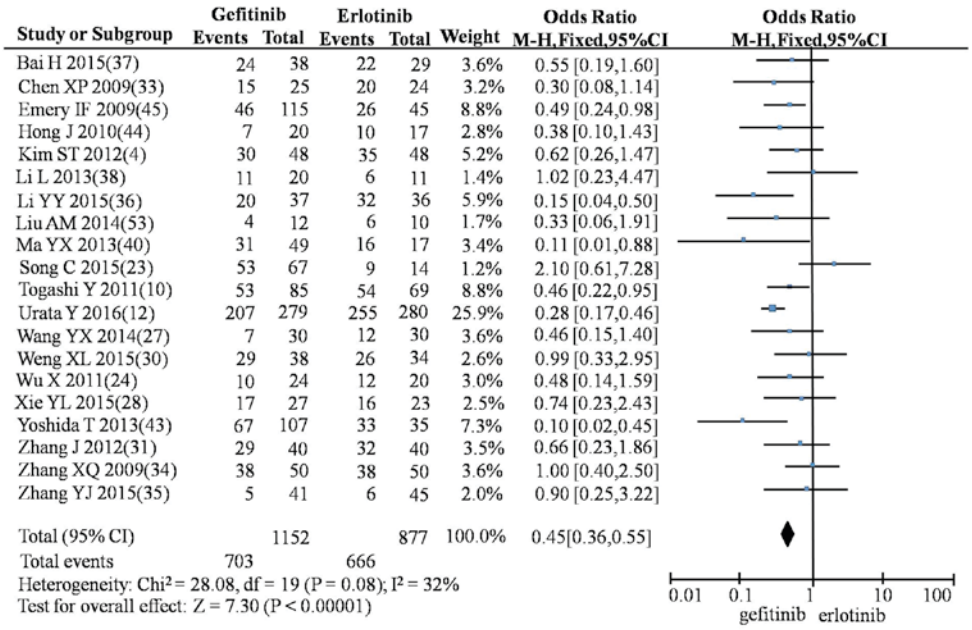

Figure 5. Forest plot comparing the incidence of rash following gefitinib and erlotinib treatment for patients with advanced non-small cell lung cancer. M-H, Mantel-Haenszel; CI, confidence interval.

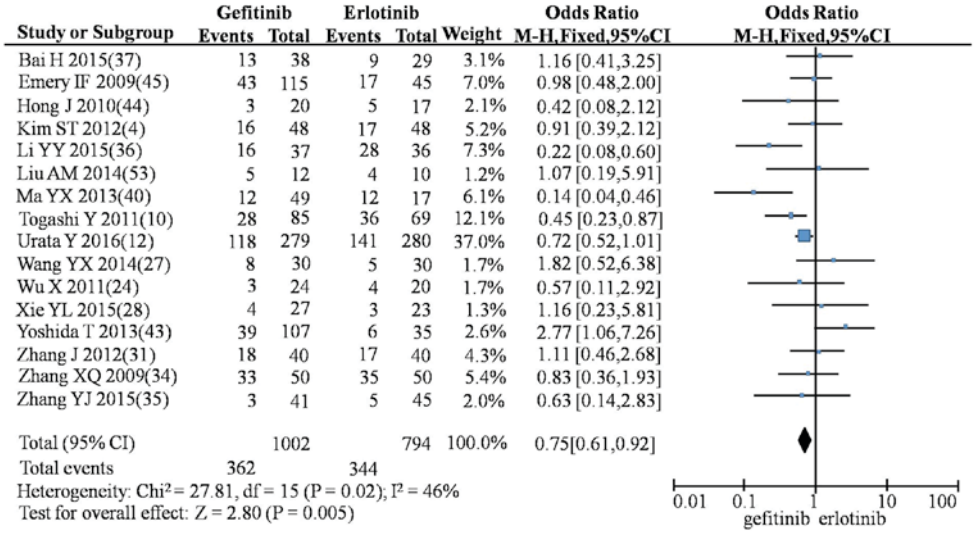

Figure 6. Forest plot comparing the incidence of diarrhea following gefitinib and erlotinib treatment for patients with advanced non-small cell lung cancer. M-H, Mantel-Haenszel; CI, confidence interval.

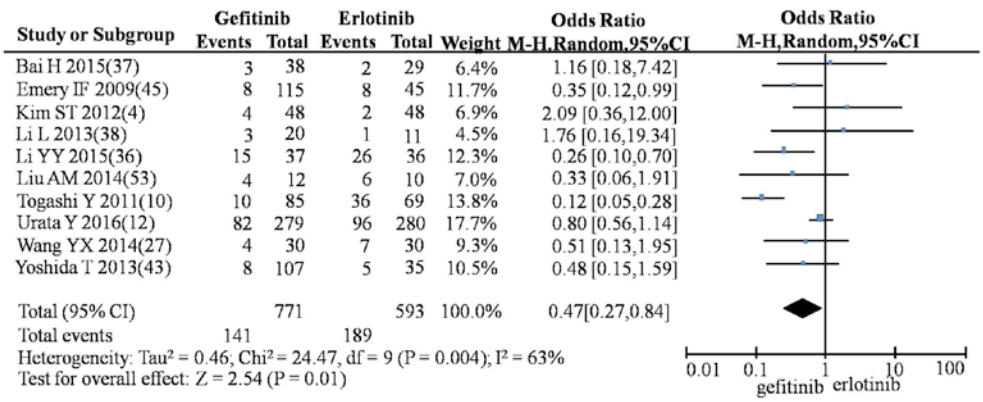

Figure 7. Forest plot comparing the incidence of nausea and vomiting diarrhea following gefitinib and erlotinib treatment for patients with advanced non-small cell lung cancer. M-H, Mantel-Haenszel; CI, confidence interval.

Table IV. Meta-analysis of the clinical efficacies and adverse events associated with G, E and I.

				Heterogeneity testing					
Indicator	Intervention	n	OR (95% CI)	χ^2	P-value	I^2	Model	Z-value	P-value
CR	G vs. E	14	0.90 (0.56-1.44)	8.11	0.84	0	Fixed	0.43	0.67
	G vs. I	2	1.17 (0.53-2.58)	0.34	0.56	0	Fixed	0.40	0.69
	E vs. I	1	1.75 (0.13-23.70)	-	-	-	-	0.42	0.67
PR	G vs. E	25	1.03 (0.88-1.21)	12.57	0.97	0	Fixed	0.41	0.68
	G vs. I	10	0.90 (0.68-1.19)	4.86	0.85	0	Fixed	0.72	0.47
	E vs. I	4	0.63 (0.30-1.35)	1.62	0.65	0	Fixed	1.19	0.23
SD	G vs. E	29	0.86 (0.75-0.99)	27.11	0.51	0	Fixed	2.08	0.04
	G vs. I	10	0.95 (0.74-1.23)	4.85	0.85	0	Fixed	0.37	0.71
	E vs. I	5	0.94 (0.55-1.62)	2.74	0.60	0	Fixed	0.21	0.83
PD	G vs. E	29	1.14 (0.99-1.31)	35.44	0.16	21	Fixed	1.87	0.06
	G vs. I	10	0.99 (0.73-1.34)	5.07	0.83	0	Fixed	0.06	0.95
	E vs. I	5	1.48 (0.85-2.59)	1.51	0.82	0	Fixed	1.38	0.17
ORR	G vs. E	29	1.03 (0.91-1.18)	23.76	0.69	0	Fixed	0.51	0.61
	G vs. I	10	0.91 (0.69-1.20)	4.81	0.85	0	Fixed	0.68	0.49
	E vs. I	5	0.68 (0.37-1.25)	1.53	0.82	0	Fixed	1.24	0.21
DCR	G vs. E	29	0.90 (0.78-1.03)	37.53	0.11	25	Fixed	1.56	0.12
	G vs. I	10	0.85 (0.64-1.13)	5.34	0.80	0	Fixed	1.11	0.27
	E vs. I	5	0.67 (0.39-1.18)	1.51	0.82	0	Fixed	1.38	0.17
Rash	G vs. E	20	0.45 (0.36-0.55)	28.08	0.08	32	Fixed	7.30	<0.01
	G vs. I	9	1.57 (1.18-2.09)	5.39	0.72	0	Fixed	3.07	<0.01
	E vs. I	5	1.37 (0.81-2.30)	3.89	0.42	0	Fixed	1.17	0.24
Diarrhea	G vs. E	16	0.75 (0.61-0.92)	27.81	0.02	46	Fixed	2.80	<0.01
	G vs. I	7	1.32 (0.94-1.85)	4.20	0.65	0	Fixed	1.60	0.11
	E vs. I	4	1.45 (0.57-3.72)	1.43	0.70	0	Fixed	0.78	0.44
Nausea and vomiting	G vs. E	10	0.47 (0.27-0.84)	24.47	0.00	63	Random	2.54	0.01
	G vs. I	3	0.99 (0.53-1.88)	2.01	0.37	1	Fixed	0.02	0.98
	E vs. I	2	0.93 (0.19-4.57)	0.00	0.95	0	Fixed	0.09	0.93
Abnormal liver function	G vs. E	13	0.73 (0.51-1.05)	10.94	0.53	0	Fixed	1.70	0.09
	G vs. I	6	1.27 (0.77-2.10)	4.33	0.50	0	Fixed	0.94	0.35
	E vs. I	3	1.34 (0.45-4.00)	0.06	0.97	0	Fixed	0.53	0.60
Fatigue	G vs. E	4	0.43 (0.24-0.76)	3.14	0.37	5	Fixed	2.89	<0.01
	G vs. I	1	0.27 (0.02-3.67)	-	-	-	-	0.98	0.33
	E vs. I	1	0.75 (0.08-6.96)	-	-	-	-	0.25	0.80

G, gefitinib; E, erlotinib; I, icotinib; n, number of included studies; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; OR, adjusted odds ratio; CI, confidence interval.

and adverse events was close to 1 (data not shown). Following node-splitting analysis of inconsistencies, no significant differences were observed for CR, PR, SD, PD, ORR, DCR, diarrhea, nausea and vomiting, fatigue or abnormal liver function (data not shown).

PFS and MST. The PFS rate for gefitinib, erlotinib and icotinib was 5.48, 5.15 and 5.81 months, respectively (Table VI). The MST was 13.26, 13.52 and 12.58 months for gefitinib, erlotinib and icotinib, respectively (Table VI). Gefitinib and icotinib had a significantly higher PFS rate compared with erlotinib (P<0.01); however, no significant difference in PFS was observed between gefitinib and icotinib (Table VI). Erlotinib had a significantly longer MST compared with gefitinib and icotinib (P<0.05), and gefitinib had a significantly longer MST compared with icotinib (P<0.05) (Table VI).

Publication bias. Funnel plots (Fig. 10) revealed that all included studies were symmetrical in terms of standard error of the effect size and the effect size centered at the comparison-specific pooled effect for CR, PR, SD, PD, ORR and DCR. This indicates that there was minimal publication bias.

Sensitivity analysis. According to sensitivity analysis, there was little difference for the pooled effect among each study for the indexes ORR and DCR (data not shown).

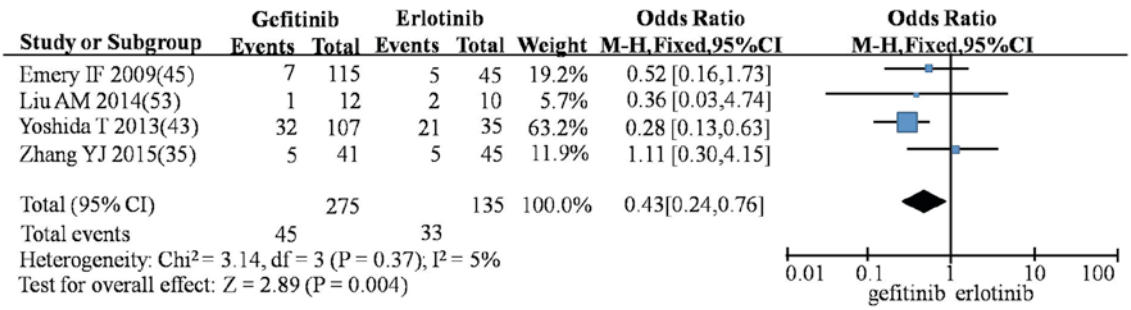

Figure 8. Forest plot comparing the incidence of fatigue diarrhea following gefitinib and erlotinib treatment for patients with advanced non-small cell lung cancer. M-H, Mantel-Haenszel; CI, confidence interval.

Table V. Ranking of interventions.

A, Stable disease

Ranking	Gefitinib (%)	Erlotinib (%)	Icotinib (%)
1	2.4	71.2	26.5
2	34.7	25.6	39.7
3	62.9	3.2	33.8

B, Diarrhea

Ranking	Gefitinib (%)	Erlotinib (%)	Icotinib (%)
1	1.7	95.0	3.2
2	77.5	4.6	18.0
3	20.8	0.4	78.8

C, Nausea and vomiting

Ranking	Gefitinib (%)	Erlotinib (%)	Icotinib (%)
1	65.8	0.2	34.0
2	34.0	15.7	50.2
3	0.1	84.1	15.8

D, Fatigue

Ranking	Gefitinib (%)	Erlotinib (%)	Icotinib (%)
1	83.6	1.4	15.0
2	15.8	62.0	22.2
3	0.6	36.6	62.8

Table VI. Comparison of PFS and MST.

Intervention	PFS (months)	MST (months)
Gefitinib	5.48[a]	13.26[a,b]
Erlotinib	5.15	13.52[a,c]
Icotinib	5.81[c]	12.58[b,c]

[a]P<0.05 gefitinib vs. erlotinib; [b]P<0.05 gefitinib vs. icotinib; [c]P<0.05 erlotinib vs. icotinib.

Discussion

Lung cancer has the highest morbidity and mortality rate of any malignant tumor type, and is most commonly NSCLC (1,2). In total >50% of patients diagnosed with NSCLC are at an advanced stage of the disease (40). Platinum-based combination chemotherapy is the most common course of treatment for patients with NSCLC, but its clinical efficacy is limited (4). Targeted therapy, including gefitinib, erlotinib and icotinib, has improved the treatment of advanced NSCLC (7,9,59). However, there remains controversy surrounding the effectiveness and adverse effects of these three drugs (1,10-14,60).

In the current meta-analysis, no significant differences for CR, PR, SD, PD, ORR, DCR, rash, diarrhea, fatigue or abnormal liver function were observed between gefitinib, erlotinib and icotinib by using network meta analysis. The frequency of fatigue, and nausea and vomiting, was lower for gefitinib compared with icotinib or erlotinib. In addition, the MST was longer for erlotinib compared with the other two drugs. Furthermore, the frequency of rash for icotinib was lower compared with the other two drugs. The present study revealed that the three drugs had similar efficacies for the treatment of patients with advanced NSCLC. Overall, gefitinib had a lower frequency of nausea and vomiting and fatigue, while erlotinib has a longer MST, but a higher frequency for rash and nausea and vomiting. A lower frequency of rash may occur with icotinib.

The results of the network meta-analysis conducted in the present study revealed that there were no significant differences between the efficacies of gefitinib, erlotinib or icotinib for the treatment of NSCLC. All three targeted drugs act as EGFR-TKIs and bind to the Mg-ATP binding site of the EGFR tyrosine kinase catalytic domain competitively (45,58). This inhibits EGFR phosphorylation and subsequent signal transduction. Thus, these drugs have antitumor activity (10,59,61). Since these drugs function via the same molecular mechanism, they may have similar efficacies in the treatment of patients with NSCLC. In the current study, no significant statistical differences were observed in CR, PR, PD, ORR or DCR by performing meta-analysis of two congruent drugs.

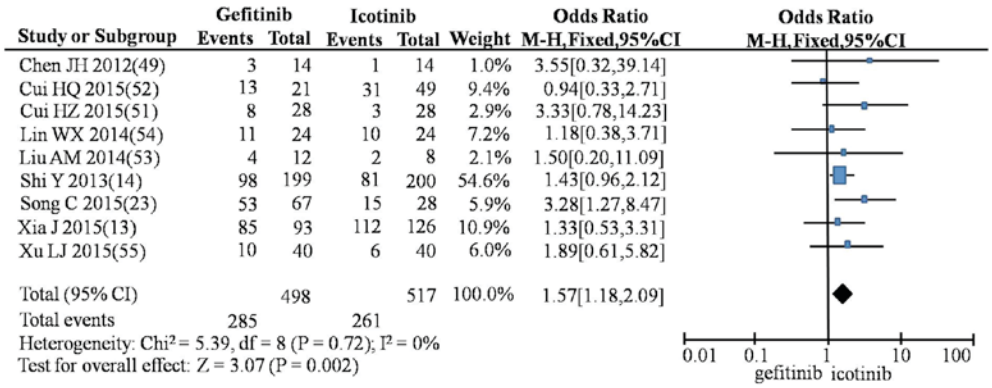

Figure 9. Forest plot comparing the incidence of rash diarrhea following gefitinib and erlotinib treatment for patients with advanced non-small cell lung cancer. M-H, Mantel-Haenszel; CI, confidence interval.

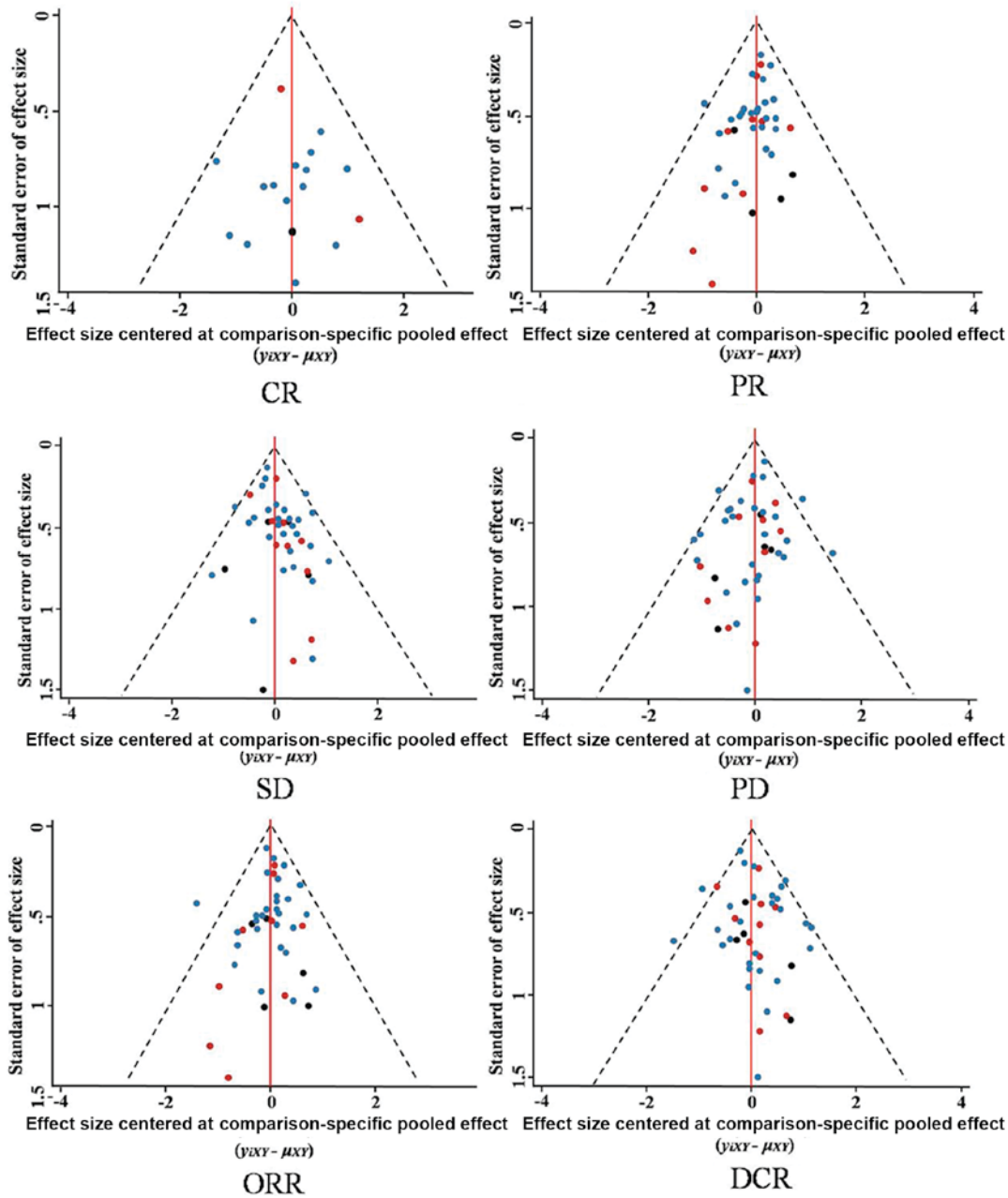

Figure 10. Funnel plots revealed that all included studies were symmetrical in terms of standard error of the effect size and the effect size centered at the comparison-specific pooled effect. Blue dots represent gefitinib vs. erlotinib; red dots represent gefitinib vs. icotinib; black dots represent erlotinib vs. icotinib. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

Rash and diarrhea were the most frequent adverse effects in patients with advanced NSCLC treated with EGFR-TKIs. The network meta-analysis conducted in the current study demonstrated that erlotinib resulted in a higher frequency of nausea and vomiting compared with gefitinib and icotinib. In addition, erlotinib resulted in a higher frequency of rash, nausea and vomiting and fatigue in patients with advanced NSCLC compared with gefitnib and icotinib in the meta-analysis for two congruent drugs and ranking interventions. The adverse events caused by erlotinib treatment can be dose-dependent (10). The approved daily dose of erlotinib (150 mg) is equal to the maximum tolerated dose (10). Therefore, the increase in the toxicity of erlotinib was associated with the dose (10). Furthermore, the adverse effects of erlotinib, icotinib and gefitinib on the liver occur through different mechanisms (62). The different toxicity profiles of these drugs are due to differences in their chemical structure and pharmacokinetics (63,64).

The results of the current study revealed that erlotinib had a longer MST compared with gefitinib and icotinib. Wu *et al* (46) reported that erlotinib had a higher efficacy compared with gefitinib for the treatment of patient with NSCLC patients without activating mutations of EGFR. The longer MST following erlotinib treatment might be associated with different characteristics of the population such as the mutation of EGFR in the population. Previous studies have revealed that the efficacy of EGFR-TKIs can be associated with the appearance of rash; the more frequent the rash, the more effective the drug was for the treatment of NSCLC (65,66). Therefore, the increased frequency of rash observed following erlotinib treatment may be associated with its longer MST. In the present study, the network meta-analysis also indicated that erlotinib may have a higher SD rate compared with erlotinib and icotinib.

The efficacy of EGFR-TKIs in the treatment of patients with advanced NSCLC may be associated with gender, smoking, ethnicity and tumor pathology (47). However, these clinical factors could not be accounted for in the current analysis due to the limited number of studies evaluated. The present study was also limited by its retrospective nature and the heterogeneity of the treatment regimens.

In the present study, the most common adverse events of EGFR-TKIs in patients with advanced NSCLC were rash and diarrhea. The efficacy of these drugs may be associated with the frequency of rash (65,66); however, the underlying molecular mechanism by which this occurs remains unknown. EGFR-TKI efficacy may also be associated with gender, smoking, ethnicity, tumor pathology, pharmacokinetics and population characteristics (47,63,64).

In conclusion, the results of the present study indicate that gefitinib, erlotinib and icotinib exhibit similar efficacy in the treatment of patients with advanced NSCLC. Erlotinib may increase survival rates compared with gefitinib or icotinib, but more frequently results in side effects. Further clinical trials evaluating the efficacy of erlotinib, icotinib and gefitinib are required.

Acknowledgements

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