Systematic Review and Meta-Analysis

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Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer

A meta-analysis

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Abstract

Background: The epidermal growth factor receptor tyrosine kinase inhibitors gefitinib and erlotinib are effective for advanced non-small cell lung cancer (NSCLC). This meta-analysis compared their effectiveness and safety.

Methods: We searched systematically in PubMed, ScienceDirect, The Cochrane Library, Scopus, Ovid MEDLINE, EMBASE, Web of Science, and Google Scholar for relevant clinical trials regarding gefitinib versus erlotinib for NSCLC. Antitumor effectiveness (overall survival [OS], progression-free survival [PFS], objective response rate [ORR] and disease control rate [DCR]) and adverse effects [AEs]) were assessed.

Results: Forty studies comprising 9376 participants were included. The results suggested that gefitinib and erlotinib are effective for advanced NSCLC with comparable PFS (95% confidence intervals [CI]: 0.98–1.11, $P = .15$), OS (95% CI: 0.93–1.19, $P = .45$), ORR (95% CI: 0.99–1.16, $P = .07$), and DCR (95% CI: 0.92–1.03, $P = .35$). For erlotinib, dose reduction was significantly more frequent (95% CI: 0.10–0.57, $P = .001$) as were grade 3 to 5 AEs (95% CI: 0.36–0.79, $P = .002$). In the subgroup analysis, the erlotinib group had a significant higher rate and severity of skin rash, nausea/vomiting, fatigue, and stomatitis.

Conclusions: Gefitinib was proven to be the better choice for advanced NSCLC, with equal antitumor effectiveness and fewer AEs compared with erlotinib. Further large-scale, well-designed randomized controlled trials are warranted to confirm our validation.

Abbreviations: AEs = adverse effects, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence intervals, DCR = disease control rate, EGFR TKI = epidermal growth factor receptor tyrosine kinase, HR = hazard ratios, ILD = interstitial lung disease, NOS = Newcastle–Ottawa scale, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, QOL = quality-of-life, RCT = randomized controlled trial, RR = risk ratios.

Keywords: erlotinib, gefitinib, meta-analysis, non-small cell lung cancer, targeted therapy

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for almost 85% of all lung cancers, and has been the leading cause of cancer-related mortality globally in recent years.[1,2] The discovery and development of therapeutics targeting epidermal growth factor receptor tyrosine kinase (EGFR TKI) was an important clinical advancement for NSCLC treatment in the past decade.[3,4] As the first generation EGFR TKIs, gefitinib (iressa) and erlotinib (tarceva) have been proved as safe and effective to treat NSCLC. Recently, both EGFR TKIs have been used widely as first line treatments of NSCLC in chemotherapy-naïve/EGFR mutation-positive patients, or line 2+ treatment after failure of chemotherapy.[5–7] In clinical practice, it is still controversial whether gefitinib or erlotinib can achieve better therapeutic effectiveness. In a phase III randomized controlled trial (RCT), Urata et al[8] reported a higher incidence of grade 3–4 skin rash but less alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation in the erlotinib arm. Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were similar between the 2 groups. In another phase III RCT, Yang et al[6] reported that gefitinib and erlotinib could achieve a similar effectiveness (PFS, OS, and ORR) for NSCLC with similar toxicities. Some studies showed a better antitumor effectiveness or less toxicity in the gefitinib group for NSCLC.[9–11] However, other studies reported the opposite results and suggested that erlotinib was more effective.[12,13]

To provide the latest and most convincing evidence for the selection of targeted drugs, we conducted a meta-analysis of studies to compare the antitumor effectiveness and adverse effects (AEs) of gefitinib and erlotinib for NSCLC.

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2. Materials and methods

This meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) scheme (Table S1, http://links.lww.com/MD/C206). As this meta-analysis was performed based on the published data, ethics committee and/or institutional board approval was not required.

2.1. Search strategy

We systematically searched PubMed, ScienceDirect, the Cochrane Library, Scopus, Web of Science, EMBASE, Ovid MEDLINE, and Google Scholar to identify all the relevant literature published from January 1, 1990 to October 1, 2017. The used combined text and MeSH terms as follows: "gefitinib," "erlotinib," and "lung cancer". The complete search we took for PubMed went: (gefitinib [MeSH Terms] OR gefitinib [Text Word] OR iressa [Text Word] OR ZDl839 [Text Word]) AND (erlotinib [MeSH Terms] OR erlotinib [Text Word] OR tarceva [Text Word] OR OSI-774 [Text Word]) AND (lung cancer [MeSH Terms] OR lung cancer [Text Word] OR lung carcinoma [Text Word] OR lung neoplasm [Text Word] OR NSCLC [Text Word]). The reference lists of the retrieved publications were also searched for further eligible articles.

2.2. Selection criteria

Studies that met the following criteria could be included: language: published in English; population: patients with histologically or cytologically confirmed NSCLC with Eastern Cooperative Oncology Group (ECOG); comparison: gefitinib versus erlotinib; outcome: PFS, OS, ORR, disease control rate (DCR), and AEs. The outcomes were directly or indirectly contained.

The most complete and novel reports could be included for data extraction and assessments if the objects were duplicated. We excluded reviews without original data, meta-analyses, animal experiments, and abstract only.

2.3. Data extraction

The following data were extracted by 2 independent investigators: first author, publication year, nation, number of participants, participant characteristics (age, sex, stage of cancer, pathological type, and treatment line), indices of antitumor effectiveness (PFS, OS, ORR, and DCR) and number of AEs (total and grade 3–5 AEs). Any disagreements were checked by a third investigator.

2.4. Quality assessment

We used the Jadad scale to assess the quality of the RCTs and the Newcastle–Ottawa scale (NOS) to assess the quality of the nonrandomized studies. The Jadad scale (5 points) contained questions for 3 main items: randomization, masking, and accountability of all patients. High quality studies scored $\geq$ 3 points.[14] The NOS evaluates the quality of studies by analyzing 3 items: selection, comparability, and exposure. High quality studies scored 8–9 points and medium quality studies scored 6–7 points.[15]

2.5. Statistical analysis

All statistical analyses were conducted using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 software (StataCorp LP, College Station, TX). For the analysis of PFS and OS, hazard ratios (HR) with 95% confidence intervals (CI) were used (HR $>$ 1 favors the erlotinib group and HR $<$ 1 favors the gefitinib group). Some studies reported relevant HR information for our outcome directly. In other studies, only Kaplan–Meier curves were provided rather than HR data. In these cases, we extracted and estimated the HR and 95% CI from the Kaplan–Meier curves according to Tierney et al.[16] For the analysis of ORR, DCR, and AEs, pooled risk ratios (RR) with 95% CIs were used (RR $>$ 1 favors the gefitinib group and RR $<$ 1 favors the erlotinib group). Heterogeneity across studies was evaluated using Cochran's Q test and the I^2 statistic. An $I^2 > 50\%$ or a P value for the Q test $<$ .1 was regarded as indicating significant heterogeneity and a random-effects model was used; otherwise, a fixed-effects model was used. A subgroup analysis of PFS, OS, and ORR was conducted to check whether the results would change in specially appointed populations according to EGFR mutation status, ethnicity, line of treatment, histology, tumor stage, and study design. Potential publication biases were assessed using Begg's rank correlation and Egger's linear regression tests. A P-value $< .05$ indicated statistical significance.

3. Results

3.1. Search results and quality assessment

We initially identified 5829 potentially eligible studies. After screening, 40 studies involving 9376 patients (5602 patients in the gefitinib group and 3774 patients in the erlotinib group) were included for the final analysis (Fig. 1).[6,8–13,17–49] Among the 40 studies, 3 were RCTs and the other 37 were retrospective studies. The results of quality assessments showed that 27 studies were of high quality (the 3 RCT scored 4–5, 6 retrospective studies scored 9 points and 18 retrospective studies scored 8 points) and 13 studies were of medium quality (9 retrospective studies scored 7 points and 4 retrospective studies scored 6 points). Table 1 summarizes the baseline characteristics and main evaluation indices of the included studies.

3.2. Antitumor effectiveness

We assessed the antitumor effectiveness in 4 aspects (FPS, OS, ORR, and DCR) between the 2 groups.

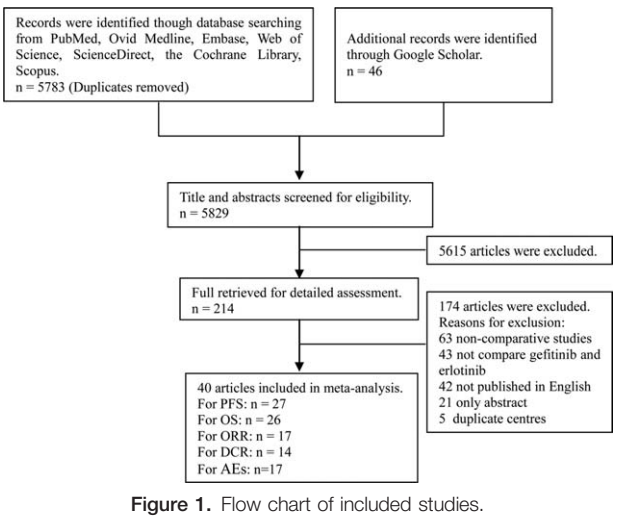

Figure 1. Flow chart of included studies.

Table 1

Characteristics of included studies.

	Study	Country	Groups	Patients (n)	Median age, years	Stage	Treatment line	EGFR mutations	Adenocarcinoma (%)	Design	Quality for RS (points)	Quality for RCT (points)
2008	Popat et al[17]	UK	G vs E	85/29	66/67	IIIb, IV	2, 3	–	45	RS	8	–
2009	Emery et al[18]	USA	G vs E	115/45	67/67	IIIb, IV or recurrent	2 or later	–	43	RS	8	–
2010	Kim et al[19]	Korea	G vs E	171/171	58/59	IIIb, IV	2, 3	–	86	RS	7	–
2010	Hotta et al[20]	Japan	G vs E	330/209	68/68	II–IV or recurrent	2, 3	–	76	RS	9	–
2010	Hong et al[21]	Keroa	G vs E	20/17	61/67	IIIb, IV	2, 3	–	75	RS	7	–
2010	Kappers et al[22]	NLD	G vs E	67/35	59/59	III, IV	–	Partial	67	RS	6	–
2011	Wu et al[23]	Taiwan	G vs E	440/276	67/67	IIIb, IV	1 or later	Partial	85	RS	9	–
2011	Shin et al[9]	KOR	G vs E	100/82	65/65	III, IV	2	Partial	0	RS	7	–
2011	Togashi et al[24]	Japan	G vs E	85/69	65/68	IIIb, IV	1 or later	Partial	82	RS	8	–
2011	Fan et al[12]	Taiwan	G vs E	715/407	–	IIIb, IV	1 or later	Partial	77	RS	8	–
2011	Jung et al[25]	Korea	G vs E	72/51	55/55	IIIb, IV	1 or later	Partial	59	RS	6	–
2012	Wu et al[26]	Taiwan	G vs E	124/100	–	IIIb, IV	1 or later	Partial	100	RS	8	–
2012	Kim et al[27]	Keroa	G vs E	48/48	59/60	IIIb, IV	2	Partial	91	RCT	–	4
2012	Suzumura et al[28]	Japan	G vs E	232/86	67/66	IIIb, IV	–	Partial	95	RS	8	–
2013	Yoshida et al[29]	Japan	G vs E	107/35	64/67	III, IV or recurrent	1 or later	Partial	84	RS	8	–
2013	Shao et al[30]	Taiwan	G vs E	655/329	61/63	IIIb, IV or recurrent	3	–	80	RS	9	–
2013	Lee et al[31]	Korea	G vs E	11/14	49/58	IV	1 or later	Partial	92	RS	8	–
2013	Yu et al[32]	China	G vs E	16/22	54/52	–	3	Partial	100	RS	8	–
2013	Sanchez et al[33]	France	G vs E	47/37	–	IIIb, IV	1 or later	All	96	RS	7	–
2014	Lim et al[34]	Korea	G vs E	121/121	58/58	IIIb, IV	1 or later	All	98	RS	9	–
2014	Sato et al[10]	Japan	G vs E	213/69	66/66	IIIb, IV or recurrent	–	Partial	86	RS	8	–
2014	Lin et al[35]	China	G vs E	57/24	–	IIIb, IV	1	All	59	RS	7	–
2014	Ren et al[36]	China	G vs E	60/142	59/59	IV	1 or later	Partial	66	RS	8	–
2014	Passaro et al[11]	Italy	G vs E	51/56	–	–	1, 2, 3	Partial	–	RS	7	–
2014	Li et al[37]	China	G vs E	53/97	59/59	IIIb, IV	2	Partial	67	RS	8	–
2014	Takeda et al[38]	Japan	G vs E	57/11	69/69	III, IV or recurrent	1 or later	All	99	RS	6	–
2015	Chanprapaph et al[39]	Thailand	G vs E	24/75	60/62	–	1 or later	Unclear	–	RS	8	–
2015	Otsuka et al[40]	Japan	G vs E	35/9	70/62	IIIb, IV	1 or later	All	91	RS	9	–
2015	Song et al[41]	China	G vs E	37/65	75/75	IIIb, IV	2 or later	Partial	83	RS	7	–
2015	Koo et al[42]	Korea	G vs E	166/56	–	IV	1, 2, 3	All	87	RS	7	–
2016	Lin et al[43]	USA	G vs E	16/121	60/60	IV	1 or later	All	100	RS	6	–
2016	Ruan et al[44]	China	G vs E	63/134	59/60	III, IV	–	All	–	RS	8	–
2016	Hirano et al[45]	Japan	G vs E	10/16	71/71	IB–IV or recurrent	–	All	81	RS	8	–
2016	Urata et al[8]	Japan	G vs E	279/280	68/67	IIIb, IV or recurrent	2, 3	Partial	100	RCT	–	5
2016	Suh et al[46]	Korea	G vs E	146/5	65/65	IIIb, IV	1	All	97	RS	7	–
2016	Kashima et al[47]	Japan	G vs E	52/11	68/68	IV	–	All	–	RS	8	–
2017	Yang et al[6]	China	G vs E	128/128	–	IIIb, IV	1, 2	All	96	RCT	–	5
2017	Kuan et al[13]	Taiwan	G vs E	304/63	65/67	IIIb, IV	1	All	–	RS	8	–
2017	Krawczyk et al[48]	Poland	G vs E	66/98	69/67	IIIb, IV	1, 2, 3	All	95	RS	8	–
2017	Li et al[49]	China	G vs E	171/108	–	IIIb, IV or recurrent	1, 2, 3	Partial	91	RS	9	–

–=not available, E=erlotinib, EGFR=epidermal growth factor receptor, G=gefitinib, RCT=randomized controlled trial, RS=retrospective study

Twenty-seven studies compared PFS (heterogeneity: $P=.05$, $I^2=32\%$). No significant difference in PFS was found between the 2 groups (95% CI: 0.98–1.11, $P=.15$; Fig. 2).

Twenty-six studies compared OS (heterogeneity: $P=.001$, $I^2=52\%$). No significant difference in OS was found between the 2 groups (95% CI: 0.93–1.19, $P=.45$; Fig. 3).

Seventeen studies compared ORR (heterogeneity: $P=.31$, $I^2=12\%$). No significant difference in ORR was found between the 2 groups (95% CI: 0.99–1.16, $P=.07$; Fig. 4A).

Fourteen studies compared DCR (heterogeneity: $P=.03$, $I^2=46\%$). No significant difference in DCR was found between the 2 groups (95% CI: 0.92–1.03, $P=.35$; Fig. 4B).

3.3. Toxicity

We compared the toxicity in 3 aspects (total AEs, grade 3–5 AEs, and subgroup analysis of 10 most reported AEs) between the 2 groups.

Five studies compared total AEs (heterogeneity: $P=.0008$, $I^2=79\%$). No significant difference in total AEs was found between the 2 groups (95% CI: 0.87–1.13, $P=.94$; Fig. 5A).

Nine studies compared grade 3–5 AEs (heterogeneity: $P=.003$, $I^2=66\%$). The incidence of grade 3–5 AEs was significantly lower in the gefitinib group than in the erlotinib group (95% CI: 0.36–0.79, $P=.002$; Fig. 5B). Drug discontinuations/reductions because of serious AEs occurred for some patients. Three studies compared drug discontinuations and found no significant difference between the 2 groups (95% CI: 0.59–1.62, $P=.92$; Fig. S1A, http://links.lww.com/MD/C206). Five studies compared drug reductions and found more drug reductions in the erlotinib group (95% CI: 0.10–0.57, $P=.001$; Fig. S1B, http://links.lww.com/MD/C206).

In the subgroup analysis of the 10 most reported AEs (skin rash, diarrhea, nausea/vomiting, fatigue, anorexia, interstitial lung disease (ILD), stomatitis, elevated liver enzymes, infection, and neutropenia), the results of all grade AEs showed no significant differences for diarrhea, nausea/vomiting, anorexia, ILD, elevated liver enzymes, infection, and neutropenia between the 2 groups. Erlotinib treatment induced significantly higher rates in skin rash (95% CI: 0.72–0.91, $P=.0002$), fatigue (95% CI: 0.26–0.90, $P=.02$), and stomatitis (95% CI: 0.24–0.67, $P=.0004$) (Fig. S2, http://links.lww.com/MD/C206). The results of grade 3–5 AEs showed no significant differences for anorexia, ILD, elevated liver enzymes, infection, and neutropenia between the 2 groups. Erlotinib treatment induced significantly higher rates of skin rash (95% CI: 0.14–0.44, $P<0.00001$), diarrhea (95% CI: 0.32–0.76, $P=.001$), nausea/vomiting (95% CI: 0.11–0.47, $P<0.0001$), fatigue (95% CI: 0.12–0.76, $P=.01$), stomatitis (95% CI: 0.08–0.99, $P=.05$) and lower rate of

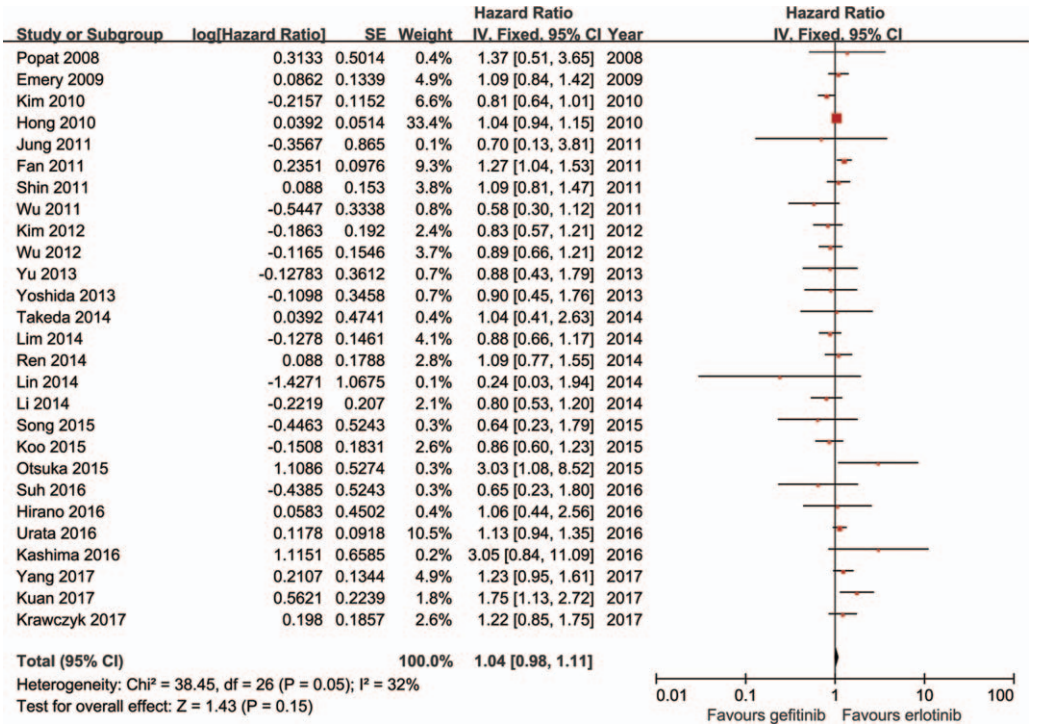

Figure 2. Forest plot of hazard ratio (HR) of progression-free survival (PFS) associated with gefitinib versus erlotinib. HR = hazard ratio, PFS = progression-free survival.

elevated liver enzymes (95% CI: 1.11–3.71, $P = .02$) (Fig. S3, http://links.lww.com/MD/C206).

3.4. Subgroup analysis

To determine whether the antitumor effectiveness of gefitinib versus erlotinib was consistent across various subgroups, the pooled efficacies for PFS, OS, and ORR were estimated within each category of the following classification variables: region, tumor stage, histology, treatment line, EGFR mutation, and study design. The results showed that all subgroup differences were not statistically significant for PFS, OS, and ORR between the 2 treatments (Table 2).

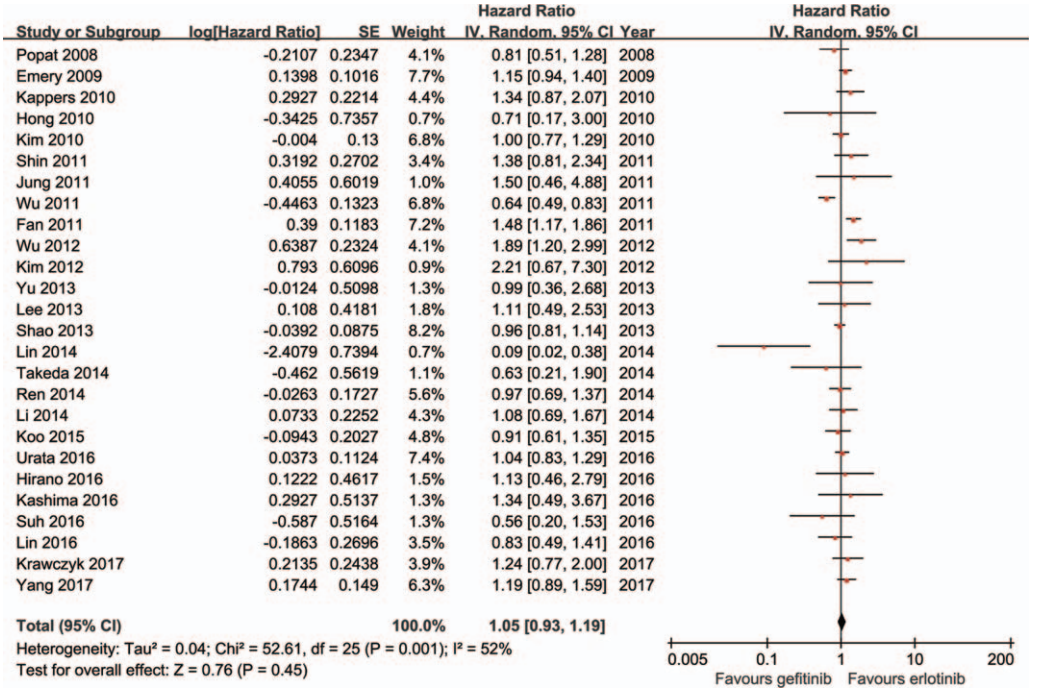

Figure 3. Forest plot of hazard ratio (HR) of overall survival (OS) associated with gefitinib versus erlotinib. HR = hazard ratio, OS = overall survival.

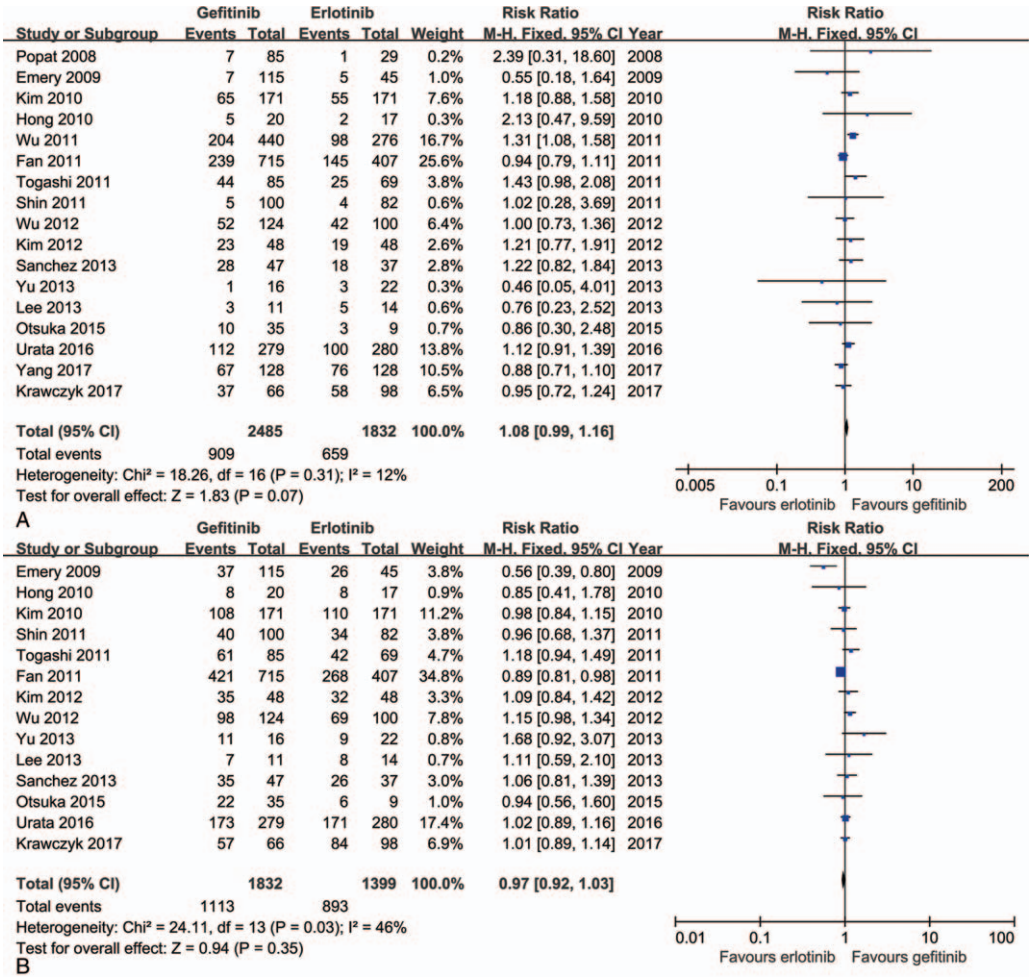

Figure 4. Forest plot of risk ratios (RRs) of objective response rate (ORR, A) and disease control rate (DCR, B) associated with gefitinib versus erlotinib. ORR = objective response rate, RRs = risk ratios.

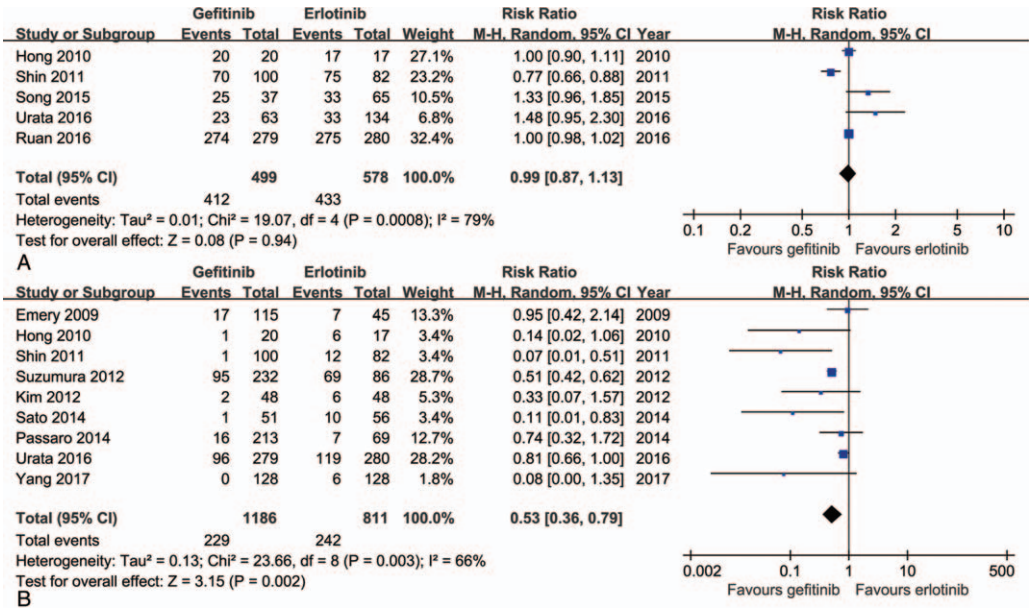

Figure 5. Forest plot of risk ratios (RRs) of all grade adverse effects (A) and grade 3–5 adverse effects (B) associated with gefitinib versus erlotinib. RRs = risk ratios.

Table 2

Subgroup analysis for progression-free survival, objective response rate and objective response rate.

	PFS				OS				ORR			
Group	No.of studies	HR (95% CI)	*P*	I^2 (%)	No.of studies	RR (95% CI)	*P*	I^2 (%)	No.of studies	RR (95% CI)	*P*	I^2 (%)
Total	27	1.04 (0.98–1.11)	.15	32	26	1.05 (0.93–1.19)	.45	52	17	1.13 (0.99–1.29)	.07	13
Region												
Asia	24	1.04 (0.97–1.10)	.26	38	21	1.04 (0.89–1.21)	.61	58	13	1.14 (0.99–1.31)	.06	21
Europe	2	1.24 (0.88–1.74)	.22	0	3	1.11 (0.81–1.51)	.52	27	3	0.14 (0.70–1.86)	.61	0
North America	1	1.09 (0.84–1.42)	.52	NA	2	1.08 (0.83–1.39)	.58	22	1	0.52 (0.16–1.73)	.28	NA
Tumor stage												
IIIb-IV	25	1.04 (0.99–1.11)	.14	37	24	1.05 (0.92–1.19)	.47	56	16	1.13 (0.99–1.29)	.06	15
I-IV	2	0.95 (0.54–1.64)	.85	0	2	1.06 (0.54–2.08)	.86	0	1	0.42 (0.04–4.48)	.47	NA
Histology												
Nonsquamous	14	1.05 (0.97–1.14)	.24	48	13	1.06 (0.88–1.24)	.56	64	10	1.12 (0.98–1.28)	.11	38
Squamous included	12	1.03 (0.95–1.12)	.45	0	12	1.04 (0.93–1.15)	.51	43	7	1.26 (0.81–1.96)	.31	0
Unclear	1	3.05 (0.84–11.09)	.09	NA	1	1.34 (0.49–3.67)	.57	NA				
Treatment line												
First line included	15	1.10 (0.99–1.21)	.07	43	13	0.98 (0.76–1.27)	.89	73	9	1.10 (0.94–1.28)	.26	42
Second line or later	10	0.66 (0.94–1.09)	.73	7	10	1.03 (0.94–1.14)	.48	0	8	1.22 (0.96–1.55)	.11	0
First line only	3	0.89 (0.32–2.49)	.82	66	2	0.24 (0.04–1.43)	.12	75				
Second line only	4	0.95 (0.78–1.16)	.6	0	4	1.08 (0.83–1.41)	.58	19	3	1.40 (0.73–2.69)	.31	0
Third line only	2	1.02 (0.58–1.82)	.94	0	3	0.94 (0.80–1.10)	.47	0	2	1.07 (0.26–4.50)	.92	5
Unclear	2	1.48 (0.72–3.08)	.29	43	3	1.30 (0.91–1.88)	.15	0				
EGFR mutation												
Partial mutation	12	1.05 (0.96–1.16)	.3	18	12	1.16 (0.94–1.44)	.16	66	9	1.17 (1.00–1.36)	.05	28
All mutation	11	1.12 (0.97–1.28)	.12	46	9	1.00 (0.84–1.20)	.99	49	4	0.89 (0.63–1.25)	.5	0
Unclear	4	1.01 (0.93–1.10)	.84	38	5	1.01 (0.91–1.13)	.83	0	4	1.26 (0.84–1.87)	.26	2
Study design												
Retrospective study	24	1.03 (0.97–1.10)	.37	34	23	1.03 (0.89–1.19)	.69	56	14	1.15 (0.99–1.34)	.07	15
RCT	3	1.11 (0.96–1.27)	.15	32	3	1.11 (0.93–1.32)	.25	0	3	1.07 (0.82–1.39)	.62	30

HR = hazard ratio, NA = not available, ORR = objective response rate, ORR = objective response rate, PFS = progression-free survival, RCT = randomized controlled trial, RR = relative risk

3.5. Publication bias

There was no evidence of publication bias for PFS (Begg's test $P = .632$; Egger's test $P = .598$, Fig. 6A) and OS (Begg's test $P = .567$; Egger's test $P = .672$, Fig. 6B).

4. Discussion

Gefitinib and erlotinib have been widely used to treat advanced NSCLC during the past decade. By analyzing 40 high quality studies, we compared the antitumor effectiveness and safety of the 2 agents for NSCLC directly.[6,8–13,17–49] Our meta-analysis provided the most up-to-date medical evidence and showed that the antitumor effectiveness (PFS, OS, ORR, and DCR) was comparable between the 2 agents. The results did not change after subgroup analysis according to region, tumor stage, histology, treatment line, EGFR mutation, and study design. However, the toxicity of erlotinib was significantly higher than that of gefitinib, especially in all-grade/grade 3–5 skin rash, nausea/vomiting, fatigue, and stomatitis.

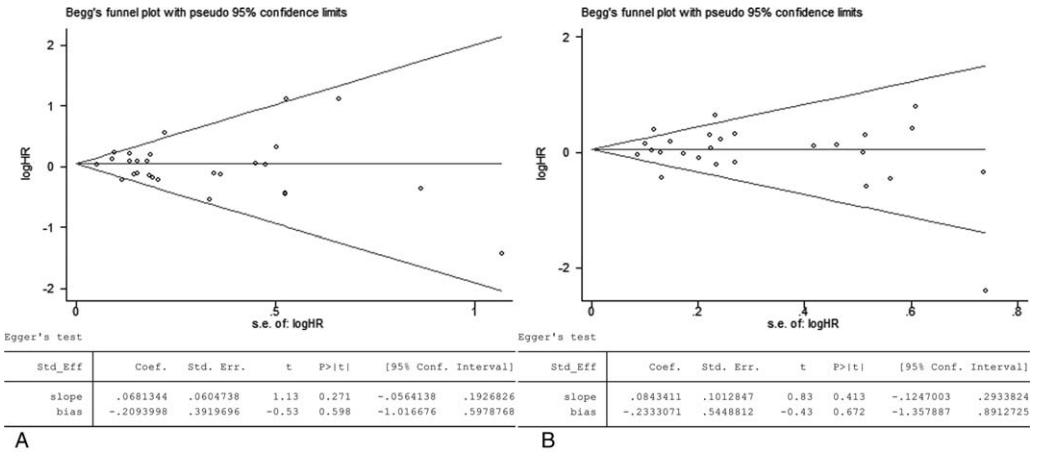

Figure 6. Begg's and Egger's test for the comparsions of progression-free survival (PFS, A) and overall survival (OS, B). OS = overall survival, PFS = progression-free survival.

Gefitinib and erlotinib are 2 similar, but different, small molecules with different binding capabilities, pharmacokinetics, and pharmacodynamic properties related to their different molecular structures.[50–52] As first generation EGFR TKIs, whether these differences could cause different antitumor effectiveness is controversial.[6,8,53] In our analysis, almost all the included studies showed no differences in all indices of antitumor effectiveness, which was the basis of our results. Only one study reported an unfavorable result against erlotinib, with both lower PFS and OS, which might relate to the presence of more patients with nonadenocarcinoma in the erlotinib group.[12] Our results also showed a tendency toward prolonged median PFS (gefitinib group, 7.6 months vs 4.9 months; erlotinib group, 7.9 months vs 3.2 months) and OS (gefitinib group, 21.1 months vs 12.0 months; erlotinib group, 15.5 months vs 11.3 months) in patients with adenocarcinoma as compared with those with squamous-included NSCLC. However, no difference was found between the 2 EGFR TKIs in this subgroup.

In the subgroup of EGFR mutation, we also found no difference between the 2 EGFR TKIs in the comparison of antitumor effectiveness. However, our results proved indirectly that both gefitinib and erlotinib are more suitable for EGFR mutation–positive NSCLC. Both median PFS (gefitinib group, 10.4 months vs 4.9 months; erlotinib group, 10.0 months vs 3.5 months) and OS (gefitinib group, 22.6 months vs 16.0 months; erlotinib group, 20.9 months vs 12.0 months) were longer in all EGFR mutation-positive subgroup than in the partial mutation-positive subgroup. Thus, we observed the phenomenon that the proportion of EGFR mutations increased year by year in the treatment of EGFR TKIs (Table 1). Multiple isoforms (exon 19, exon 21 or others) of EGFR mutations were identified and which is more suitable for gefitinib or erlotinib remains unclear. A phase III RCT compared gefitinib and erlotinib in EGFR mutation-positive NSCLC and found that EGFR exon 19 mutations were associated with a significantly higher RR and longer median OS than those with exon 21 mutations treated with erlotinib or gefitinib. However, no difference was found between gefitinib and erlotinib for both mutations.[6] Similar results were reported by another RCT involving more mutation isoforms (exon 19, exon 21, T790M, etc.).[8] However, Kuan's et al[13] study suggested that erlotinib treatment was associated with significantly longer progression free survival and lower risk of progression than gefitinib in patients with exon 19 deletions. Limited by the quantity of published studies and included patients, further larger, well-designed randomized controlled trials focusing on single EGFR mutations are warranted to select the best EGFR TKIs.

It remains a matter of debate regarding which treatment line EGFR TKIs should be used in for NSCLC. In mainstream thinking, EGFR TKIs were regarded as line 2 or later treatments after chemotherapy failure or line 1 treatment for patients unable to tolerate chemotherapy. However, Table 1 shows that more studies used gefitinib and erlotinib as the first line treatment for advanced NSCLC.[13,35,46] In our analysis, both median PFS (11.4 months vs 3.75 months) and OS (26.15 months vs 12.3 months) were longer in the first line treatment subgroup than in the subgroup of line 2 or later. This comparison was not accurate enough because of too many confounders. However, no differences were found in PFS, OS, and ORR between gefitinib and erlotinib in each subgroup according to treatment line. Wu et al. conducted a phase III RCT and suggested that first-line erlotinib could provide a significant improvement in PFS versus gemcitabine+cisplatin in patients with EGFR mutation-positive NSCLC.[54] Another phase III RCT suggested that PFS was significantly longer with gefitinib for patients with mutation-positive NSCLC as compared with carboplatin+paclitaxel.[55] Similar results were reported by several other high-quality RCTs.[56–58] Based on these positive results, gefitinib was approved by the FDA for the first-line treatment of EGFR mutation-positive NSCLC.[59] In the 2017 NCCN guidelines for NSCLC, both gefitinib and erlotinib were also suggested as first-line treatments of EGFR mutation-positive NSCLC.[60]

Drug toxicity is an important problem for erlotinib. In our analysis, high incidences of drug reactions, skin rash, diarrhea, nausea/vomiting, fatigue, and stomatitis were found in the erlotinib arm. Although the results might not affect the survival time, they greatly affected the quality-of-life (QOL) of the patients.[61,62] Two reasons might be responsible for these results: the oral dose of erlotinib (150 mg/day) was closer to its maximum tolerated dose (150 mg/day) compared with that of gefitinib (oral dose: 250 mg/d; maximum tolerated dose: 600 mg/day);[63,64] the pharmacokinetics are different between the 2 EGFR TKIs. After absorption, more gefitinib is accumulated in tumor tissue than in the plasma, which is opposite to the kinetics of erlotinib.[65] In the subgroup analysis by region, more severe AEs were found in the population of East Asia compared with those in Europe and America (gefitinib group, 18/166 [10.84%] vs 211/1020 [20.69%], $P = .003$; erlotinib group, 17/91 [18.68%] vs 225/710 [31.69%], $P = .011$). ILD, one of the most important AEs, can lead to a worse prognosis and an increased risk of death.[66] However, the results of our analysis and of other published studies show that most ILDs were reported in the East Asia population and are rare in Western populations. The smaller physique of Asians might explain this phenomenon. Yeo reduced the dose of erlotinib down to 25 mg/day in a retrospective study and achieved a similar or even better prognosis compared with the standard dose.[67] Similar results were also reported in other retrospective studies.[10,68–70] Therefore, we suggest that individualized drug doses, based on weight or body surface area, might be more suitable than a fixed oral dose. Further large, well-designed RCTs are needed to confirm the best dose of gefitinib and erlotinib for each patient.

Several potential limitations should be taken into consideration when interpreting our results. First, to ensure the quality of the data, we only included high quality studies published in English, which might result in a language bias. Second, only 3 RCTs were included, which would weaken the quality of the results. Third, significant heterogeneity existed in some comparisons (OS and total/grade 3–5 AEs), which would weaken the reliability of the results. Fourth, the type and rate of EGFR mutations were different between the included studies, which might increase the heterogeneity and weaken the quality of the results. Fifth, QOL and survival time were 2 equally important evaluating indicators for treatment. QOL could not simply be replaced by the quantity of AEs. However, no quality-of- life was compared between the 2 EGFR TKIs in all the included studies. Thus, we suggest that quality-of-life should be regarded as an essential indicator in future studies of drug evaluation.

Based on the present evidence, both gefitinib and erlotinib are effective for advanced NSCLC, with comparable PFS, OS, ORR, and DCR. Erlotinib treatment induced a significantly higher rate and severity in skin rash, nausea/vomiting, fatigue, and stomatitis, which might have caused the observed higher rate of dose reduction. Thus, we suggest that individualized drug doses, based on weight or body surface area, might be more suitable than a fixed oral dose for both agents. However, because of the inherent

limitations of our meta-analysis, further large-scale, high-quality RCTs are warranted to confirm this conclusion.

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