Systematic Review and Meta-Analysis

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Combination strategies based on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors for cancer patients

Pooled analysis and subgroup analysis of efficacy and safety

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Abstract

Background: Combination therapy based on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is an emerging trend in cancer treatment, but the clinical value of EGFR-TKIs combination therapy remains controversial. Thus, we conducted a comprehensive analysis of randomized controlled trials (RCTs) comparing EGFR-TKIs combination therapies with monotherapies, aiming to evaluate the safety and efficacy of EGFR-TKIs based combination therapy and to find a more beneficial combination strategy.

Methods: We searched for clinical studies that evaluated EGFR-TKIs combination therapy in cancer. We extracted data from these studies to evaluate the relative risk (RR) of overall response rate (ORR) and grade 3/4 treatment-related adverse events (AEs), the hazard ratios (HRs) of overall survival (OS), and progression-free survival (PFS).

Results: Fourteen RCTs were identified (n = 3774). Treatments included combinations of EGFR-TKIs and chemotherapy, combinations of EGFR-TKIs and radiotherapy, and combinations of EGFR-TKIs and bevacizumab. EGFR-TKIs combination therapies showed higher ORR [RR: 1.62; 95% confidence interval (95% CI):1.16–2.26; $P = .005$], PFS (HR: 0.76; 95% CI: 0.64–0.89; $P = .001$), and OS (HR: 0.88; 95% CI: 0.79–0.97; $P = .013$) values than monotherapies. However, higher grade 3/4 treatment-related AEs (RR: 1.79; 95% CI: 1.02–3.15; $P = .000$) were observed in combination therapy than in monotherapy.

Conclusion: Our pooled analysis and subgroup analysis results showed that the addition of chemotherapy to EGFR-TKIs better benefits PFS and safety. Adding bevacizumab was associated with better ORR and OS. The efficacy and safety of a bevacizumab-EGFR-TKIs-chemotherapy combination should be investigated further.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, EGFR = epidermal growth factor receptor, HR = hazard ratio, LC = lung carcinoma, NSCLC = non-small cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression free survival, RCT = randomized controlled trial, RR = relative risk, TKIs = tyrosine kinase inhibitors.

Keywords: combination therapy, epidermal growth factor receptor, erlotinib, gefitinib

1. Introduction

Personalized therapy is a novel idea and has becoming an emerging trend in the treatment of cancer. The epidermal growth factor receptor (EGFR) and its downstream signaling, including the Ras-Raf-MAP, PI3K, and Akt pathways, play a vital role in the regulation of cell proliferation, survival, and differentiation.[1–3] Therefore, targeting EGFR has become a focus of investigation, including research in EGFR tyrosine kinase inhibitors (EGFR-TKIs). EGFR-TKIs can inhibit enzyme tyrosine kinase that involved in signal transduction cascade and downstream activation of many proteins.[4] EGFR-TKIs such as gefitinib and erlotinib have been approved by the US Food and Drug Administration (FDA).[5,6]

Gefitinib, a selective EGFR (ErbB1) tyrosine kinase inhibitor, can also inhibit the growth of some ErbB2-overexpressing tumor cells.[7,8] Gefitinib has been shown to improve OS in patients with nonsmall cell lung cancer (NSCLC) after failure of chemotherapies.[7] Erlotinib is a potent and selective inhibitor of the EGFR tyrosine kinase.[9] It can block cell cycle progression in the G1 phase.[10] Erlotinib has been shown to reduce symptoms and increase survival in patients with advanced stage III or IV NSCLC.[11] In addition, Erlotinib has also been reported to be

Editor: Eric Bush.

These authors contributed equally to this work.

All authors gave final approval for submission of the manuscript.

The authors report no conflicts of interest.

The author(s) of this work have nothing to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2019) 98:13(e14135)

Received: 29 July 2018 / Received in final form: 18 December 2018 / Accepted: 20 December 2018

http://dx.doi.org/10.1097/MD.0000000000014135

associated with alleviation of tumor-related symptoms in patients who were positive for ErbB1.[12]

EGFR tyrosine kinase inhibitors combination therapy has gained popularity and there are several preclinical trials on EGFR-TKIs combination therapies, as well as phase I and phase II studies. However, the clinical value of EGFR-TKIs combination therapy remains under debate. Recent studies have begun to examine EGFR-TKIs combination therapy, though whether the benefits outweigh potential toxicities remains uncertain.

This study aims to evaluate the safety and efficacy of EGFR-TKIs combination therapy, and to investigate an appropriate combination type.

2. Methods

2.1. Study design and search strategy

All relevant information was identified from published trials that compared combination of EGFR-TKIs therapies with monotherapy to evaluate the clinical value of EGFR-TKIs based combination therapy. We searched for the trials based on the following computerized bibliographic databases: PubMed/Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar without any language restrictions. The following Keywords were included: combination therapy, EGFR-TKIs, gefitinib, and erlotinib. In order to find potential publications, we reviewed a reference list of related articles for further analysis.

2.2. Selection criteria

We identified eligible studies according to the following four criteria: Phase II or phase III Trials for cancer; An intervention that combined EGFR-TKIs with other treatments, such as chemotherapy or radiotherapy; Evaluating the clinical value or adverse events (AEs) of treatment; and Comparing combination therapy with monotherapy.

The exclusion criteria were studies were not related to EGFR-TKIs or not clinical trials; Conference documents; and Studies lacked necessary data.

2.3. Data extraction

Three reviewers (RX, HS, JZ) independently extracted data with a standardized form. We reviewed all studies and extracted the following information from the studies: the first author, published year, intervention in the experimental groups and control groups, progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and grade 3/4 treatment-related AEs. ORR was collected directly or calculated according to CRR and PRR. Initially, reviewers measured ORR and OS. Secondary reviewers assessed PFS and grade 3/4 treatment-related AEs.

2.4. Assessment of the study quality and risk of bias

Cochrane Collaboration's tool was used to evaluate the risk of bias, and any controversies were resolved by mutual discussion. We assessed the study quality based on the latest 2009 version of the initial Stroke Therapy Academic Industry Roundtable (STAIR) standard, which includes sample-size calculation, inclusion and exclusion criteria, allocation concealment, blinded assessment of outcome, reporting of patients excluded from analysis, and reporting potential conflicts of interest and study funding. All reviewers assessed the qualities in all included studies. The "unclear" means that the quality was not clear. Details on the risk of bias in 14 studies are illustrated in Supporting Information Figure S4, http://links.lww.com/MD/C888.

2.5. Statistical analysis

Statistical analysis, forest plots, sensitivity analysis, and detection of publication bias were calculated by Stata/SE 12.0 (Stata Corp, College Station, TX), and we used Review Manager (RevMan5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to assess the risk of bias. In addition, we used an Excel spreadsheet developed by Matthew Sydes and Jayne Tierney of the MRC Clinical Trials Unit, London, UK, to evaluate the ln (HR) values and se(ln(HR)) values.[13,14] Relative risk (RR) and hazard ratios (HRs) were used for evaluation. Publication bias was assessed by Egger test and Begg test. All analyses (OS, ORR, PFS, and grade 3/4 treatment-related AEs) were performed using a random-effects model (M–H heterogeneity).[15] In addition, we calculated 95% confidence intervals (95% CIs) for each estimate.

2.6. Data availability

All data generated during and/or analyzed in this study are included in this published article (and its supplementary information files).

2.7. Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

2.8. Informed consent

For this type of study, formal consent is not required.

3. Results

3.1. Search results and study characteristics

A total of 533 potentially relevant studies were retrieved from initial database search from PubMed/Medline, Embase, CENTRAL, and Google Scholar, of which 14 articles met all inclusion criteria.[16–29] All the studies evaluated the efficacy of EGFR-TKIs combination therapies, combining EGFR-TKIs with other therapies. We found several types of combination trials: 7 combinations of EGFR-TKIs with chemotherapies (n=2615), 4 combinations of EGFR-TKIs with radiotherapies (n=453), and 3 combinations of EGFR-TKIs with bevacizumab (n=706). The detailed studies selection process is illustrated in "PRISMA Flow Diagram."

A total of 3774 patients were included in the analysis, of whom 2858 had nonsmall-cell lung cancer, 71 had lung carcinoma, and 706 had colorectal cancer. The safety analysis included 2109 of these patients. In total, 2146 patients received combination therapies, including 7 combinations of EGFR-TKIs with chemotherapies (n=1544), 4 combinations of EGFR-TKIs with radiotherapies (n=247), and 3 combinations of EGFR-TKIs with bevacizumab (n=355). Patients receiving monotherapy served as the controls (n=1628). Main characteristics of those trials are available in Table 1.

Table 1

Characteristics of the included studies in the meta-analysis.

Study	Year	Cancer	Phase	Type	N	Additional treatment	Overall response		Grade 3/4	
							Events	Total	Events	Total
Thatcher et al[16]	2005	NSCLC	III	RCT	1439	Chemotherapy	77	959	NR	NR
Kelly et al[17]	2008	NSCLC	III	RCT	243	Radiotherapy	81	118	86	118
Goss et al[18]	2009	NSCLC	II	RCT	201	Chemotherapy	76	100	25	100
Gaafar et al[19]	2011	NSCLC	III	RCT	173	Chemotherapy	10	86	69	86
Lee et al[20]	2014	NSCLC	II	RCT	80	Radiotherapy	NR	80	6	40
Pesce et al[21]	2012	NSCLC	II	RCT	59	Radiotherapy	NR	59	5	16
Johnsson et al[22]	2013	CRC	III	RCT	159	Bevacizumab	NR	159	NR	NR
Tournigand et al[23]	2015	CRC	III	RCT	421	Bevacizumab	48	213	102	210
Hagman et al[24]	2016	CRC	III	RCT	126	Bevacizumab	NR	126	2	36
Mok et al[25]	2009	NSCLC	II	RCT	154	Chemotherapy	27	76	27	76
Wu et al[26]	2013	NSCLC	II	RCT	451	Chemotherapy	97	226	13	226
Yu et al[27]	2014	NSCLC	II	RCT	111	Chemotherapy	27	54	13	58
Choi et al[28]	2015	NSCLC	II	RCT	86	Chemotherapy	18	43	NR	NR
Zhuang et al[29]	2013	LC	II	RCT	71	Radiotherapy	10	46	NR	NR

CRC = colorectal cancer, LC = lung carcinoma, NR = not recorded, NSCLC = nonsmall cell lung cancer, RCT = randomized controlled trial.

3.2. Efficacy outcomes

The OS was reported in all 14 trails.[16–29] The ORR was reported in 10 of the trails.[16–19,23,25–29] The PFS was reported in 12 of the trails.[17–20,22–29] The ORR, OS, and PFS of combination therapies were significantly higher than monotherapies (Fig. 1). Combination of EGFR-TKIs and other therapies was associated with significantly higher ORRs than monotherapies (RR: 1.62, 95% CI: 1.16–2.26, $P = .005$)

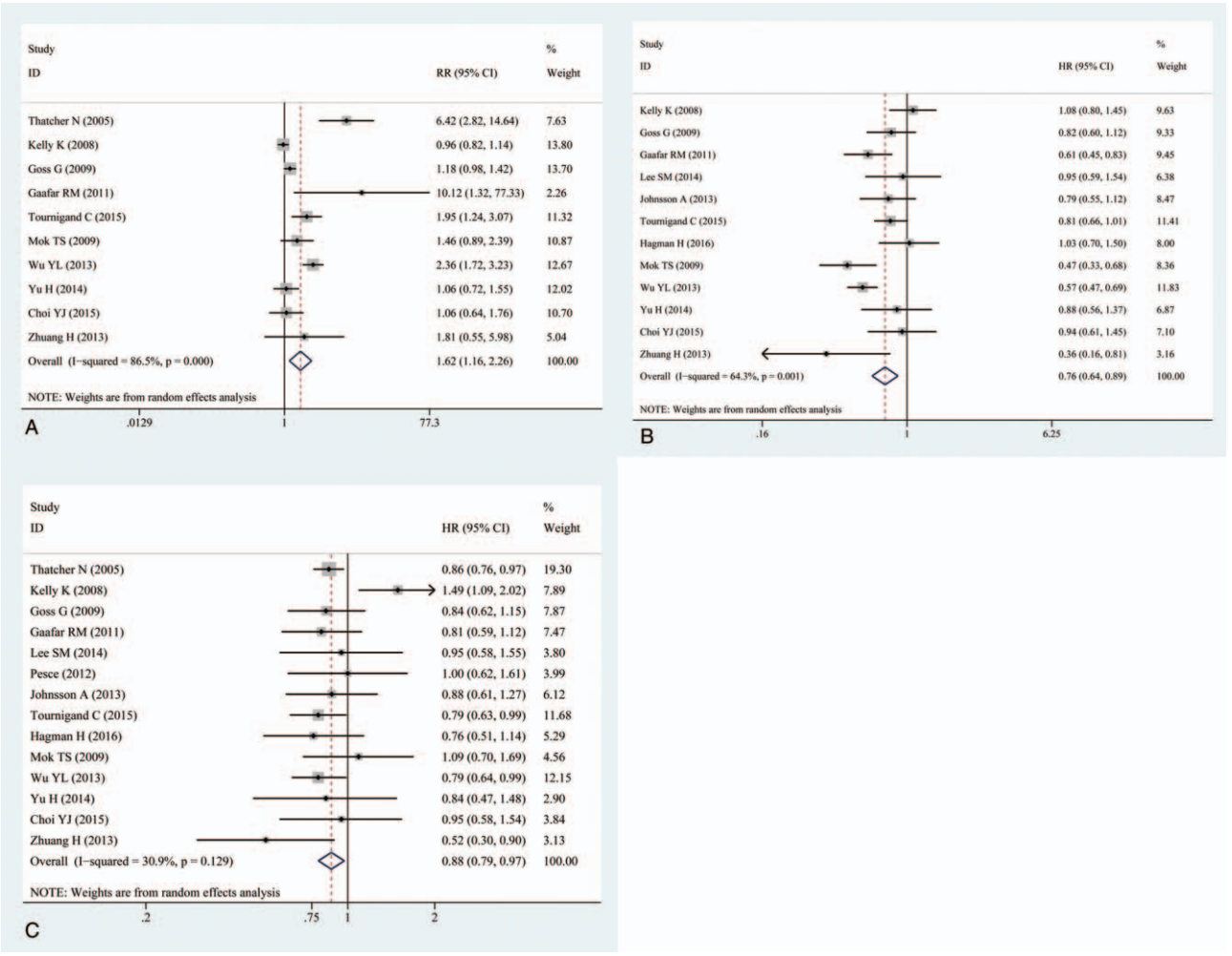

Figure 1. Pooled analysis of overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). (A) overall response rate (ORR); (B) progression-free survival (PFS); (C) overall survival (OS).

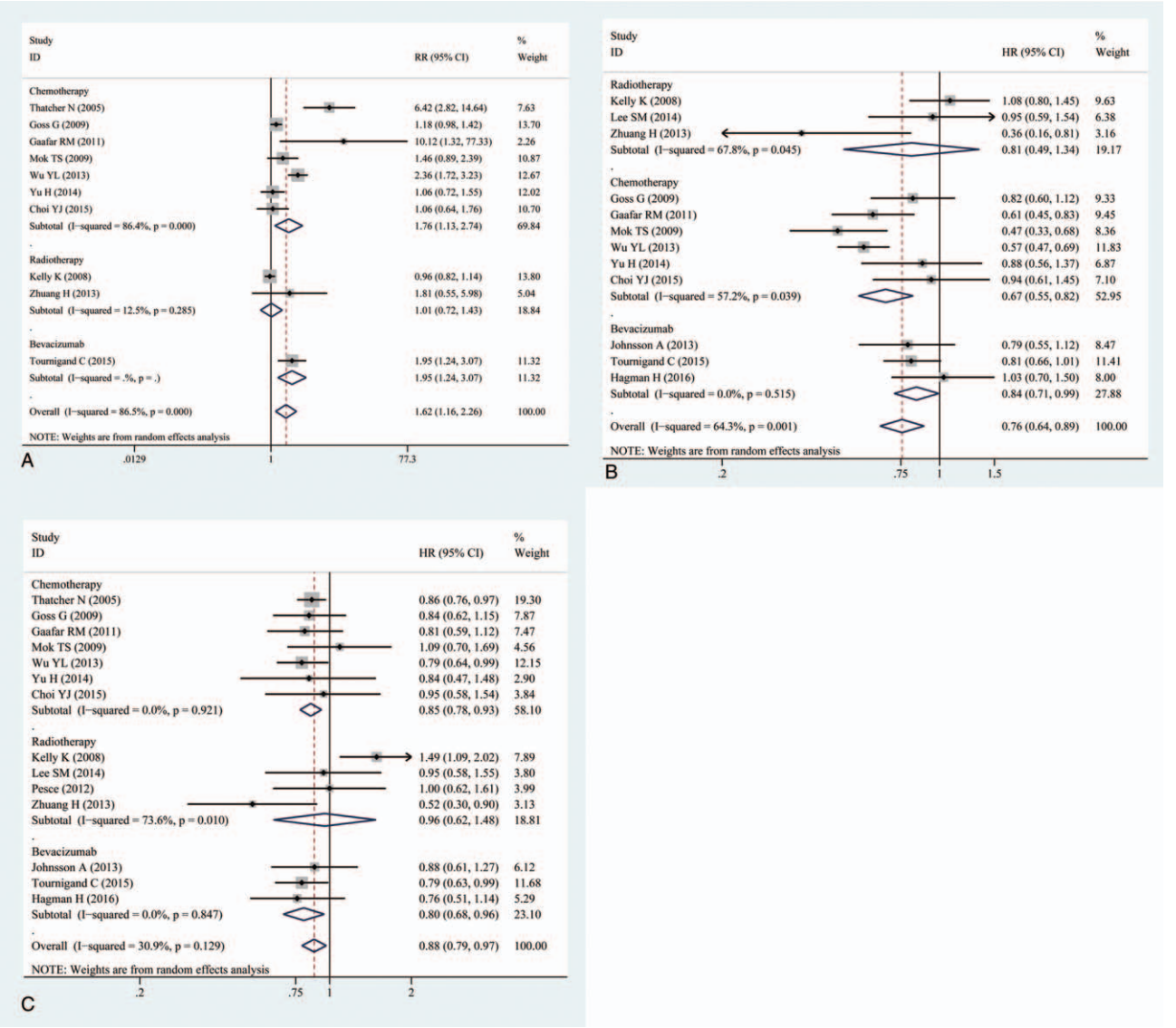

Figure 2. (A) Subgroup analysis of overall response rate (ORR); (B) subgroup analysis of progression-free survival (PFS); (C) subgroup analysis of overall survival (OS) by type of combination.

(Fig. 1A). Compared with monotherapies, combination therapy significantly prolonged PFS (HR: 0.76, 95% CI: 0.64–0.89, $P=.001$) (Fig. 1B). In addition, the OS of combination therapies was also significantly higher than monotherapies (HR: 0.88, 95% CI: 0.79–0. 97, $P=.013$) (Fig. 1C). There was high heterogeneity in the ORR ($I^2=86.5\%$) and PFS ($I^2=64.3\%$) analyses, while heterogeneity in OS ($I^2=30.9\%$) was low. Subgroup analysis of combination type and cancer type are shown in Figs. 2 and 3 and Table 2. Detailed heterogeneity analyses are shown in Supporting Information Figure S1, http://links.lww.com/MD/C888. Subgroup analysis of combination type showed that combination of bevacizumab and EGFR-TKIs can better benefit ORR and OS (Fig. 2A,C), and combination of chemotherapy and EGFR-TKIs can better benefit PFS (Fig. 2B).

3.3. Safety outcomes

The grade 3/4 treatment-related AEs of EGFR-TKIs combination therapies were reported in ten trials.[17–21,23–27] Analysis shows significantly high rate of grade 3/4 AEs in combination therapies (RR: 1.79, 95% CI: 1.02–3.15, $P=.000$) (Fig. 4A), with high heterogeneity ($I^2=90.1\%$). Tests of heterogeneity and subgroup analyses by type of combination and cancer are shown in Fig. 4B, C and Table 3. Combination of EGFR-TKIs and bevacizumab showed the highest rate of grade 3/4 treatment-related AEs (RR: 5.02, 95% CI: 3.29–7.66) (Fig. 4B). The grade 3/4 treatment-related AEs of EGFR-TKIs combination therapies in CRC are higher than that in NSCLC (Fig. 4C).

3.4. Sensitivity analysis and publication bias

All sensitivity analysis performed in this study indicated a stable result. No sensitivity analysis shows positive results. Detailed sensitivity analysis is shown in Supporting Information Figure S2, http://links.lww.com/MD/C888. Our publication bias was based on both Begg test and Egger test. In Begg test, the P values were .210 for ORR, .474 for grade 3/4 treatment-related AEs, .837 for

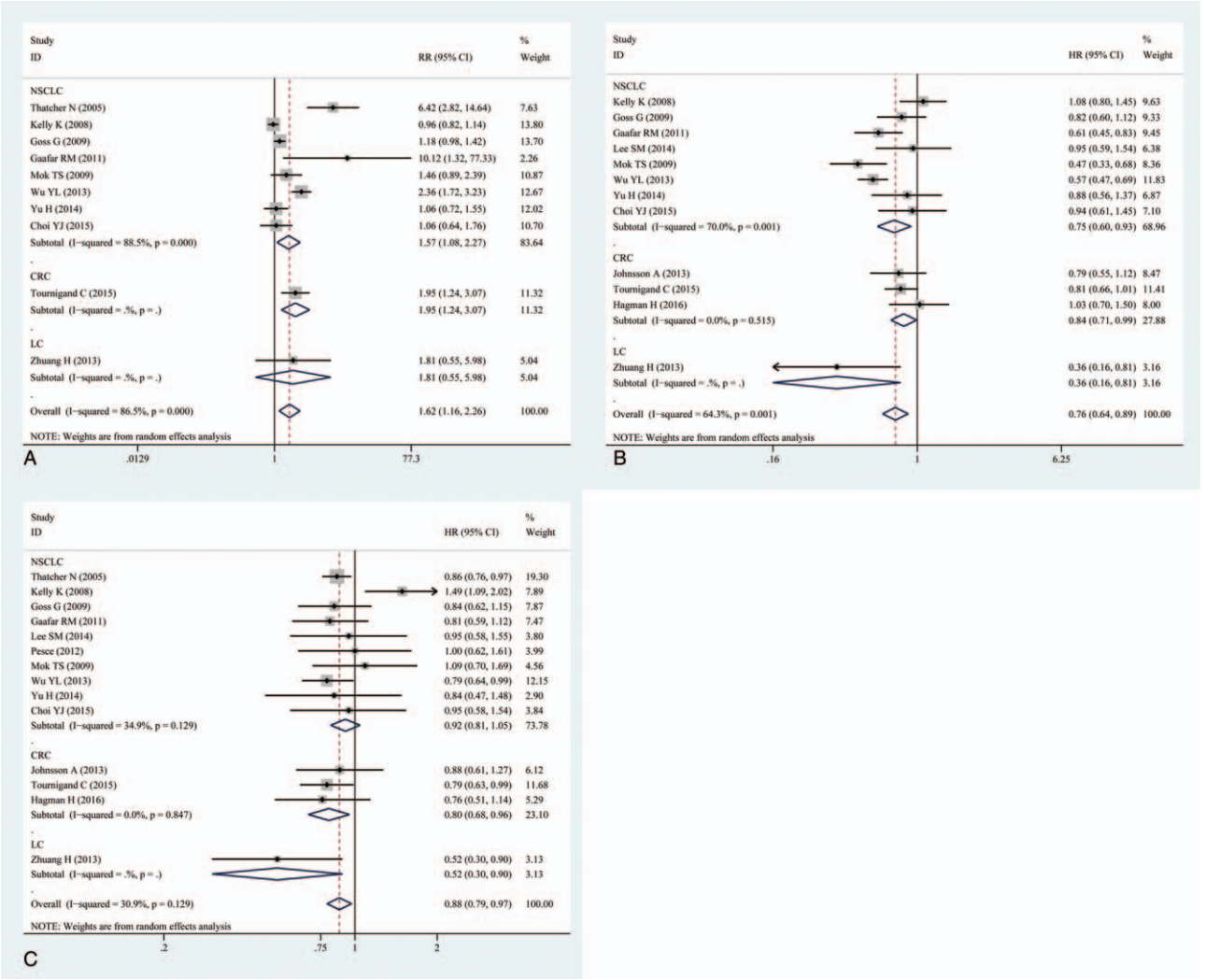

Figure 3. (A) Subgroup analysis of overall response rate (ORR); (B) subgroup analysis of progression-free survival (PFS); (C) subgroup analysis of overall survival (OS) by cancer type.

Table 2

Subgroup analysis by type of EGFR-TKIs combination and cancer type.

(A)					
ORR	**Heterogeneity**	**Dof**	***P***	I^2	**Tau²**
EGFR-TKIs + Chemotherapy versus Monotherapy	44.19	6	.000	86.4%	0.2653
EGFR-TKIs + Radiotherapy versus Monotherapy	1.14	1	.285	12.5%	0.0270
EGFR-TKIs + bevacizumab versus Monotherapy	0.00	0	—	—	0.0270
Overall	66.68	9	.000	86.5%	0.2026
OS	**Heterogeneity**	**Dof**	***P***	I^2	**Tau²**
EGFR-TKIs + Chemotherapy versus Monotherapy	1.98	6	.921	0.0%	0.0000
EGFR-TKIs + Radiotherapy versus Monotherapy	11.34	3	.010	73.6%	0.1420
EGFR-TKIs + bevacizumab versus Monotherapy	0.33	2	.847	0.0%	0.0000
Overall	18.82	13	.129	30.9%	0.0106
PFS	**Heterogeneity**	**Dof**	***P***	I^2	**Tau²**
EGFR-TKIs + Chemotherapy versus Monotherapy	11.69	5	.039	57.2%	0.0349
EGFR-TKIs + Radiotherapy versus Monotherapy	6.21	2	.045	67.8%	0.1292
EGFR-TKIs + bevacizumab versus Monotherapy	1.33	2	.515	0.0%	0.0000

(*continued*)

Table 2

(continued).

PFS	Heterogeneity	Dof	P	I^2	Tau^2
Overall	30.85	11	.001	64.3%	0.0492

(B)

ORR	Heterogeneity	Dof	P	I^2	Tau^2
NSCLC	60.94	7	.000	88.5%	0.2088
CRC	0.00	0	—	—	0.2088
LC	0.00	0	—	—	0.2088
Overall	66.68	9	.000	86.5%	0.2026
OS	**Heterogeneity**	**Dof**	**P**	I^2	Tau^2
NSCLC	13.83	9	.129	34.9%	0.0124
CRC	0.33	2	.847	0.0%	0.0000
LC	0.00	0	—	—	0.0000
Overall	18.82	13	.129	30.9%	0.0106
PFS	**Heterogeneity**	**Dof**	**P**	I^2	Tau^2
NSCLC	23.33	7	.001	70.0%	0.0636
CRC	1.33	2	.515	0.0%	0.0000
LC	0.00	0	—	—	0.0000
Overall	30.85	11	.001	64.3%	0.0492

CRC = colorectal cancer, Dof = Degrees of freedom, LC = lung carcinoma, NSCLC = nonsmall cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival.

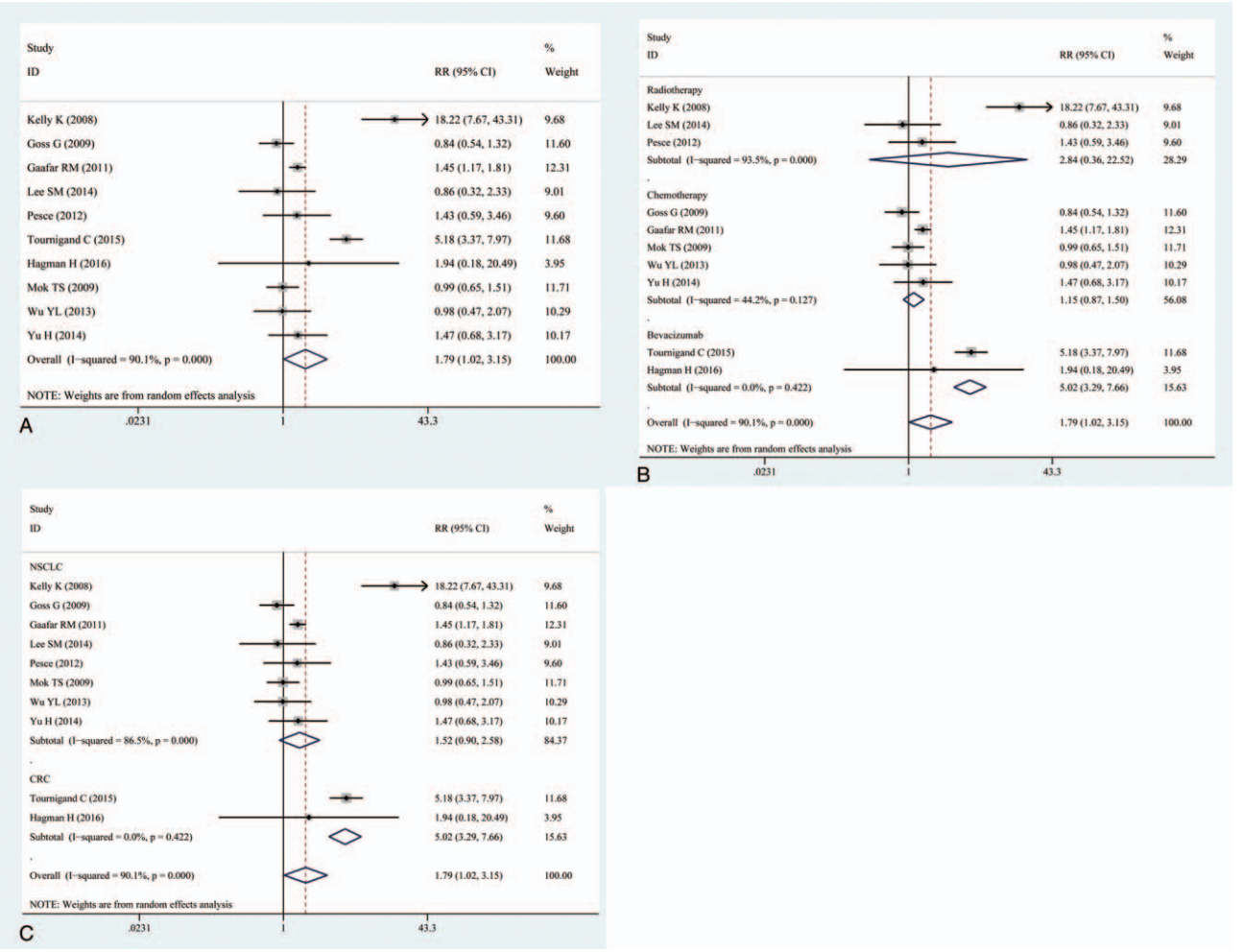

Figure 4. (A) Pooled analysis of grade 3/4 treatment-related adverse events; (B) subgroup analysis of grade 3/4 treatment-related adverse events by type of combination (C) subgroup analysis of grade 3/4 treatment-related adverse events by cancer type.

Table 3

Grade 3/4 treatment-related adverse events, analyzed by type of EGFR-TKIs combination and by cancer type.

(A)

G3/4 trAEs	Heterogeneity	Dof	*P*	I^2	Tau^2
EGFR-TKIs + Chemotherapy versus Monotherapy	7.17	4	.127	44.2%	0.0400
EGFR-TKIs + Radiotherapy versus Monotherapy	30.81	2	.000	93.5%	3.1287
EGFR-TKIs + bevacizumab versus Monotherapy	0.64	1	.422	0.0%	0.0000
Overall	90.79	9	.000	90.1%	0.6632

(B)

G3/4 trAEs	Heterogeneity	Dof	*P*	I^2	Tau^2
NSCLC	51.74	7	.000	86.5%	0.4568
CRC	0.64	1	.422	0.0%	0.0000
Overall	90.79	9	.000	90.1%	0.6632

CRC = colorectal cancer, Dof = degrees of freedom, G3/4 trAEs = Grade 3/4 treatment-related adverse events, LC = lung carcinoma, NSCLC = nonsmall cell lung cancer.

PFS, and .743 for OS. In Egger test, the *P* values were .042 for ORR, .680 for grade 3/4 treatment-related AEs, .627 for PFS, and .933 for OS. The Begg graphs are shown in Fig. 5, and the Egger graphs are shown in Supporting Information Figure S3, http://links.lww.com/MD/C888.

4. Discussion

To our knowledge, this is the first comprehensive analysis with RCTs to assess the efficacy and safety of EGFR-TKIs combination therapies. The current trials have some limitations, but we think that outcomes can still provide insights into EGFR-TKIs combination therapies. Outcomes of studies on EGFR-TKIs combination therapies, including chemotherapy, radiotherapy, and bevacizumab have been published, but efficacy and safety of combination therapies are still under debate. Outcomes of several trials did not improve the clinical outcome of cancer patients.[27,28] Therefore, we performed this comprehensive analysis to evaluate the value and toxic effects of EGFR-TKIs combination therapies; in addition, subgroup analyses were warranted to evaluate the optimal combination strategies.

The pooled analyses showed that EGFR-TKIs combination therapies led to significantly improved ORR, OS, and PFS in

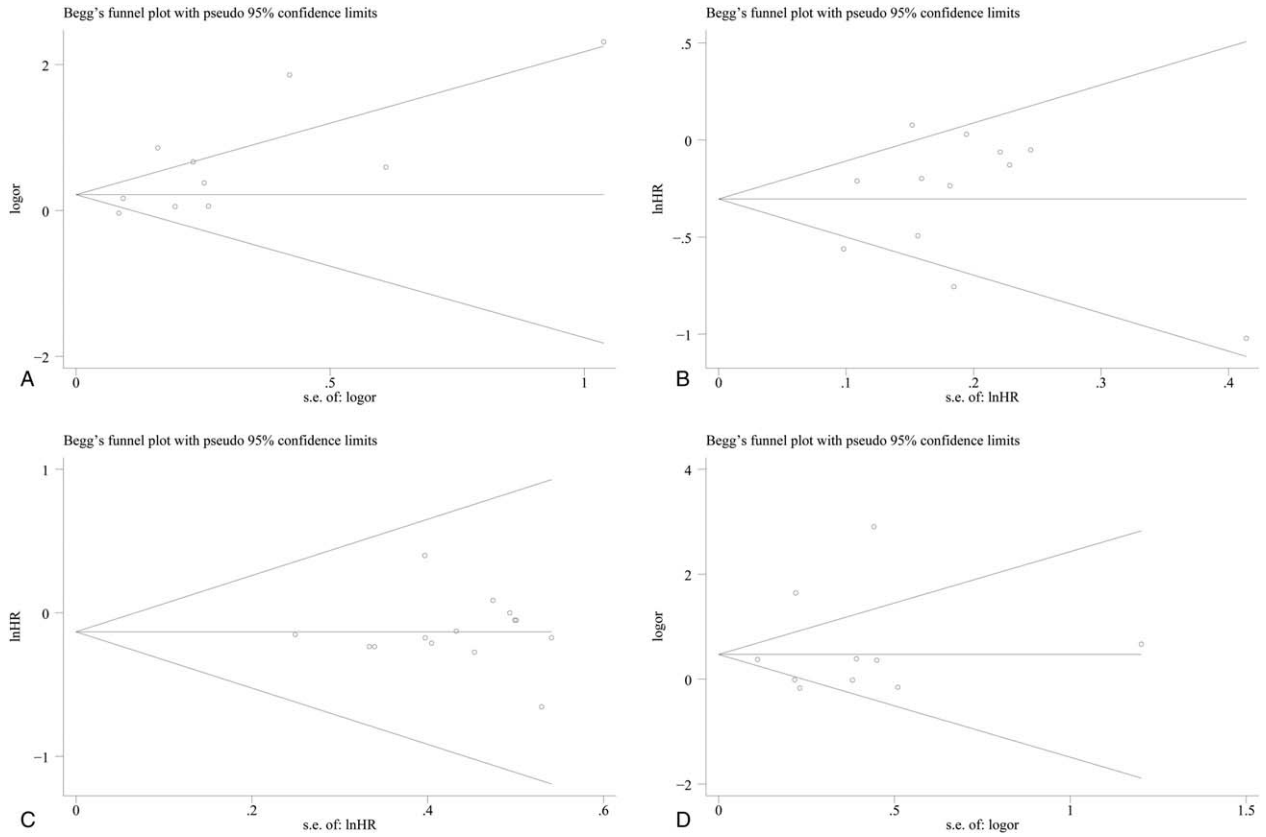

Figure 5. Publication bias assessed by Begg test. (A) ORR; (B) PFS; (C) OS; (D) AEs.

comparison with monotherapies. However, most combinations were associated with higher rate of grade 3/4 treatment-related AEs. After all EGFR-TKIs combination therapies were evaluated, we found that combining EGFR-TKIs with bevacizumab yielded the best ORR, combining EGFR-TKIs with chemotherapy improved ORR. However, combining EGFR-TKIs with radiotherapies did not improve ORR compared with monotherapies. Improvements in PFS were documented in all combinations. Both combining EGFR-TKIs with chemotherapy and combining EGFR-TKIs with bevacizumab led to improved OS significantly. While combinations of EGFR-TKIs and radiotherapies were associated with only slight OS improvement. In terms of toxicity, we found that combining EGFR-TKIs with bevacizumab led to the highest rate of grade 3/4 treatment-related AEs, and combinations of EGFR-TKIs with chemotherapy showed the lowest rate of grade 3/4 treatment-related AEs.

Our study indicates that combining EGFR-TKIs with bevacizumab showed more benefits in ORR and OS among all the combinations, but this combination also showed high toxicity. In addition, combining EGFR-TKIs with chemotherapy led to significant benefits in PFS, and this combination showed the lowest toxicity. The efficacy and safety of bevacizumab-EGFR-TKIs-chemotherapy combination therapy should be investigated further for its potential to extend the clinical success.

Previous studies have assessed the efficacy of EGFR-TKIs.[30–36] Some of them showed that EGFR-TKIs can improve the clinical outcome, but they only evaluate 1 or 2 clinical outcomes.[31] One analysis compared efficacy and toxicity in different EGFR-TKIs treatment, suggesting a high efficacy-moderate toxicity pattern of erlotinib and a medium efficacy-moderate toxicity pattern of gefitinib.[36] As far as we know, no other analysis assessed the added benefits against the toxicity of different combination types.

Some certain limitations of our study should be mentioned. Our analysis did not exclude publication bias; in addition, some studies have reported only short-term follow-up and lack of long-term outcomes. Lastly, the ORR, PFS, and grade 3/4 treatment-related AEs were not available in some of the reports. More study investigation is required in future.

5. Conclusion

Our results indicated that combining EGFR-TKIs with bevacizumab showed more benefits in ORR and OS among all the combinations, but this combination also showed high toxicity. In addition, combining EGFR-TKIs with chemotherapies led to significant benefits in PFS, and this combination showed the lowest toxicity. The efficacy and safety of bevacizumab-EGFR-TKIs-chemotherapy combination therapy should be investigated further for its potential to extend the clinical success.

Acknowledgment

The authors thank the data provided by the authors of included trials.

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