Systematic Review and Meta-Analysis

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Angiogenesis inhibitors for the treatment of small cell lung cancer (SCLC)

A meta-analysis of 7 randomized controlled trials

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Abstract

Background: This study aimed to assess the effectiveness and safety of angiogenesis inhibitors for the treatment of patients with small cell lung cancer (SCLC) via meta-analysis.

Methods: Electronic databases including PubMed, Embase, and Cochrane Library were searched to look for eligible studies through February 1, 2016. RCTs comprising angiogenesis inhibitors and nonangiogenesis inhibitors for SCLC patients were investigated. The extracted data including overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were summarized. In addition, the common adverse events (AEs) were also explored.

Results: There were 7 phase II/III RCTs, encompassing 1322 SCLC patients eligible for meta-analysis. In comparison to nonangiogenesis inhibitors, angiogenesis inhibitors treatment was not associated with improvement of PFS [HR = 0.87, 95% CI (0.74–1.02), $P = 0.09$), OS [HR = 0.99, 95% CI (0.88–1.12), $P = 0.91$], or ORR [OR = 1.12, 95% CI (0.85–1.47), $P = 0.41$). Also, there was no improvement in 1-year survival rate [OR = 0.96, 95% CI (0.74–1.19), $P = 0.63$)], 2-year survival rate [OR = 1.00, 95% CI (0.66–1.51), $P = 1.00$)] or 1-year progression-free survival rates [OR = 0.95, 95% CI (0.69–1.31), $P = 0.76$)]. However, from subgroup analyses, it was observed that angiogenesis inhibitors improved ORR [HR = 1.66 (95% CI 1.02–2.71), $P = 0.04$] in phase II studies and bevacizumab improved PFS [HR = 0.73 (95% CI 0.42–0.97), $P = 0.04$]. It is important to note that angiogenesis inhibitors reduced emesis [OR = 0.38, 95% CI (0.17–0.85), $P = 0.02$], but increased incidence of constipation [OR = 4.02, 95% CI (2.14–7.55), $P < 0.0001$) and embolism [OR = 2.24, 95% CI (1.45–3.47), $P = 0.0003$).

Conclusion: Adding angiogenesis inhibitors to chemotherapy did not improve PFS, OS, ORR, 1-year survival rate, 2-year survival rate or 1-year progression-free survival rate for SCLC. However, subgroup analysis revealed that bevacizumab enhanced PFS. Angiogenesis inhibitors also had a high incidence of constipation and embolism.

Abbreviations: 95% CI = 95% confidence intervals, Ab = antibody, AEs = adverse events, Bev = bevacizumab, CGIs = cytokine-generated inhibitors, CR = complete response, EC = etoposide and carboplatin, ED-SCLC = extensive-stage disease small cell lung cancer, EP = etoposide and cisplatin, FGF = fibroblast growth factor, HR = hazard ratio, LD-SCLC = limited-stage disease small cell lung cancer, NM = not mentioned, NSCLC = nonsmall cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, PCDE = cisplatin-cyclophosphamide-epidoxorubicin-etoposide, PFS = progression-free survival, PR = partial response, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial, SCLC = small-cell lung cancer, TKIs = tyrosine kinase inhibitors, VECPs = anti-vascular endothelial cell proliferation, VEGFR = vascular endothelial growth factor receptor.

Keywords: angiogenesis, meta-analysis, small-cell lung cancer, survival

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1. Introduction

Lung cancer is one of the most highly malignant neoplasms representing the leading cause of cancer-related death worldwide. Still worse, the morbidity and mortality continue to rise sharply.[1,2] Small cell lung cancer (SCLC) accounts for approximately 15% of cases and is considered a highly invasive form of lung cancer.[3] It is characterized by short doubling time, high recurrence rate, and early onset of dissemination, etc.[4]

At present, combination chemotherapy is the cornerstone of treatment for patients with SCLC.[5] For limited-stage disease small cell lung cancer (LD-SCLC), the response rate with first-line chemotherapy is about 80%, compared with 50% for extensive-stage disease (ED-SCLC). Despite relatively high initial response rates after first-line chemotherapy, most patients are subject to relapse within a short time.[6] Even worse, only 30% of SCLC patients present with limited disease at diagnosis and chemo-resistance ensues rapidly.[7] As a consequence, the prognosis of SCLC is still dismal and the final survival time is as short as 8 to 12 weeks after relapse.[8] Therefore, exploring novel, more specific, and effective agents for SCLC is still urgently needed. Nowadays, applying targeted therapy to treat SCLC is gaining attention, especially some drugs already in clinical practice, among which anti-angiogenesis therapy may be a promising strategy. Moreover, it is widely accepted that angiogenesis is critical for the progression of SCLC.[9,10]

Currently, the overall efficacy of angiogenesis inhibitors for treating SCLC remains undetermined. So, in this work, a systematic review and meta-analysis of 7 randomized clinical trials (RCTs) was conducted to investigate the efficacy and safety of angiogenesis inhibitors for SCLC patients.

2. Methods

2.1. Ethical approval

The requirement for ethical approval was waived because this study included neither confidential personal patient data nor interventions with patients.

2.2. Search strategy

The meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] Eligible RCTs were systematic searched by 2 authors independently, using PubMed, Embase, and Cochrane library databases through February 1, 2016. These were limited to studies in English. The following search terms were conducted: ("Small Cell Lung Carcinoma", OR "Small Cell Lung Cancer" OR "Oat Cell Lung Cancer" OR "Small Cell Cancer the Lung" OR "Carcinoma, Small Cell Lung" OR "Oat Cell Carcinoma of Lung") AND ("Randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "placebo" OR "drug therapy" OR "randomly" OR "trial" OR "groups") AND ("Angiogenesis" OR "Angiogenesis inhibitors" OR "targeted therapy" OR "bevacizumab" OR "aflibercept" OR "ramucirumab" OR "sorafenib" OR "sunitinib" OR "nintedanib" OR "pazopanib" OR "motesanib" OR "vandetanib," OR "cediranib" OR "endostatin"). To acquire relevant RCTs, we also manually examined some unavailable data, such as meeting abstracts and so on. What is more, the references of identified studies were also manually reviewed to obtain additional articles. Any disagreements were double-checked and arbitrated by a second reviewer.

2.3. Study selection

Studies that were eligible had to include the following criteria: patients with SCLC confirmed by pathological evidence; phase II or III RCTs that investigated angiogenesis inhibitors versus nonangiogenesis inhibitors in treating SCLC; RCTs showing sufficient data regarding the hazard ratio (HR) with 95% confidence interval (95% CI) of progression-free survival (PFS), overall survival (OS), or objective response rate (ORR); with regard to the duplicate data, the most complete trials were included.

Exclusion criteria were as follows: articles not be written in English language; nonrandomized studies; single-armed studies; retrospective studies; duplicate data; phase II studies; insufficient information about outcomes; reviews, letters, case reports, editorials, or expert opinion.

2.4. Data extraction and quality assessment

According to the standardized data-abstraction forms, 2 reviewers extracted the data from the eligible trials independently. When the 2 reviewers had discrepancies, these were identified and settled by consensus. The following data were extracted: first author's name and year of publication; trial phase; study population characteristics (patient stage, sample size, median age, sex, race); study design (RCT or not); targeted treatment; outcome measures (PFS, OS, ORR, 1-year survival rate, 2-year survival rate, 1-year PFS rate) and HR and 95% CI; common adverse events (AEs)

The Jadad scores were used to evaluate the quality of each eligible study (Table S1, http://links.lww.com/MD/B609) and RCTs were assessed based on the following criteria: whether studies performed sequence generation (scores 0–2); whether studies performed allocation concealment (scores 0–2); whether studies used a suitable blind method (scores 0–2); whether studies performed appropriate dropouts (scores 0–1). Trials with a score of 4 to 7 were considered to be of high quality.

2.5. Statistical analysis

Review Manger (version 5.3 for Windows; Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corporation, College Station, TX) were used for statistical analyses. The arm of using angiogenesis inhibitors was considered the experimental arm, and the nonangiogenesis inhibitors arm was defined as the control arm. The principal summary measurement of PFS and OS was reported as HR with 95% CI and P values. The odds ratio (OR) and 95% CI were used to measure ORRs, risk of AEs, 1-year PFS rate,1- and 2-year survival rates. The 95% CI no overlap with 1 and/or 2-tailed $P < 0.05$ were deemed to be statistically significant. All results were delineated as forest plots. For the heterogeneity between the RCTs, inconsistency statistic (I^2) and forest plot were used for assessment. When $P < 0.05$ and/or $I^2 > 50\%$, the heterogeneity was statistically significant, and a random-effects model was used. Otherwise, a fix-effects model was applied.[12] Publication bias was estimated with Egger and Begg funnel plot test.[13,14]

3. Results

3.1. Study characteristics

3.1.1. Results of the search. The flow chart of eligible RCTs selection is outlined in Fig. 1. In total, 2531 references were identified from the initial electronic search. After scanning the titles and abstracts, 1013 duplicates and 951 directly irrelevant

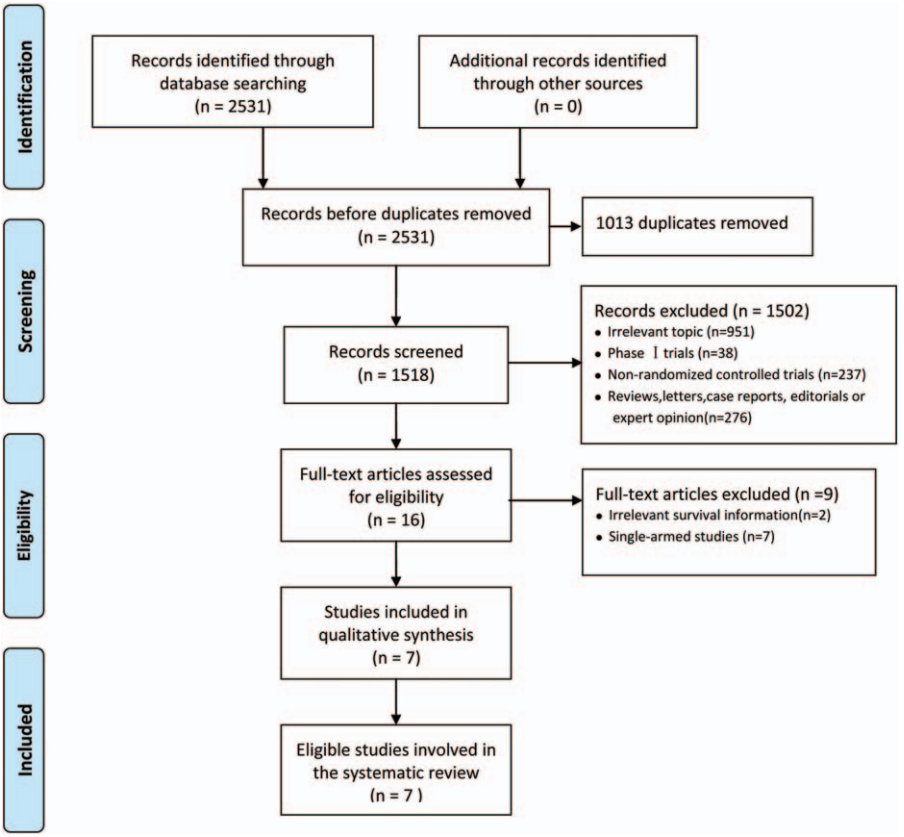

Figure 1. Flowchart of meta-analysis.

studies were excluded. In order to further assessment, 16 potentially eligible studies were retrieved for full text, while 9 trials were excluded because of irrelevant survival information[15,16] or were single-armed studies.[17–23] Finally, 7 eligible studies[24–30] met the inclusion criteria, and were used for this meta-analysis.

3.1.2. Included studies. The baseline characteristics of the 7 eligible studies are summarized in Table 1. There were 4 phase II,[24,26,29,30] 2 phase III,[25,27] and 1 phase II–III trials.[26] These studies enrolled 1322 subjects (669 received angiogenesis inhibitors and 653 received nonangiogenesis inhibitors). There were 5 kinds of angiogenesis inhibitors: bevacizumab (Bev),[28,30]

Table 1

Characteristics of all 7 included randomized controlled trials.

First author	Year	Trial phase	Patient stage (ED/LD)	Sample size		Median age (range)		Male/female		Race (White %)	
				Trial	Control	Trial	Control	Trial	Control	Trial	Control
Spigel et al[30]	2011	II	102/0	52	50	60.0 (38–77)	64 (47–82)	26/26	30/20	90	86
Pujol et al[28]	2015	II–III	74/0	37	37	61.2 (43–75)	60.1 (46–72)	25/12	26/11	NM	NM
Pujol et al[27]	2007	III	92/0	49	43	59.5 (NM)	59.6	39/10	34/9	NM	NM
Lee et al[25]	2009	III	356/368	365	359	65.0 (38–85)	65 (40–86)	211/154	201/158	NM	NM
Arnold et al[24]	2007	II	61/46	53	54	56.9 (NM)	62.4 (NM)	27/26	31/23	98.1	94.4
Ready et al[29]	2015	II	85/0	44	41	59.3 (39–69)	60.8 (43–77)	18/26	20/21	93.2	97.6
Lu et al[26]	2015	II	138/0	69	69	56.0 (40–76)	59.0 (36–73)	56/13	57/12	NM	NM

First author	Year	Design	Therapy		HR (95% CI)		Jadad score
			Trial	Control	PFS	OS	
Spigel et al[30]	2011	RCT	Bevacizumab	Placebo	M	M	5
Pujol et al[28]	2015	RCT	Bevacizumab	Placebo	M	M	6
Pujol et al[27]	2007	RCT	Thalidomide	Placebo	M	M	6
Lee et al[25]	2009	RCT	Thalidomide	Placebo	M	M	7
Arnold et al[24]	2007	RCT	Vandetanib	Placebo	M	M	6
Ready et al[29]	2015	RCT	Sunitinib	Placebo	M	M	6
Lu et al[26]	2015	RCT	Rh-Endostatin	Placebo	M	M	2

ED = extensive disease, LD = limited disease, M = mentioned in the paper, NM = not mentioned.

thalidomide,[25,27] vandetanib,[24] sunitinib,[29] and endostatin[26] with comparable data. All 7 trials used antiangiogenesis drugs as maintenance and first-line therapies were platinum-based chemotherapy. Among these investigations, Spigel et al[30] for the first time evaluated the effects of Bev on ED-SCLC. In their study, angiogenesis inhibitors group contained Bev (15 mg/kg), etoposide and cisplatin/carboplatin (EP/EC), with placebo and EP/EC being the control group. In Pujol investigation,[28] the initial chemotherapy was EP/cisplatin-cyclophosphamide-epidoxorubicin-etoposide (PCDE), and the angiogenesis inhibitors group used Bev (7.5 mg/kg) after 2 additional cycles of PCDE. In the study by Lee et al, the experimental group contained thalidomide (100–200 mg/d) with chemotherapy (EP/EC) and the control group included placebo and chemotherapy (EP/EC). Pujol et al[27] explored the effects of thalidomide on treating ED-SCLC. The initial chemotherapy was PCDE, and after 2 cycles, the experimental group was treated with PCDE and thalidomide (400 mg/d); the control group received PCDE plus placebo. Arnold et al[24] chose LD-SCLC and ED-SCLC patients to carry out their study, in which the experimental group was treated with vandetanib (300 mg/d) and the control group was given placebo after patients had achieved complete response (CR) or partial response (PR) with chemotherapy. In the study by Ready et al[29] ED-SCLC patients were treated with chemotherapy (EP/EC). After 4 to 6 cycles, patients exhibiting no progression were randomly classified into 2 groups, where 1 group was assigned to placebo and the other with sunitinib (37.5 mg per day) until disease progression; cross-over after progression was allowed. Lu et al[26] conducted a multicenter, open-label, randomized phase II study that selected ED-SCLC patients. Their experimental group was treated with EC and rh-endostatin and the control group was given only EC. Sample size of the studies varied from 74 to 724, and among the 1322 patients there were 801 males and 521 females. The median or mean age ranged from 56 to 65 years. Furthermore, the patients were mostly Caucasian (86% to 98.1%), and most had ED-SCLC (68.7%). PFS and OS were reported in all 7 trials and corresponding HR with 95% CI were acquired directly. According to the Jadad score instrument, all studies were qualified enough with a score varying from 4 to 7 except the study 26 (Table S1, http://links.lww.com/MD/B609). As shown in Fig. 2, there was no potential bias in the 7 studies. The overall methodological quality of the included trials was generally good and fair.

3.2. Effects of interventions

3.2.1. Progression-free survival. All of the 7 studies reported available data concerning PFS. Median PFS of angiogenesis inhibitor and control arms varied from 2.7 to 7.6 months, 2.1 to 7.6 months, respectively. HR (angiogenesis inhibitors versus control) varied from 0.53 (95% CI 0.33–0.86) to 1.10 (95% CI 0.48–2.50). Pooled HR was 0.87 (95% CI 0.74–1.02, $P = 0.09$), which indicated that there was no significant difference between

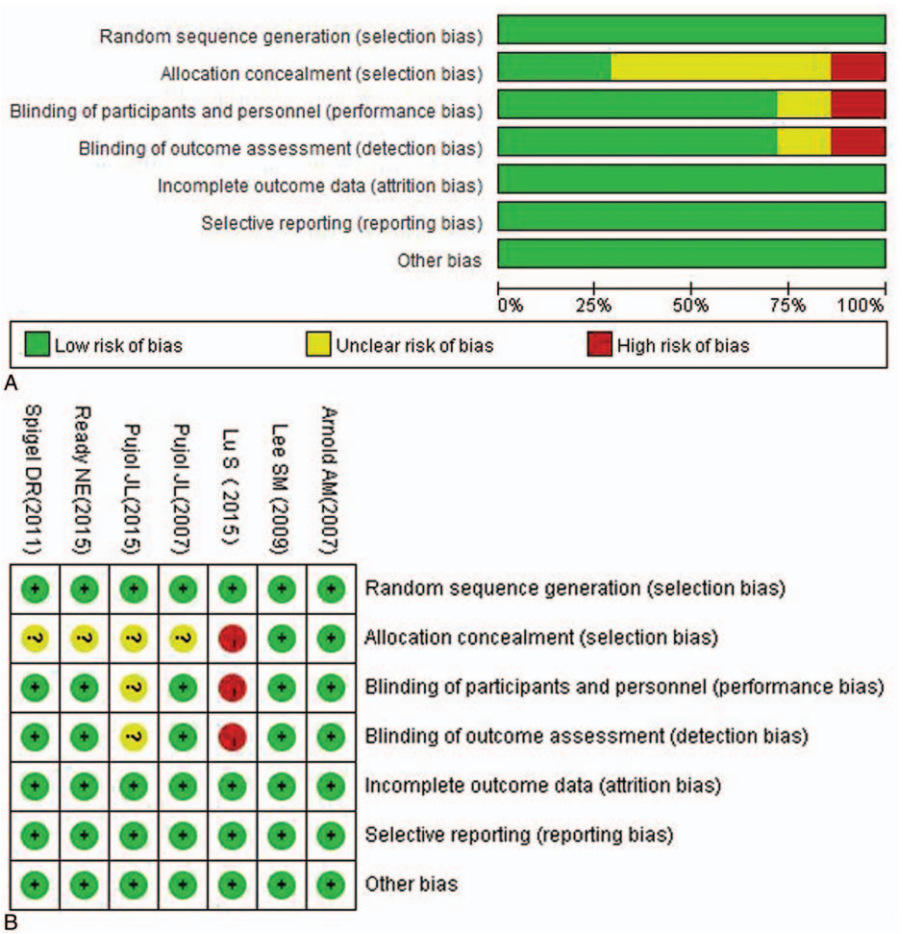

Figure 2. Appraisal of risk of bias of included trials using Cochrane risk-of-bias tool.

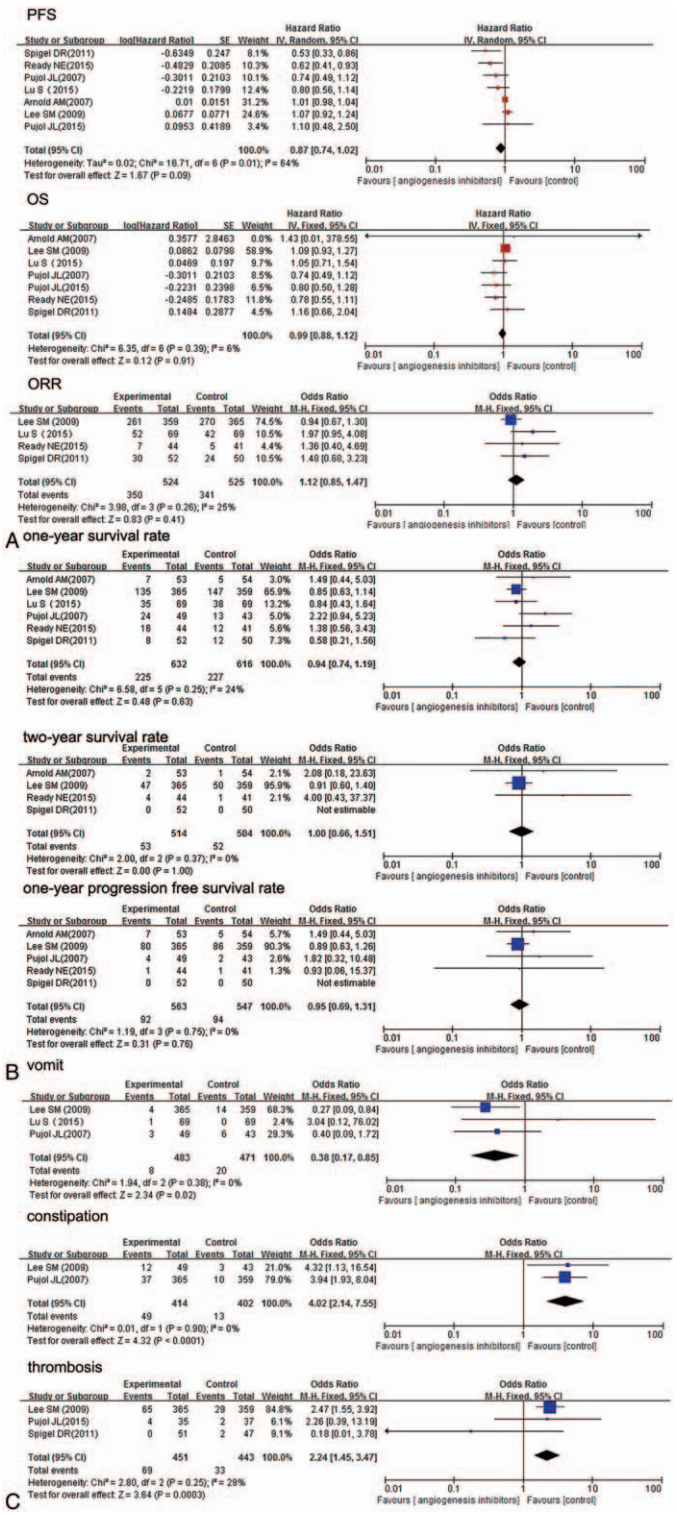

Figure 3. Forest plot of merged analyses for (A) HR with 95% CI for OS and PFS, OR with 95% CI for ORR; (B) 1- and 2-year survival rate and 1-year progression-free survival rate; (C) the incidence of adverse effects for SCLC patients treated with angiogenesis inhibitors versus control group. HR = hazard ratio, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, SCLC = small-cell lung cancer, TKIs = tyrosine kinase inhibitors.

the 2 groups and angiogenesis inhibitors did not prolong PFS (Fig. 3, Table S2, http://links.lww.com/MD/B609). Significant heterogeneity was detected ($P = 0.01$, $I^2 = 64\%$), so random-efforts model was performed for the pooled HR. Remarkably, as shown Table 2, subgroup analyses stratified by different drug class indicated that significant PFS benefit was found in antibodies (Abs) group [HR = 0.73 (95% CI 0.42–0.97), $P = 0.04$].

3.2.2. Overall survival. Concerning OS, 6 studies reported available HR and 95% CI data. Median OS of angiogenesis inhibitors arms varied from 9.0 to 12.1 months, and control arm from 6.9 to 12.4 months. Thus, anti-angiogenesis therapy displayed no improvement in OS. Furthermore, as shown in Fig. 3 (Table S2, http://links.lww.com/MD/B609), HR for OS (angiogenesis inhibitors versus control) ranged from 0.74 (95% CI 0.49–1.12) to 1.43 (95% CI 0.01–378.55). Pooled HR was 0.99 (95% CI 0.88–1.12, $P = 0.91$), without statistical significance between the 2 groups. The pooled model showed angiogenesis inhibitors did not prolong OS. Apparent heterogeneity was not observed among the trials ($P = 0.39$, $I^2 = 6\%$). Therefore, we used fixed-effects model. Exploratory subgroup analyses were conducted according to trials phase, drug class, and extent of disease or patient age. As shown in Table 2, these variables did not alter the effects of angiogenesis inhibitors on OS.

3.2.3. Objective response rate. Among the 7 studies, OR for ORR were available in 4. The ORR of angiogenesis inhibitors arm varied from 16% to 73%, and the control arm from 12% to 74%. As shown in Fig. 3 (Table S2, http://links.lww.com/MD/B609), the OR for ORR (angiogenesis inhibitors versus control) ranged from 0.94 (95% CI 0.67–1.30) to 1.97 (95% CI 0.95–4.08). The combined OR (1.12, 95% CI = 0.85–1.47, $P = 0.41$) demonstrated that angiogenesis inhibitors did not improve objective response rate. Statistical heterogeneity was not observed among the studies ($P = 0.26$, $I^2 = 25\%$); therefore, a fixed-effects model was used. From subgroup analyses (Table 2), it was observed that angiogenesis inhibitors substantially improved the ORR in phase II studies, in which the HR was 1.66 (95% CI 1.02–2.71, $P = 0.04$).

3.2.4. One-year survival rate. Six trials evaluated ORs for 1-year survival rate. The 1-year survival rates of angiogenesis inhibitors and control varied from 13% to 50%, 9% to 55%, respectively. As seen in Fig. 3 (Table S2, http://links.lww.com/MD/B609), OR for survival at 1 year (angiogenesis inhibitors versus control) ranged from 0.58 (95% CI 0.21–1.56) to 2.22 (95% CI 0.94–5.23), and the pooled OR was 0.94 (95% CI 0.74–1.19, $P = 0.63$). The pooled results showed that angiogenesis inhibitors did not improve survival rate at 1 year. There was no significant heterogeneity ($P = 0.25$, $I^2 = 24\%$) among the studies, so a fixed-effects model was used for this analysis.

3.2.5. Two-year survival rate. Four studies among the 7 RCTs reported available data concerning the 2-year survival rate. The survival rate of the angiogenesis inhibitors group varied from 0% to 13%, with the control arm ranging from 0% to 14%. The OR for survival at 2 years (angiogenesis inhibitors vs control) ranged from 0.91 (95% CI 0.60–1.40) to 3.28 (95% CI 0.54–19.78). The pooled OR (1.00, 95% CI = 0.66–1.51, $P = 1.00$) indicated that anti-angiogenesis therapy had no obvious effect on improving 2-year survival (Fig. 4). We did not observe any statistical heterogeneity ($P = 0.37$, $I^2 = 0\%$), so a fixed-effects model was used.

3.2.6. One-year progression-free survival rate. Five trials reported available data about the 1-year PFS rate. The OR for

Table 2

Subgroup analysis for PFS, OS, ORR.

Outcomes	Subgroups	No. of studies	HR (95% CI)	Effect size		Heterogeneity*	
				Z	*P* value	*P* value	I^2
	Phase						
	II	4	1.00 (0.97, 1.03)	0.23	0.82	0.003	78%
	II–III	3	1.03 (0.89, 1.18)	0.37	0.71	0.25	27%
PFS	Class						
	Abs	**2**	**0.64 (0.42, 0.97)**	**2.10**	**0.04**	**0.13**	**56%**
	TKIs	2	1.01 (0.98, 1.04)	0.49	0.62	0.02	82%
	CGs	2	1.02 (0.89, 1.18)	0.33	0.74	0.10	63%
	VECPs	1	0.80 (0.56, 1.14)	1.23	0.22		
	Extent of disease						
	Limited	1	0.80 (0.38, 1.66)	0.60	0.55		
	Extensive	7	0.94 (0.83, 1.05)	1.11	0.27	0.01	64%
	Age group						
	<60	4	0.82 (0.64, 1.06)	1.53	0.13	0.03	68%
	≥60	3	0.85 (0.52, 1.41)	0.62	0.53	0.02	73%
	Phase						
	II	4	0.93 (0.74, 1.18)	0.57	0.57	0.58	0%
	II–III	3	1.01 (0.88, 1.12)	0.20	0.20	0.13	51%
OS	Class						
	Abs	2	0.93 (0.65, 1.34)	0.38	0.70	0.32	0%
	TKIs	2	0.78 (0.55, 1.11)	1.38	0.17	0.83	0%
	CGs	2	1.04 (0.90, 1.20)	0.50	0.62	0.09	66%
	VECPs	1	1.05 (0.71, 1.54)	0.24	0.81		
	Extent of disease						
	Limited	2	0.89 (0.72, 1.11)	1.04	0.30	0.32	0%
	Extensive	7	1.05 (0.81, 1.37)	0.39	0.69	0.006	67%
	Age group						
	<60	4	0.85 (0.68, 1.05)	1.50	0.13	0.61	0%
	≥60	3	1.06 (0.92, 1.23)	0.84	0.40	0.45	0%
	Phase						
	II	**3**	**1.66 (1.02, 2.71)**	**2.03**	**0.04**	**0.82**	**0%**
	II–III	1	1.12 (0.85, 1.47)	0.39	0.70	0.26	25%
ORR	Class						
	Abs	1	1.48 (0.68, 3.32)	0.98	0.33		
	TKIs	1	1.36 (0.40, 4.69)	0.49	0.62		
	CGs	1	0.94 (0.67, 1.30)	0.39	0.70		
	VECPs	1	1.97 (0.95, 4.08)	1.81	0.07		
	Age group						
	<60	2	1.79 (0.95, 3.35)	1.81	0.07	0.62	0%
	≥60	2	1.00 (0.74, 1.36)	0.03	0.98	0.29	10%

HR for PFS, OS.OR for ORR. Bold fonts indicate significant differences between effects of angiogenesis inhibitors, control.

Abs = antibodies, CGs = cytokine-generated inhibitors, HR = hazard ratio, OR = odd ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, TKIs = tyrosine kinase inhibitors, VEGPs = vascular endothelial cell proliferation.

* Heterogeneity tests area available only when >1 study included.

PFS at 1 year (angiogenesis inhibitors vs control) ranged from 0.89 (95% CI 0.63–1.26) to 1.77 (95% CI 0.34–9.20). As shown in Fig. 3 (Table S2, http://links.lww.com/MD/B609), the pooled OR was 0.95 (95% CI 0.69–1.31, $P = 0.76$), without statistical significance between 2 arms, which suggested antiangiogenesis therapy has no obvious effect on improving 1-year progression-free survival rate. We used fixed-effects model to analyze pooled data due to no heterogeneity ($P = 0.75$, $I^2 = 0\%$).

3.2.7. Serious adverse event. All 7 trials evaluated grade 3 to 5 AEs. The correspondingly pooled OR is shown in Table 3. There were 6 types of hematological AEs and 20 types of nonhematological AEs. Angiogenesis inhibitor-related deaths were not reported. As shown in Fig. 3 (Table S2, http://links.lww.com/MD/B609), antiangiogenesis therapy group patients had reduced emesis [OR 0.38, 95% CI (0.17–0.85), $P = 0.02$], but an increased incidence of constipation [OR 4.02, 95% CI (2.14–7.55), $P < 0.0001$], embolism [OR 2.24, 95% CI (1.45–3.47), $P = 0.0003$].

3.3. Sensitivity analyses

In order to evaluate the stability of our result, sensitivity analyses were carried out by sequentially removing single trials. As seen in Table 4, no individual studies altered the pooled results for PFS, OS, or ORR, indicating that outcomes were stable enough for this meta-analysis.

3.4. Publication bias

Funnel plots were performed on all 7 studies investigating PFS, OS, and ORR to evaluate the reliability of our results. As shown in Fig. 4, Funnel plots showed symmetry, and no evidence was observed to reveal publication bias (all $P > 0.05$).

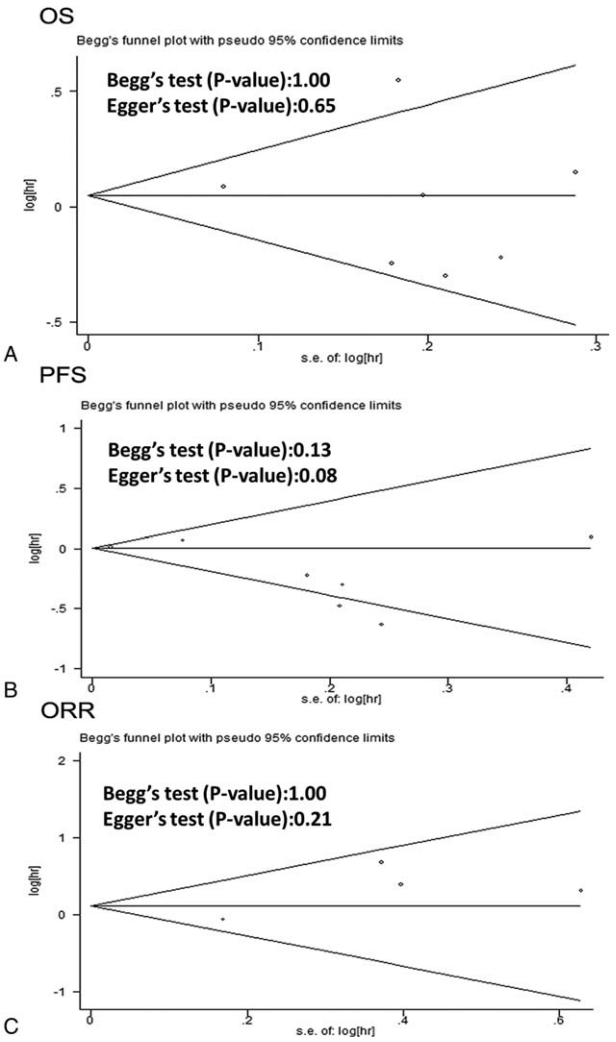

Figure 4. Publication bias analysis by funnel plot graphic. A, OS. B, PFS. C, ORR.

4. Discussion

SCLC is still a major challenge in clinical practice. Currently, the combination of platinum-based doublet with etoposide is the globally accepted standard of treatment.[31] However, most patients relapse soon after discontinuing chemotherapy, and the median survival, even for limited-stage patients, is no more than 2 years. In addition, trials of new chemotherapy regimens in recent 3 decades have failed to significantly improve survival.[32] Numerous methods have been attempted to enhance the therapeutic effectiveness, such as dose intensification, bone marrow transplantation, and maintenance therapy with both chemotherapy as well as other agents. However, unfortunately none of these strategies has achieved a significant effect on survival.[33,34] In contrast, several trials have shown that added therapy was only more toxic, with sometimes negative impact on quality of life.[35] Thus, therapeutic progress in SCLC is long overdue and new therapies and drugs are highly desired.

Angiogenesis is critical for carcinogenesis. Research has shown that SCLC exhibits a higher microvessel density than nonsmall cell lung cancer (NSCLC).[36] Targeted therapy against angiogenesis is well established in NSCLC.[37] Previous studies have revealed that SCLC patients express functional vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3 and elevated the levels of serum vascular endothelial growth factor (VEGF).[38,39] Blocking angiogenesis could, therefore, inhibit the growth, invasion, and metastasis of tumors. So, angiogenesis inhibitors seem promising to treat SCLC. However, studies of angiogenesis inhibitors, including bevacizumab and thalidomide, in SCLC have produced mixed results.

To the best of our knowledge, few of previous researches are investigating the effect of angiogenesis inhibitors on patients with SCLC.[40] In this study, the pooled results revealed that angiogenesis inhibitors did not improve OS [HR = 0.99 (95% CI 0.88–1.12), $P = 0.91$], PFS [HR = 0.87 (95% CI 0.74–1.02), $P = 0.09$] or ORR [HR = 0.94 (95% CI 0.74–1.19), $P = 0.89$].

However, when we conducted subgroup analysis by trial phase, it is noteworthy that angiogenesis inhibitors can enhance ORR [HR = 1.66 (95% CI 1.02–2.71), $P = 0.04$] in phase II studies. According to different drug targets, the investigated 7 randomized controlled trials were classified into 4 subgroups, including 2 Abs(bevacizumab), 2 with tyrosine kinase inhibitors (TKIs) (vandetanib, sunitinib), 2 with cytokine-generated inhibitors (CGIs) (thalidomide), and 1 with an anti-vascular endothelial cell proliferation drug (VECPs) (endostatin). Compared with control, Abs were demonstrated to improve the PFS [HR = 0.64 (95% CI 0.42–0.97), $P = 0.04$]. In order to eliminate the influences of different disease extents and patient ages, stratified analyses were performed. However, neither of these variables altered the results. Upon close analysis, we found that anti-angiogenesis inhibitors failed to improve the outcome of 1-year OS rate [OR = 0.94 (95% CI 0.74–1.19), $P = 0.63$], 2-year OS rate [OR = 1.00 (95% CI 0.66–1.51), $P = 1.00$], or 1-year PFS rate [OR = 0.95 (95% CI 0.69–1.31), $P = 0.76$]. Antiangiogenesis therapy increased adverse effects including constipation [OR = 4.02 (95% CI 2.14–7.55), $P < 0.0001$] and occurrence of embolism [OR = 2.24 (95% CI 1.45–3.47), $P = 0.0003$]. However, in general, angiogenesis inhibitors proved to be safe with mild toxicity.

Although the present meta-analysis suggested that TKIs did not enhance survival of SCLC patients, it was worth mentioning that 1 study[29] reported that sunitinib led to improvement of PFS for patients with ED-SCLC and with satisfactory safety. One explanation is that inhibition of VEGFR kinase activity is neutralized very rapidly by upregulating alternative pro-angiogenic factors, including fibroblast growth factor 1 (FGF1) and FGF2, ephrin A1 (Efna1), Efna2, and angiopoietin 1 (Angpt1).[41] Another possible reason is that the sample size was small, which could affect the results to a certain degree. In addition, the present research revealed that angiogenesis inhibitors did not significantly improve the prognosis (OS, PFS, ORR) of SCLC patients, but in detail, bevacizumab enhanced the PFS of SCLC. On the contrary, numerous studies suggested angiogenesis inhibitors were generally demonstrated to be effective to NSCLC.[41–44] Particularly, Gao et al[45] conducted a meta-analysis encompassing over 452 advanced NSCLC patients who previously received bevacizumab and found that angiogenesis inhibitors improved clinical benefits. Therefore, different subtypes of diseases should be considered when using angiogenesis inhibitors in lung cancer.

Several potential limitations should be acknowledged and some results of meta-analysis need to be cautiously interpreted. First, the number of eligible trails was limited, and the meta-analysis was not based on individual patient data. Second, we failed to evaluate the effect of the combined strategy on other

Table 3

Summary of results: pooled HRs/ORs with 95% CI.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	7	1322	Hazard ratio (IV, fixed, 95% CI)	0.99 [0.88,1.12]
2 Progression-free survival	7	1322	Hazard ratio (IV, random, 95% CI)	0.87 [0.74,1.02]
3 Objective response rate	4	1049		1.12 [0.85,1.47]
4 One-year survival rate	6	1248		0.94 [0.74,1.19]
5 Two-year survival rate	4	1018		1.00 [0.66,1.51]
6 One-year progression-free survival rate	5	1110		0.95 [0.69,1.31]
7 Neutropenia	7	1313		1.09 [0.86,1.38]
8 Febrile nuetropenia	2	190		1.67 [0.73,3.84]
9 Leucopenia	2	808		1.24 [0.85,1.81]
10 Thrombocytopenia	6	1161		1.05 [0.74,1.49]
11 Anemia	4	1026		1.30 [0.88,1.91]
12 Rash	3	901		2.14 [0.20,22.50]
13 Nausea	3	967	Odds ratio (M-H, fixed, 95% CI)	1.19 [0.51,2.78]
14 Vomit	3	954		0.38 [0.17,0.85]
15 Anorexia	2	862		0.99 [0.36,2.73]
16 Neuropathy	2	816		3.09 [1.60,5.99]
17 Fatigue	2	189		1.77 [0.73,4.26]
18 Hypertension	3	228		1.90 [0.40,9.11]
19 Infection	2	796		1.25 [0.79,1.96]
20 Respiratory	3	275		0.71 [0.32,1.59]
21 Urinary system	2	796		2.24 [0.50,10.02]
22 Embolus	3	894		2.24 [1.45,3.47]
23 Gastrointestinal	3	254		1.82 [0.51,6.50]
24 Fluid and electrolyte disorders	4	346		1.63 [0.65,4.14]
25 Dizziness	1	724		0.92 [0.45,1.89]
26 Somnolence	1	724		0.91 [0.43,1.92]
27 Skin	2	796		2.93 [0.07,130.31]
28 Auditory	1	72	Odds ratio (M-H, random, 95% CI)	0.34 [0.01,8.70]
29 Pain	1	72		3.26 [0.13,82.75]
30 Pancytopenia	1	98		0.18 [0.01,3.78]
31 Diarrhea	4	1065		2.03 [0.44,9.31]
32 Constipation	2	816		4.02 [2.14,7.55]

meaningful endpoints such as quality of life, etc. Finally, these trials had different treatment schedules, where the chemotherapy regimens, targeted drugs, and disease stages were different. Thus, heterogeneity existed. Further, more powerful phase III trials will be necessary to further assess the effect of angiogenesis inhibitors on survival of SCLC.

Table 4

Sensitive analyses for OS, PFS, ORR.

Outcome	Study omitted	Resulting HR (95% CI)
	Pujol et al (2007)	1.02 (0.90, 1.16)
	Arnold et al (2007)	0.99 (0.88, 1.12)
	Lee et al (2009)	0.87 (0.72, 1.05)
OS	Spigel et al (2011)	0.99 (0.87, 1.11)
	Ready et al (2015)	1.03 (0.90, 1.17)
	Pujol et al (2015)	1.01 (0.89, 1.14)
	Lu et al (2015)	0.99 (0.87,1.12)
	Pujol et al (2007)	0.89 (0.75, 1.05)
	Arnold et al (2007)	0.79 (0.61, 1.02)
	Lee et al (2009)	0.78 (0.61, 1.00)
PFS	Spigel et al (2011)	0.94 (0.82, 1.07)
	Ready et al (2015)	0.93 (0.80, 1.07)
	Pujol et al (2015)	0.86 (0.73, 1.02)
	Lu et al (2015)	0.88 (0.74, 1.05)
	Spigel et al (2011)	1.08 (0.81, 1.44)
	Lee et al (2009)	1.66 (1.02, 2.71)
ORR	Ready et al (2015)	1.11 (0.84, 1.47)
	Lu et al (2015)	1.02 (0.76, 1.37)

ORR = objective response rate, OS = overall survival, PFS = progression-free survival.

5. Conclusion

In summary, despite certain limitations existing, the present results suggest that angiogenesis inhibitors do not improve PFS, OS, ORR, 1-year survival rate, or 2-year survival rates and 1-year progression-free survival rate. However, subgroup analysis did reveal that bevacizumab seemed to enhance PFS. Further, large-scale RCTs with larger samples are required for confirmation.

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