Meta-analysis of the role of bevacizumab in extensive stage small cell lung cancer

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Abstract. Progress in the treatment options for small cell lung cancer (SCLC) remains poor. Concerns exist regarding the efficacy of bevacizumab in SCLC. The present study aimed to evaluate the efficacy of bevacizumab in extensive stage (ES)-SCLC. A meta-analysis on studies conducted and listed on the Medline, Cochrane Trials, ASCO, ESMO and Clinical-Trial databases, and Chinese databases prior to April 2015 was performed. All clinical trials in which patients with ES-SCLC were treated with bevacizumab were considered. Survival rates at specific time points were extracted from the reported survival curves. Hazard ratios (HR) for progression-free survival (PFS) and overall survival (OS), rates for PFS, OS, overall response rate (ORR), and side-effects were synthesized using random-effects or fixed-effects model. Two randomized control trials (RCT) (176 patients) and six single-arm trials (292 patients) were identified. In RCTs, no statistically significant differences were observed in PFS [HR, 0.70; 95% confidence interval (CI), 0.41-1.19; P=0.19] or OS (HR, 1.21; 95% CI, 0.84-1.75; P=0.31). In the first-line trials, pooled 6-month and 1-year PFS rates were 57% (95% CI, 39-76%) and 10% (95% CI, 4-16%), respectively. Synthesized 1-year and 2-year OS rates were 45% (95% CI, 36-54%) and 10% (95% CI, 6-14%), respectively. Reported median PFS and OS times for pretreated patients were 2.7-4.0 months and 6.3-7.4 months, respectively. Pooled ORRs were 71% (95% CI, 59-82%) in the first-line trials and 18% (95% CI, 11-25%) in the second-line trials. The most common types of reported toxicities were chemotherapy-associated, including neutropenia, leukopenia, fatigue and thrombocytopenia. According to the RCTs, bevacizumab did not appear to improve the PFS or OS for patients with ES-SCLC, with low quality of evidence. Due to the disappointing pooled efficacy in the single-arm trials, more clinical studies on bevacizumab in SCLC may not be valuable, although the evidence was with low quality.

Introduction

Small cell lung cancer (SCLC) is a rare disease; however, it accounts for 12-15% of all lung cancer cases and the majority of patients with SCLC present with the extensive-stage (ES) at diagnosis (1). Since the introduction of platinum plus etoposide in the early 1980s, there has been limited progression in ES-SCLC therapy. Despite its chemosensitivity, SCLC demonstrates a high relapse rate, with a median progression free survival (PFS) time of 4-7 months. The median overall survival (OS) time following relapse rarely exceeds 7 months (2-5). Thus, the development of novel therapies to improve the efficacy of treatment for patients with ES-SCLC is warranted.

Molecular targeted therapies have achieved evident efficacies in other types of solid tumor, providing a more promising direction for the treatment of SCLC. In SCLC, increased vascular endothelial growth factor (VEGF) expression within the tumor and the blood supply peripheral to the tumor, and increased microvasculature surrounding the tumor have been observed (6,7). Thus, it has been suggested that bevacizumab may be an effective therapeutic agent for SCLC. However, concerns regarding the efficacy of bevacizumab have been made apparent in various randomized control trials (RCT) (8,9). In the SALUTE trial, the duration of PFS for patients in the bevacizumab treatment group (5.5 months) was longer compared with the placebo group (4.4 months) (8). By contrast in the IFCT-0802 trial, no significant differences in PFS or OS times were identified between the bevacizumab and chemotherapy combination treatment group and the chemotherapy alone group (9). Therefore in the present study, a literature-based meta-analysis of clinical trials was performed to investigate the efficacy and side-effects of bevacizumab in ES-SCLC.

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Materials and methods

Searching strategy. Relevant papers were identified through a systematic search until 2 April 2015 on Medline (PubMed; www.ncbi.nlm.nih.gov/pubmed), American Society of Clinical Oncology (www.asco.org), European Cancer Societies (www.esmo.org), ClinicalTrial (http://www.clinicaltrials. gov/), Cochrane Library (www.cochranelibrary.com/) and on Chinese databases, including VIP (http://qikan.cqvip.com/), CNKI (http://www.cnki.net/), CBM (www.sinomed.ac.cn/), and WANFANG DATA (www.wanfangdata.com.cn/). The words 'small cell lung cancer' or 'SCLC' and 'avastin' or 'bevacizumab' were used to search through all titles, abstracts and keywords. Furthermore, the reference sections of review and original papers were scanned in order to identify any missing trials.

Trial identification and data extraction. All control and single-arm trials in which patients with ES-SCLC were treated with bevacizumab were considered. Data for time to tumor progression (TTP) or PFS, OS, overall response rate (ORR) and side-effects were extracted by two separate researchers (Ms. Yan-juan Zhu and Ms. Yi-hong Liu; Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China). Survival data (survival rates) in the reported survival curves at specific time points were extracted using DigitizeIt (version 2.0; Braunschweig, Germany; http://www.digitizeit.de/) (10).

Trial quality evaluation. For the RCTs, bias assessments were performed by two separate researchers (Ms. Yan-juan Zhu and Mr. Hai-Bo Zhang, Guangdong Provincial Hospital of Chinese Medicine) using RevMan (version 5.3; The Cochrane Collaboration- Oxford, UK) following recommendations from the Cochrane Handbook (version 5.1.0) (11). Bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting were assessed. For the single-arm trials, bias assessments were performed according to the Cochrane Handbook, as no alternative tool was identified following literature search or advice from senior colleagues. However, bias due to random sequence generation, allocation concealment or blinding was not assessed. For the first-line trials, bias assessments were completed by Ms. Yan-Juan Zhu and Mr. Yong Li. For the second-line trials, the assessments were performed by Ms. Li-Rong Liu and Mr. Jian-Ping Bai.

Data synthesis. For RCTs, hazard ratios (HR) with 95% confidence intervals (CI) for PFS and OS were extracted, and synthesized. As only two RCTs were identified, the random-effect model was used with RevMan 5.3 due to the known clinical heterogeneity, as indicated by the I^2 index. PFS and OS rates at specific time points were extracted from the reported survival curves. Rates for survival, ORR and side-effects were pooled using Stata/SE (version 11.0; Stata-Corp LP, College Station, TX, USA) with the random-effect model if there was significant heterogeneity, or with the fixed-effect model if no heterogeneity was present.

Evidence quality evaluation. The quality of evidences for PFS, OS and ORR was evaluated according to the GRADE guidelines (http://www.gradeworkinggroup.org/publications/JCE_series.htm), using GRADEpro (GDT, http://www. gradepro.org).

Results

Selected trials. Three RCTs and six single-arm trials were identified (Fig. 1). One RCT (GOIRC-AIFA FARM6PMFJM trial) was excluded, as it is an ongoing trial without any reported data (12). The other two RCTs, IFCT-0802 (74 patients) (9) and SALUTE (102 patients) (8), and three of the single-arm trials, CALGB-30306 (64 patients) (13), LUN-90 (51 patients) (14) and ECOG-E3501 (63 patients) (15) evaluated the efficacy of bevacizumab as a first-line treatment for ES-SCLC. Survival curves for PFS and OS, in addition to the side-effects were reported in these five trials. ORRs were also reported, with the exception of in the IFCT-0802 trial. In the other three single-arm trials by Mountzios *et al* (16), Jalal *et al* (17) and Spigel *et al* (18), 114 prior treated patients were enrolled in total. Median OS, PFS, ORRs and side-effects were reported. The studies by Mountzios *et al* (16) and Spigel *et al* (18) reported survival curves for OS. Only the study by Spigel *et al* (18) reported the survival curve for PFS. Details of the nine studies described above are summarized in Table I.

Trial quality. Randomization in the two RCTs was stratified, however the random sequence generation or the allocation concealment was not reported. The IFCT-0802 trial was an open randomized study without blinding of participants, personnel or outcome assessment. The SALUTE was a placebo-controlled study, but the blindness of the outcome assessment was not reported. Considering that PFS and OS are objective outcomes, non-blinding is unlikely to introduce bias. In the IFCT-0802 trial, 8.6% of the bevacizumab-treated and 16.2% of the chemotherapy-treated groups of patients did not complete the protocol program. In the SALUTE trial, 30.8% of the bevacizumab-treated and 34.0% in the chemotherapy-treated groups did not complete protocol program. The two trials reported the intention-to-treat population analysis and were registered on the ClinicalTrial database. The SALUTE trial reported all the pre-specified outcomes of the protocol, while the IFCT-0802 trial did not report complete response length or quality of life, although these were planned in the protocol. According to the protocol of the IFCT-0802 study, the planned enrollment number was 143, while 74 patients were studied. No other biases were identified in the SALUTE trial.

Completed planned cycles of treatment were achieved in 64% of patients in the CALGB-30306, 57% of patients in the LUN-90 and a minority of the patients in the Jalal *et al* (17) trials. However, the majority of the reasons for incomplete planned cycles were due to disease progression or side-effects. Reasons for incomplete planned cycles in the other three trials were due to accepted patient withdrawals. A total of 5/6 single-arm trials are registered on the ClinicalTrial database, with the exception of the Mountzios *et al* (16) trial. The Spigel *et al* (18) study did not report the duration of tumor response [period from the first time of complete response (CR) or partial response (PR) to the first time of progressive disease (PD)] or time to tumor response (period from randomization to the first time of

Table I. Details of identified trials on patients with small cell lung cancer treated with bevacizumab.

Study	No. of patients	Chemotherapy regimens	Bevacizumab strategy	Median PFS/ TTP, months	Median OS, months	ORR, %	Most common types of toxicity (grades 3-4)	(Refs.)
First-line RCT								
IFCT-0802	37 (BC), 37 (C)	EP (81.1%): Etoposide 120 mg/m² d1-3, cisplatin 80 mg/m² d2 every 3 weeks; PCDE (18.9%): Etoposide 75 mg/m² d1-3, cisplatin 75 mg/m² d2, 4'-epidoxorubincin 30 mg/m² d1, cyclophosphamide 300 mg/m² d1-3 every 3 weeks	Chemo x2 cycles, then chemo + Bev 7.5 mg/kg d1 every 3 weeks x4 cycles, without maintenance	6.8 (BC); 7.0 (C); HR, 0.91 (95% CI, 0.59-1.43)[a]	12.6 (BC); 14.8 (C); HR, 1.25 (95% CI, 0.77-2.00)[a]	-	Neutropenia, 42.9 (BC), 35.1 (C); thrombocytopenia, 20 (BC), 10.7 (C); embolism, 11.4 (BC), 5.4 (C); mortality, 1 case with subdural hematoma and hypertension in bev group	(9)
SALUTE	52 (BC), 50 (PC)	EP (31.4%): Etoposide 100 mg/m² d1-3, cisplatin 75 mg/m² d1 every 3 weeks; EC (68.6%): Etoposide 100 mg/m² d1-3, carboplatin AUC 5 mg/ml/min d1 every 3 weeks	Chemo + Bev 15 mg/kg d1 every 3 weeks x4 cycles, with maintenance	5.5 (BC); 4.4 (PC); HR, 0.53 (95% CI, 0.32-0.86)	9.4 (BC); 10.9 (PC); HR, 1.16 (95% CI, 0.66-2.04)	58 (BC); 48 (BC)	Total, 75 (BC); 60 (PC); neutropenia, 35.3 (BC), 40.4 (PC); pneumonia, 5.9 (BC), 4.3 (PC); hypertension, 5.9 (BC), 4.3 (PC); mortality, 2 cases in bev group, including 1 with hemoptysis, 2 cases in the chemo group	(8)
First-line single arm trials								
CALGB-30306	64	IP: Cisplatin 75 mg/m² d1,8, irinotecan 65 mg/m² d1,8 every 3 weeks	Chemo + Bev 15 mg/kg d1 every 3 weeks x6 cycles, without maintenance	7.00	11.6	75	Total, 64; neutropenia, 25; electrocyte, 23; diarrhea, 16; mortality, 3 cases (congestive heart failure, pneumonia, CNS hemorrhage)	(13)
LUN-90	51	IC: Carboplatin AUC 4 mg/ml/min d1, irinotecan 60 mg/m² d1,8,15, every 4 weeks	Chemo + Bev 10 mg/kg d1,15 every 4 weeks x6 cycles, with maintenance	9.13	12.1	84	Neutropenia, 39; thrombocytopenia, 22; diarrhea, 31; mortality, 3 cases (2 with infection and 1 with liver failure)	(14)

Table I. Continued.

Study	No. of patients	Chemotherapy regimens	Bevacizumab strategy	Median PFS/ TTP, months	Median OS, months	ORR, %	Most common types of toxicity (grades 3-4)	(Refs.)
ECOG-E3501	63	EP: Etoposide 120 mg/m^2 d1-3, cisplatin 60 mg/m^2 d1 every 3 weeks	Chemo + Bev 15 mg/kg d1 every 3 weeks x4 cycles, with maintenance	4.70	10.9	63.5	Neutropenia, 57.8; thrombocytopenia, 14.1; fatigue, 14.1; mortality, 2 cases (1 with pneumonia caused by neutropenia, 1 with MOF)	(15)
Single arm trials in prior treated patients								
Mountzios et al	30	Paclitaxel 90 mg/m^2 d1,8,15 every 4 weeks	Chemo + Bev 10 mg/kg d1,15 every 4 weeks x6 cycles, without maintenance	2.70	6.3	20.0	Leukopenia, 20; neutropenia, 16.7; diarrhea, 10	(16)
Jalal et al	34	Paclitaxel 90 mg/m^2 d1,8,15 every 4 weeks	Chemo + Bev 10 mg/kg d1,15 every 4 weeks x4-6 cycles, with maintenance	3.40	7.0	18.1	Fatigue, 26; neutropenia, 17.6; dyspnea, 14.7	(17)
Spigel et al	50	Oral topotecan 2.3 mg/m^2 d1-5 every 3 weeks	Chemo + Bev 15 mg/kg d1 every 3 weeks ≥ x4 cycles, until progression	4.01	7.4	16.0	Thrombocytopenia, 32; neutropenia, 28; anemia, 18; mortality, 5 cases (4 were associated with the study medication, including 2 with sepsis, 1 with pneumonia andrespiratory failure, 1 with thrombocytopenia and GI hemorrhage)	(18)

[a]Median PFS reported was 5.3 (BC) vs. 5.5 (C) months, and median OS reported was 11.1 (BC) vs. 13.3 (C) months, which was 2 cycles of chemotherapy (6 weeks) subsequent to the initiation of treatment. PFS, progression-free survival; TTP, time to tumor progression; OS, overall survival; ORR, overall response rate; RCT, randomized control trial; BC, bevacizumab + chemotherapy; C, chemotherapy alone; EP, cisplatin + etoposide; EC, carboplatin + etoposide; PCDE, cisplatin + etoposide + 4'-epidoxorubincin + cyclophosphamide; chemo, chemotherapy; bev, bevacizumab; HR, hazard ratio; CI, confidence interval; IP, cisplatin + irinotecan; IC, carboplatin + irinotecan; CNS, central nervous system; AUC, area under the curve; PC, placebo + chemotherapy; MOF, multi-organ failure; GI, gastrointestinal.
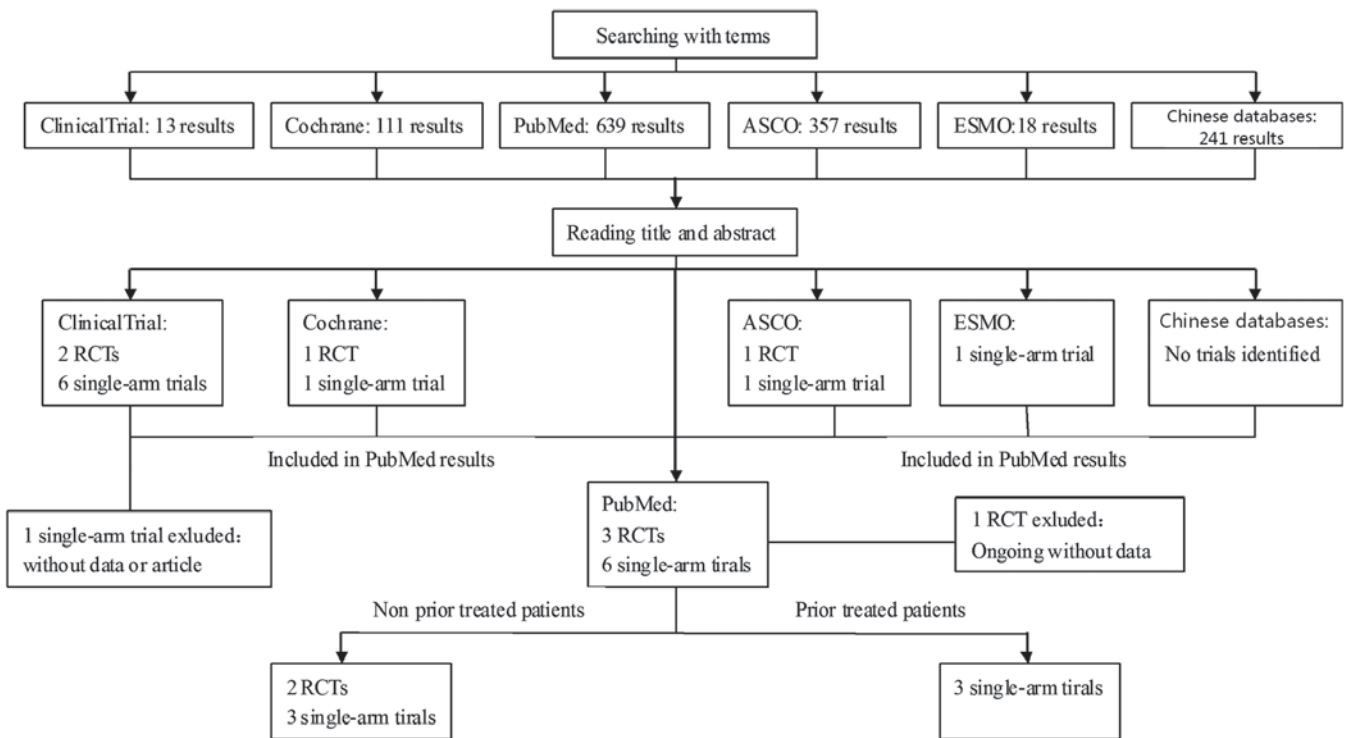
Figure 1. Outline of the search-flow diagram using multiple databases. 'Small cell lung cancer' or 'SCLC' and 'avastin' or 'bevacizumab' were used to search through all titles, abstracts, and keywords. ASCO, American Society of Clinical Oncology; ESMO, European Cancer Societies; RCTs, randomized clinical trials; SCLC, small cell lung cancer.

CR/PR), although planned in the protocol, while the other four trials reported all the pre-specified outcomes. The risk of bias for these trials is illustrated in Fig. 2.

PFS and OS. In RCTs, no statistically significant differences were observed in PFS (HR, 0.70; 95% CI, 0.41-1.19; P=0.19) or OS (HR, 1.21; 95% CI, 0.84-1.75; P=0.31) between patients treated with or without bevacizumab. The heterogeneity for PFS was significant (I^2=61%), but insignificant for OS (I^2=0%; Fig. 3).

A total of two RCTs and three single-arm trials evaluated the efficacy of bevacizumab as a first-line treatment for ES-SCLC. The PFS and OS rates were extracted from the survival curves reported, and the rates at specific time points were subsequently synthesized. The 6-month and 1-year PFS rates were 57% (95% CI, 39-76%; I^2=91.3%), and 0.10 (95% CI, 4-16%; I^2=55.2%), respectively. The 1-year and 2-year OS rates were 45% (95% CI, 36-54%; I^2=60.8%), and 10% (95% CI, 6-14%; I^2=0.0%), respectively. Pooled PFS and OS rates at specific time points are illustrated in Fig. 4 and Table II.

Three of the single-arm trials evaluated the efficacy of bevacizumab in patients with ES-SCLC who had received previous treatment. The median OS and PFS times are detailed in Table I. Only two trials reported survival curves for OS and one PFS survival curves. Survival rates were not synthesized due to the limited data reported.

ORR. ORRs for bevacizumab combined with chemotherapy as a first-line treatment were reported in one RCT and three single-arm trials. The synthesized ORR value for bevacizumab combined with chemotherapy from these four trials

Figure 2. Risk of bias for each of the eight studies identified on the effects of bevacizumab on patients with small cell lung cancer.
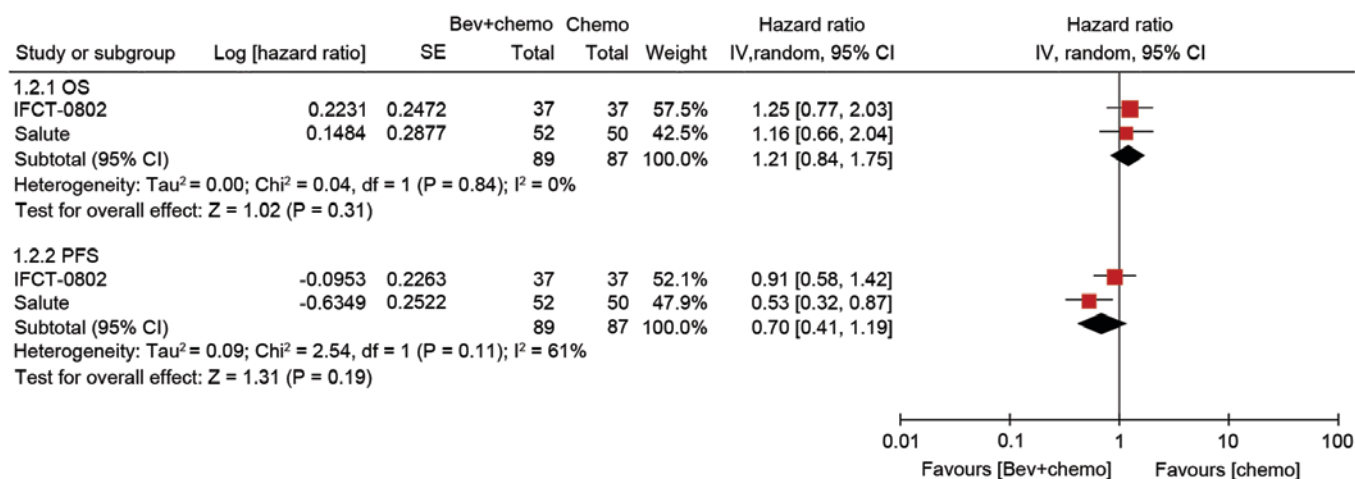
Figure 3. Meta-analysis of the hazard ratios of PFS and OS for patients with small cell lung cancer treated with chemotherapy with or without bevacizumab. Bevacizumab and chemotherapy combination treatment appeared not to improve PFS or OS for ES-SCLC, compared with treatment with chemotherapy alone. PFS, progression-free survival; OS, overall survival; bev, bevacizumab; chemo, chemotherapy; SE, standard error of the mean; CI, confidence interval; df, degrees of freedom; I^2, heterogeneity index; ES-SCLC, extensive stage small cell lung cancer.
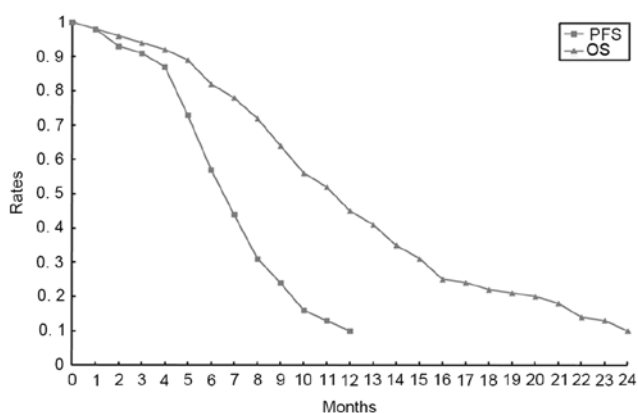

Figure 4. Pooled PFS and OS rates at specific time points for patients with small cell lung cancer treated with bevacizumab combined with chemotherapy as first-line therapy. PFS, progression-free survival; OS, overall survival.

was 71% (95% CI, 59-82%), with significant heterogeneity (I^2=75.9%; P=0.006). The synthesized ORR value for bevacizumab and chemotherapy combined treatment from the three single-arm trials for patients who had received prior treatment was 18% (95% CI, 11-25%), without significant heterogeneity (I^2=0.0%; P=0.901).

Safety. In Table III, the synthesized grade 3-4 toxicities are detailed. No unexpected toxicity was reported. The most common types of reported toxicities were chemotherapy-associated, including neutropenia (39.8%), leukopenia (20.4%), fatigue (13.4%), diarrhea (13.0%) and thrombocytopenia (12.2%) in the first-line treatment patients. Thrombocytopenia (32.0%), neutropenia (21.0%) and fatigue (15.4%) were most common in patients who had received previous treatment. A total of 16 mortalities were reported, including seven with infection (two with sepsis), two with central nerve system hemorrhage, one with congestive heart failure, one with hemoptysis, one with gastrointestinal hemorrhage, one with liver failure and one with multi-organ failure.

Evidence quality. Considering the serious risk of bias, inconsistency and imprecision, the quality of evidence for PFS in the RCTs was very low. The quality of evidence for OS in the RCTs was low, with serious risk of bias and imprecision. Since the risk of bias, inconsistency, indirectness and imprecision are all serious, the quality of evidence for PFS rates, OS rates, ORR and side-effects was very low (Table IV).

Discussion

The standard treatment strategy for SCLC has not changed in decades, with disappointing therapeutic progress. First line chemotherapy with etoposide-platinum (EP) or irinotecan-platinum (IP) are able to achieve a median PFS time of 4-7 months and a median OS time of 9-11 months in patients with ES-SCLC (3,19-22). Furthermore, second-line therapy with paclitaxel, docetaxel, topotecan, or amrubicin have been demonstrated to achieve a median PFS of ~3 months and OS of 6-8 months (23-26). According to the two reported RCTs, the addition of bevacizumab to the first-line therapy did not improve OS (HR, 1.21; P=0.31) or PFS (HR, 0.70; P=0.19) durations. The pooled survival data from the five first-line trials revealed a median PFS time of 6-7 months for bevacizumab and chemotherapy combined treatment and a median OS time of ~11 months, which are similar with values reported in other previous trials with chemotherapy alone (3,19-22). Compared with previous reports on the use of second-line chemotherapy (median PFS, ~3 months; OS, 6-8 months) (23-26), treatment with a combination of bevacizumab and chemotherapy failed to prolong PFS or OS in previously treated patients with ES-SCLC.

Bevacizumab is a recombinant humanized monoclonal antibody, which inhibits VEGF-A binding to VEGF receptors (VEGFRs), primarily VEGFR-2 (27). There are other VEGFs, including VEGF-B that primarily binds to VEGFR-1 and VEGF-C/D, which binds to VEGFR-3 (28). The inhibition of VEGF-A causes an up regulation of the other VEGFs (29). However, other VEGF antibodies or VEGFR inhibitors failed to improve efficacy for ES-SCLC. Studies performed by the

Table II. Pooled PFS and OS rates for patients with small cell lung cancer treated with bevacizumab as first-line therapy.

Months	Rates % (95% CI)	I^2 (%)	Months	Rates % (95% CI)	I^2 (%)	Months	Rates % (95% CI)	I^2 (%)
Pooled PFS rates								
1	0.98 (0.96-1.00)	38.6	2	0.93 (0.85-0.97)	67.7	3	0.91 (0.86-0.95)	44.1
4	0.87 (0.80-0.94)	66.5	5	0.73 (0.58-0.87)	87.7	6	0.57 (0.39-0.76)	91.3
7	0.44 (0.27-0.61)	89.5	8	0.31 (0.14-0.48)	91.6	9	0.24 (0.10-0.38)	89.7
10	0.16 (0.08-0.23)	67.6	11	0.13 (0.05-0.22)	75.9	12	0.10 (0.04-0.16)	55.2
Pooled OS rates								
1	0.98 (0.97-1.00)	0.0	2	0.96 (0.93-0.99)	51.4	3	0.94 (0.90-0.98)	64.3
4	0.92 (0.86-0.97)	71.0	5	0.89 (0.84-0.89)	35.1	6	0.82 (0.77-0.87)	6.3
7	0.78 (0.73-0.83)	0.0	8	0.72 (0.65-0.79)	38.2	9	0.64 (0.55-0.72)	55.7
10	0.56 (0.45-0.66)	67.3	11	0.52 (0.43-0.60)	53.7	12	0.45 (0.36-0.54)	60.8
13	0.41 (0.33-0.50)	52.7	14	0.35 (0.26-0.44)	60.2	15	0.31 (0.24-0.38)	43.8
16	0.25 (0.20-0.31)	0.0	17	0.24 (0.19-0.29)	0.0	18	0.22 (0.17-0.27)	0.0
19	0.21 (0.16-0.26)	0.0	20	0.20 (0.15-0.25)	0.0	21	0.18 (0.13-0.22)	0.0
22	0.14 (0.10-0.19)	0.0	23	0.13 (0.09-0.18)	0.0	24	0.10 (0.06-0.14)	0.0

PFS, progression-free survival; OS, overall survival; CI, confidence interval; I^2, heterogeneity index.

Table III. Pooled grade 3 to 4 toxicities for patients with small cell lung cancer treated with bevacizumab.

	Patients who did not receive prior treatment			Patients who received prior treatment		
Toxicity	Rates % (95% CI)	I^2 (%)	No. of synthesized studies	Rates % (95% CI)	I^2 (%)	No. of synthesized studies
Neutropenia	39.8 (28.0-51.6)	76.3	5	21.0 (13.6-28.4)	0.0	3
Febrile neutropenia	6.4 (2.9-10.0)	0.0	3	3.3	-	1
Leukopenia	20.4 (9.5-31.2)	71.8	3	14.3 (6.6-21.9)	0.0	2
Thrombocytopenia	12.2 (5.9-18.5)	63.8	5	32.0	-	1
Anemia	6.2 (2.1-10.3)	0.0	2	10.0 (0-24.4)	81.4	2
Hypertension	7.1 (3.7-10.5)	0.0	4	-	-	0
Infection	5.8 (2.6-9.0)	0.0	4	3.3	-	1
Dyspnea	2.2 (0.2-4.2)	0.0	4	14.7	-	1
Dehydration	5.8 (0.8-10.9)	70.8	4	-	-	0
Diarrhea	13.0 (3.6-22.3)	84.0	4	10.0 (3.4-16.6)	0.0	2
Gastrointestinal perforation	2.0 (0-4.5)	0.0	2	-	-	0
Embolism	2.1 (0.3-4.0)	9.5	5	-	-	0
Fatigue	13.4 (8.5-18.4)	0.0	3	15.4 (0.7-30.1)	83.1	3
Nausea/vomiting	10.4 (5.3-15.5)	17.3	3	8.5 (2.4-14.6)	0.0	2
Hemorrhage	4.5 (0-9.9)	68.4	3	-	-	0
Electrocyte	11.2 (6.1-16.4)	34.9	4	-	-	0

CI, confidence interval; I^2, heterogeneity index.

Francophone Intergroup on Thoracic Cancer and the National Cancer Institute of Canada reported no benefit of maintenance thalidomide or vandetanib in ES-SCLC (30,31). A phase II study at the Southwest Oncology Group demonstrated an improvement of 3 months in PFS, but no improvement in OS following treatment with aflibercept, a soluble VEGF receptor (32). In fact, there are different types of angiogenic factors, including VEGF, platelet-derived growth factor, fibroblast growth factor (aFGF and bFGF), transforming growth factor-β, pleiotrophin, angiogenin and angiotropin (33). An important challenge is that SCLC often occurs with multiple coexisting genomic abnormalities, the majority of which promote the

Table IV. Quality of evidence for bevacizuamb in small cell lung cancer, according to the GRADE guidelines.

Outcome	Study design	Quality assessment				Other considerations	Quality of evidence[a]
		Risk of bias	Inconsistency	Indirectness	Imprecision		
PFS	RCTs	Serious (-1)[b]	Serious (-1)	Not serious	Serious (-1)	None	Very low
OS	RCTs	Serious (-1)	Not serious	Not serious	Serious (-1)	None	Low
PFS, OS, ORR rates and side-effects	RCTs and single arm trials	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)	None	Very low

[a]Quality of evidence ranks four grades, which are high, moderate, low and very low. [b]The risk of bias is serious, so the grade of evidence quality should be reduced 1 level from the high grade, which was marked as '-1'. PFS, progression-free survival; RCTs, randomized clinical trials; OS, overall survival; ORR, overall response rate.

expression of angiogenesis factors, including: Widespread inactivation of Tumor protein 53 and RB transcriptional corepressor 1; MYC proto-oncogene bHLH transcription factor, FGFR1, SRY-box 2, and epidermal growth factor receptor amplification; phosphatase and tensin homolog mutation, rearranged L-myc fusion-MYC1 fusion; and alterations in histone modification genes, including KRAS proto-oncogene GTPase, B-Raf proto-oncogene serine/threonine kinase, MET proto-oncogene receptor tyrosine kinase, FGFR2 and Janus kinase 3 and phosphatidylinositol-4 5-bisphosphate 3-kinase catalytic subunit α (34-37).

As a result, the efficacy of VEGF/VEGFR inhibitors is limited. Previous studies have demonstrated that elevated circulating VEGF levels predict poor overall survival in patients with SCLC (38,39). Notably, circulating VEGF levels (13,15) or polymorphisms (17) have not been identified to be associated with bevacizumab efficacy. This may be partially due to the multi-genomic abnormalities that co-exist with SCLC. Therefore, next generation sequencing may improve the understanding on SCLC, and may aid in directing the choice of therapeutic agents for the treatment of SCLC.

Shojaei *et al* (40) reported that granulocyte-colony stimulating factor (G-CSF), which is overexpressed in SCLC, stimulates Cd11b+Gr1+ myeloid cells, and may subsequently cause resistance to bevacizumab. In addition, anti-G-CSF was revealed to increase the efficacy of anti-VEGF in a mouse model (41). In the identified studies of the present meta-analysis, as well as in clinical practice, grade 3-4 neutropenia and leukopenia have been reported as common side-effects, and recombinant G-CSF is widely used to prevent and treat myelosuppression. Thus, the efficacy of bevacizumab may also be limited due to the use of recombinant G-CSF as part of the therapeutic regimen for patients with SCLC.

The heterogeneity of the identified studies was significant, resulting partially from different bevacizumab strategies and chemotherapy regimens applied. Bevacizumab with maintenance in the SALUTE study achieved beneficial PFS rates, whereas in the IFCT-0802 study, without maintenance, no significant improvements were observed. Furthermore, the dose of bevacizumab in the IFCT-0802 study was lower compared with that in the other studies discussed. In the LUN-90 and CALGB-30306 studies, which

use similar chemotherapy regimens with IP as the first-line chemotherapy, addition of bevacizumab with maintenance in the LUN-90 study achieved a median PFS and OS time of 9.13 and 12.10 months, respectively, which were longer compared with the PFS and OS observed in CALGB-30306 without maintenance (7.0 and 11.6 months, respectively). The efficacy of bevacizumab maintenance remains controversial. Preclinical studies also suggested that cessation of anti-VEGF therapy may be associated with accelerated recurrence, more aggressive tumors upon recurrence and increased mortality rates. However, the efficacy of maintenance of bevacizumab remains controversial. Bevacizumab has been used as part of the maintenance therapy in NSCLC (42). However in the treatment of colorectal cancer, the efficacy of bevacizumab maintenance has not been demonstrated to be higher compared with discontinuation (43). A meta-analysis of five placebo-controlled randomized phase III trials, including on colorectal, breast, renal and pancreatic cancer, identified no significant difference in TTP or mortality between patients with or without continuation of bevacizumab (44). An ongoing multicenter phase III study on SCLC conducted by the Italian Oncology Group for Clinical Research, is investigating the effects of bevacizumab combined with EP chemotherapy as a first-line treatment and maintenance therapy; however, the results remain pending (12).

Another cause of heterogeneity may be the different chemotherapy regimens in the first-line studies discussed. It appears that patients on the irinotecan-platinum (IP) regimen and bevacizumab treatment achieve longer PFS and OS times compared with those on the etoposide-platinum (EP) regimen. In certain multicenter phase III trials, no significant difference in PFS and OS times between EP or IP regimens as a first-line therapy was observed (3,19-22). However, in a number of phase II trials, the efficacy of IP regimen (median PFS, 9.0; median OS, 12.8 months) has demonstrated to be improved compared with EP regimen (median PFS, 6.0; median OS, 9.4 months) (2,45). Therefore, it remains unclear whether the longer PFS and OS times are due to the combination of IP and bevacizumab treatment or results from a greater efficacy of IP compared with EP regimen.

The main limitation of the present meta-analysis derives from the limited studies identified, with a moderate risk of bias.

However, synthesized survival rates and ORRs were provided. The pooled data indicated limited efficacy of bevacizumab treatment in SCLC, although the quality of evidence was low. Thus, more clinical trials may not be valuable. Additionally, no tool was identified to evaluate the risk of bias for single-arm trials. Thus, the bias evaluation may be subjective. In order to compare the efficacy of chemotherapy with the bevacizumab and chemotherapy combination treatment in SCLC, the survival data for patients with SCLC treated with chemotherapy should be only pooled based on literature search. However, it is suggested that this would not be valuable, since the efficacy of bevacizumab treatment in the present studies discussed was weak.

In conclusion, according to the RCTs, bevacizumab treatment did not appear to improve the PFS or OS for patients with ES-SCLC, with a low quality of evidence. Due to the weak pooled efficacy in the single-arm trials, although the quality of evidence was low, further clinical studies on the use of bevacizumab in the treatment of SCLC may not be valuable.

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