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Angiogenesis Inhibitors for the Treatment of Ovarian Cancer

An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

Haihong Wang, BS, Tie Xu, BS, Lifen Zheng, BS, and Guiling Li, MD

Background: Angiogenesis inhibitors showed activity in ovarian cancer, but preliminary data could not accurately reflect the survival benefit. We thus did a systematic review and meta-analysis of randomized controlled trials to reassess the efficacy and safety of angiogenesis inhibitors combined with chemotherapy for ovarian cancer.

Methods: We searched PubMed, EMBASE, Cochrane, and ClinicalTrials.gov for randomized controlled trials comparing angiogenesis inhibitors containing therapy with conventional chemotherapy alone or no further treatment. Our main outcomes were the progression-free survival (PFS), overall survival (OS), and common adverse events.

Results: Fifteen trials were included (N = 8721 participants). For newly diagnosed ovarian cancer, combination treatment with angiogenesis inhibitors and chemotherapy yielded a lower risk of disease progression (hazard ratio [HR], 0.83; 95% confidence interval (CI), 0.71–0.97) and no improved OS (HR, 0.95; 95% CI, 0.86–1.05). In the high-risk progression subgroup, the addition of bevacizumab significantly improved PFS (HR, 0.72; 95% CI, 0.65–0.81) and OS (HR, 0.84; 95%CI, 0.74–0.96). In recurrent patients, the combined HR was 0.58 (95% CI, 0.52–0.65) for PFS, and for OS, the combined HR was 0.86 (95% CI, 0.79–0.94). We found no significant improvement for either PFS (HR, 0.80; 95% CI, 0.63–1.01) or OS (HR, 1.06; 95% CI, 0.88–1.28) in the pure maintenance therapy.

In the overall population, angiogenesis inhibitors increased the incidence of gastrointestinal perforation (risk ratio [RR], 2.57; 95% CI, 1.66–3.97), hypertension (RR, 7.60; 95% CI, 2.79–20.70), arterial thromboembolism (RR, 2.27; 95% CI, 1.34–3.84), proteinuria (RR, 4.31; 95% CI, 2.15–8.64), and complication of wound healing (RR, 1.72, 95% CI, 1.12–2.63).

Conclusions: Combination treatment with angiogenesis inhibitors and chemotherapy significantly improved PFS and OS in both patients with high-risk of progression and recurrent ovarian cancer, with an increased incidence of common adverse events. Conversely, we detected no statistically significant survival benefit in the pure maintenance setting. The main limitation of the review is clinical heterogeneity across the studies.

Key Words: Ovarian neoplasms, Angiogenesis inhibitors, Chemotherapy, Systematic review, Meta-analysis

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Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

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Address correspondence and reprint requests to Guiling Li, MD, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. E-mail: lgl6714@163.com.

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Description of the Condition

Worldwide, ovarian cancer is the leading cause of gynecological cancer–associated death.[1] It is the fifth leading cause of cancer-related deaths in female patients in developed countries.[2] The poor prognosis is usually attributed to advanced stage at diagnosis and treatment resistance.[3] Approximately 60% of women are diagnosed with late-stage disease that has already spread within the abdomen.[1,4]

Platinum/taxane doublet chemotherapy is the upfront standard of care in advanced ovarian cancer and yields an objective response in up to 80% of patients,[5] but almost all will experience multiple recurrences of disease, with ever shorter disease-free intervals.[6,7]

Given the therapeutic limitations of conventional chemotherapy, recent investigations have explored molecularly guided therapies to target pathways of oncogenesis. A number of studies have shown that tumor growth and progression are partly dependent on angiogenesis.[8,9]

Description of the Intervention

Angiogenesis is recognized as a hallmark of several types of tumors including ovarian cancer.[10] One of the most important cytokines responsible for tumor-mediated angiogenesis is vascular endothelial growth factor (VEGF), which is secreted by tumor cells and binds to the VEGF receptor that is present on normal endothelial cells, stimulating new blood vessel formation.[11] Hence, efforts to block this pathway, either by inhibiting VEGF or its receptor, have emerged as attractive strategies for cancer treatment.[12,13]

Why it is Important to do This Review?

The good news is that there were clinical trials suggesting that angiogenesis inhibitors showed activity in ovarian cancer. However, the survival benefit was different in these trials. It is important to establish whether the addition of these new drugs to conventional chemotherapy regimens has additional survival benefit, if so, at what cost, and additional harmful effects. Moreover, there remain a lot of controversies. Should they be used as part of first-line therapy, recurrent setting, or to maintain patients with stable disease later in the course of their disease?

The most recently published meta-analysis[14] indicated that antiangiogenic therapy showed clear progression-free survival (PFS) benefit with increased toxicity, but its role in overall survival (OS) was undefined for ovarian cancer. We therefore did a systematic review and meta-analysis of RCTs comparing angiogenesis inhibitors containing therapy with conventional chemotherapy alone or no further treatment for ovarian cancer to reassess the efficacy and safety of angiogenesis inhibitors in different clinical setting, including newly diagnosed ovarian cancer, recurrent patients, and pure maintenance setting. In this present study, the final data and 3 new randomized controlled trials (RCTs)[15–17] were included.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.

We searched PubMed, EMBASE, Central (Cochrane clinical trials database) database, and clinicaltrial.gov. We searched the database from 1994 to March 2017. We sought articles in all languages and there were no translations necessary. We used the following combined text and MeSH terms: "Ovarian Neoplasms", "Angiogenesis Inhibitors", "Bevacizumab", "Avastin", "Pazopanib", "GW786034", "Votrient", "Trebananib", "AMG386", "Nintedanib", "vargatef", "BIBF1120", "cediranib", "AZD2171", "recentin", "Sorafenib", "BAY 545-9085", "BAY43-9006", "Nexavar", "NSC724772", "sunitinib", and "SU11248".

Study Selection and Data Extraction

We regarded studies as eligible for inclusion if they were RCTs in women with histologically proven epithelial ovarian cancer of any stage (age, ≥18 years), compared angiogenesis inhibitors plus conventional chemotherapy with conventional chemotherapy alone, or angiogenesis inhibitors to no further treatment.

Two investigators independently reviewed study titles and abstracts, and excluded those studies that clearly did not meet our inclusion criteria. We then obtained copies of the full text of potentially relevant references. Trials selected for detailed analysis and data extraction were analyzed by 2 investigators. We resolved disagreements by discussion between the 2 authors and documented the reasons for exclusion. We

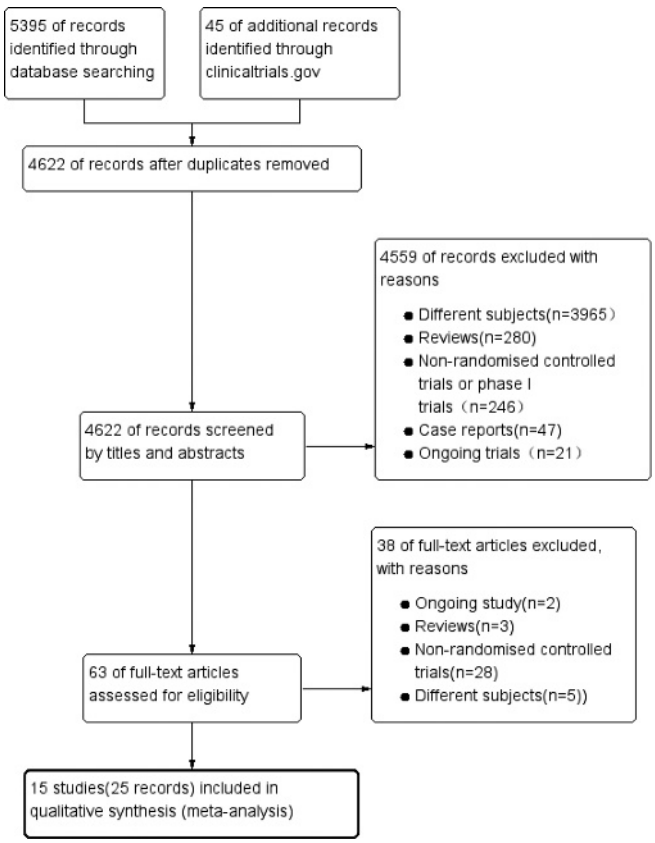

FIGURE 1. Flow chart indicating the study selection procedure.

TABLE 1. Characteristics of included RCTs

	Year	Stage	Patients Enrolled	Sample Size	Control Arm	Experimental Arm	Primary Endpoint
Burger et al, 2011[3]	2011	Phase 3	Newly diagnosed, FIGO stage III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer GOG PS 0-2	1248	Cycles1–6: T (175 mg/m^2) + C (AUC 6) + PL, q3w Cycles 7–22: PL,q3w	Cycles 1–6: T (175 mg/m^2) + C (AUC 6) + Bev (15 mg/kg), q3w Cycles 7–22: Bev(15 mg/kg), q3w	PFS
Aghajanian et al, 2012[21]	2012	Phase 3	Platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma ECOG PS 0-1	484	Cycles 1–10: G (1000 mg/m^2, days 1 and 8) + C (AUC 4, day 1) + PL (15 mg/kg, day 1), q3w	Cycles 1–10: G (1000 mg/m^2 on days 1 and 8) + C (AUC 4 on day 1) + Bev (15 mg/kg on day 1), q3w	PFS
Oza et al, 2015[22]	2015	Phase 3	Newly diagnosed, High-risk FIGO stage I–IIA or IIB–IV ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer ECOG PS 0-2	1528	Cycles 1–6: T (175 mg/m^2) + C (AUC 5 or 6), q3w	Cycles 1–6:T (175 mg/m^2) + C (AUC 5 or 6) + Bev (7.5 mg/kg), q3w Cycles 7–18: Bev (7.5 mg/kg), q3w	PFS
Pujade-Lauraine et al, 2014[23]	2014	Phase 3	Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer ECOG PS 0-2	361	Cycles 1-PD: PLD (40 mg/m^2, day 1, q4w); PAC (80 mg/m^2 on days 1, 8, 15, and 22, q4w); or TOP (4 mg/m^2, days 1, 8, 15, q4w or 1.25 mg/m^2, days 1–5, q3w);	Cycles 1-PD: PLD (40 mg/m^2, day 1q4w) or PAC (80 mg/m^2, days 1, 8, 15, and 22, q4w);or TOP (4 mg/m^2, days 1, 8, 15, q4w or 1.25 mg/m^2, days 1–5, q3w); + Bev (15 mg/kg, q3w or 10 mg/kg, q2w)	PFS
Coleman et al, 2015[16]	2015	Phase 3	Platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer GOG PS 0-2	748	T (175 mg/m2) + C (AUC5),q3w	T (175 mg/m^2) + C (AUC5) + Bev (15 mg/kg), q3w followed by Bev maintenance	OS

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TABLE 1. *(Continued)*

	Year	Stage	Patients Enrolled	Sample Size	Control Arm	Experimental Arm	Primary Endpoint
Bois et al, 2016[24]	2016	Phase 3	Chemotherapy-naive, FIGO stage IIB–IV epithelial ovarian cancer, fallopian tube or primary peritoneal cancer ECOG PS 0-2	1366	Cycles1-6: T (175 mg/m^2) + C (AUC5 or 6) + PL (200 mg, twice a day, days 2–21, q3w) followed by PL maintenance	Cycles1-6: T (175 mg/m^2) + C (AUC5 or6) + Nintedanib (200 mg twice a day, days 2–21), q3w followed by Nintedanib maintenance	PFS
Ledermann et al, 2011[25]	2011	Phase 2	Advanced ovarian carcinoma, fallopian tube carcinoma or primary peritoneal cancer of serous type with recurrent disease and who responded to second, third, or fourth line chemotherapy. ECOG PS 0-1	83	Cycles1-9: maintenance PL (250 mg, twice a day, q4w)	Cycles1-9: maintenance Nintedanib (250 mg twice a day), q4w	PFS Rate at 36 Weeks
Monk et al, 2016[26]	2016	Phase 3	Recurrent partially platinum-sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancers GOG PS 0-1	919	Cycles1-PD: PAC (80 mg/m^2, days 1, 8, 15, q4w) + PL	Cycles1-PD: PAC(80 mg/m^2, days 1, 8, 15,q4w) + trebananib (15 mg/kg. qw)	PFS
Karlan et al, 2012[18]	2012	Phase 2	Recurrent epithelial ovarian (FIGO stage II–IV), fallopian tube or primary peritoneal cancer ECOG PS 0-1	161	PAC (80 mg/m^2, days 1, 8, 15, q4w) + AMG 386 placebo	PAC (80 mg/m^2, days 1, 8, 15, q4w) + AMG 386 (3 mg/kg, qw) or AMG386 (10 mg/kg, qw)	PFS
Pignata et al, 2015[27]	2015	Phase 2	Platinum-resistant or refractory ovarian cancer ECOG PS 0-1	73	Cycles1-PD: PAC (80 mg/m^2, days 1, 8, 15, q4w)	Cycles1-PD: PAC (80 mg/m^2, days 1, 8, 15, q4w) + pazopanib(800 mg, orally, once daily)	PFS

du Bois et al, 2014[28]	2014	Phase 3	FIGO stage II–IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma who have not progressed after first line chemotherapy ECOG PS 0-1	940	Maintenance PL (800 mg, orally, once daily), for 104 wks (24 mos).	Maintenance Pazopanib (800 mg, orally, once daily for 104 wks (24 mos)	PFS
Sehouli et al, 2016[17]	2016	Phase 2	Platinum-resistant recurrent epithelial ovarian cancer, primary peritoneal carcinomatosis or fallopian tube cancer	172	Cycles 1–6: TOP (1.25 mg/m^2, days 1–5, q3w) + PL (400 mg orally twice a day, days 6–15, q3w) followed by PL maintenance for 12 mos	Cycles 1–6: TOP (1.25 mg/m^2, days 1–5, q3w) + Sorafenib (400 mg orally twice a day, days 6–15, q3w) followed by sorafenib maintenance for 12 mos	PFS
Herzog et al, 2013[29]	2013	Phase 2	FIGO stage III–IV ovarian epithelial cancer or primary peritoneal cancer who have achieved a response after standard platinum/taxane containing chemotherapy (first-line therapy) ECOG PS 0-1	246	Cycles1-PD: maintenance PL (400 mg orally twice a day q4w)	Cycles1-PD: maintenance Sorafenib(400 mg orally twice a day, q4w)	PFS
Ledermann et al, 2016[30]	2016	Phase 3	Platinum-sensitive relapsed epithelial ovarian cancer, primary peritoneal carcinomatosis or fallopian tube cancer after first-line platinum-based chemotherapy ECOG PS 0-1	282	Cycles 1–6: recommended chemotherapy (TC/GC/C), q3w + PL (20 mg once daily) followed by PL maintenance (20 mg once daily) for 18 mos or PD	Cycles 1–6: recommended chemotherapy (TC/GC/C), q3w cediranib (20 mg once daily) followed by cediranib maintenance (20 mg once daily) for 18 mos or PD	PFS

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TABLE 1. *(Continued)*

	Year	Stage	Patients Enrolled	Sample Size	Control Arm	Experimental Arm	Primary Endpoint
Gotlieb et al, 2012[15]	2012	Phase 2	Platinum-resistant, and TOP-resistant and/or PLD-resistant disease; Advanced ovarian cancer patients with recurrent symptomatic malignant ascites ECOG PS 0-2	55	PL (4.0 mg/kg intravenous q2w)	Aflibercept(4.0 mg/kg intravenous q2w)	Time to Repeat Paracentesis

AUC, area under curve; Bev, bevacizumab; C, carboplatin; ECOG, Eastern Cooperative Oncology Group; GOG, Gynaecological Oncology Group; G, gemcitabine; PAC, weekly paclitaxel; PD, progressive disease; PL, placebo; PLD, pegylated liposomal doxorubicin; PS, performance status; T, paclitaxel; TOP, topotecan.

extracted the following data from each selected trial: participant characteristics, study interventions, and outcomes.

Assessment of Risk of Bias in Included Studies

Cochrane Collaboration's tool was used to assess the risk of bias in included RCTs. We had presented results in both a risk of bias graph and a risk of bias summary.

Data Analysis and Statistical Methods

We assessed the effect and safety of angiogenesis inhibitors–containing therapy on 3 outcomes: OS, PFS, and incidence of adverse events. For time-to-event data (OS and PFS), we pooled the hazard ratios (HRs) and two-sided 95% confidence interval (CI) using the generic inverse variance facility of RevMan 5.3. For dichotomous outcomes (toxicity), we used the risk ratio (RR). The Karlan 2012[18] trail had multiple treatment groups (3-arm trial), and so we divided the control group between the treatment groups (with different dose), and treated comparisons between each treatment group and a split control group as independent comparisons.

The χ^2 test and Cochran Q-test were used to evaluate heterogeneity among trials, and $I^2 > 50\%$ indicated a moderate-to-high heterogeneity.[19] We used random-effects models for PFS and toxicity based on the large heterogeneity among the different trials. We pooled OS in a fixed effect model. Subgroup analysis was adopted to determine whether there is clinical benefit for patients in the subgroup classified by prognostic factors or different response to platinum-containing therapy. The meta-analysis software RevMan 5.3 provided by the Cochrane library was used for the data analysis.

We assessed the possibility of publication bias by constructing a funnel plot. We assessed funnel plot asymmetry using Begg and Egger tests, and defined significant publication bias as a $P < 0.1$.[20] We used Stata (version 12.0) for the statistical analysis.

RESULTS

We initially identified 5440 articles from all searched database of which 15 trials (with data for 8721 participants) were retained after a full-text screening for inclusion in our review after excluding duplicates, reviews, case report, and phase I trials (Fig. 1). Two[16,17] of the references were conference abstracts that described RCTs that met our inclusion criteria. The 15 trials were all published between 2011 and 2016.

The main characteristics of 15 RCTs were summarized in Table 1, and the data of outcomes were summarized in Table 2.

The assessment of risk of bias in the trials was shown in Figure 2. The risk of bias was unclear in the 2 studies that were published in an abstract form. Other RCTs reported sufficient information for randomization excluding 2 trials,[28,29] for which "Randomize" was used in abstract and text, but further details were not reported, and none was stopped early. Moreover, 3 studies[22,23,27] lacked blinding to participants and personnel, the other 2 trials[25,29] did not specify whether data collectors and outcome assessors were masked to treatment allocation, and only 4[3,22,27,30] were not funded by industry.

TABLE 2. Efficacy results of included RCTs

References	Arms	Size	Patients Enrolled	Primary Endpoint	PFS			OS		
					Median (mo)	HR	HR, 95%CI	Median (mo)	HR	HR, 95%CI
Burger et al, 2011 (GOG-0218)[3]	TC + PL	625	Newly diagnosed	PFS	10.3	0.717	0.625–0.824	39.3	0.885	0.750–1.040
	TC + Bev + Bev(m)	623			14.1			39.7		
Aghajaniann et al, 2012 (OCEANS)[21]	GC + PL + PL(m)	242	Platinum-sensitive recurrent	PFS	8.4	0.484	0.388–0.605	32.9	0.952	0.771–1.176
	GC + Bev + Bev(m)	242			12.4			33.6		
Oza et al, 2015 (ICON 7)[22]	TC	764	Newly diagnosed	PFS	17.5	0.93	0.83–1.05	58.6	0.99	0.85–1.14
	TC + Bev + Bev(m)	764			19.9			58		
Pujade-Lauraine et al, 2014 (AURELIA)[23]	PLD/PAC/TOP	182	Platinum-resistant recurrent	PFS	3.4	0.48	0.380–0.600	13.3	0.85	0.66–1.080
	PLD/PAC/TOP + Bev	179			6.7			16.6		
Coleman et al, 2015 (GOG-0213)[16]	TC	374	Platinum-sensitive recurrent	OS	10.4	0.614	0.522–0.722	37.3	0.827	0.683–1.005
	TC + Bev + Bev(m)	374			13.8			42.2		
Bois et al, 2016 (AGO-OVAR 12)[24]	TC + nintedanib + nintedanib(m)	911	Newly diagnosed,	PFS	17.2	0.84	0.72–0.98	34	0.99	0.77–1.27
	TC + PL + PL(m)	455			16.6			32.8		
Ledermann et al, 2011[25]	BIBF1120	43	Pure maintenance	PFS rate at 36 wks	NA	0.65	0.41–1.02	NA	0.84	0.51–1.39
	PL	40			NA			NA		
Monk et al, 2016 (TRINOVA-1)[26]	PAC + trebananib	461	Recurrent disease	PFS	7.2	0.66	0.57–0.77	19.3	0.95	0.81–1.11
	PAC + PL	458			5.4			18.3		
Karlan et al, 2012[18]	PAC + AMG386 (10 mg/kg)	53	Recurrent	PFS	7.2	0.76	0.49–1.18	22.5	0.60	0.34–1.06
	PAC + PL	55			4.6			20.9		
Karlan et al, 2012[18]	PAC + AMG 386 (3 mg/kg)	53	Recurrent	PFS	5.7	0.75	0.48–1.17	20.4	0.77	0.45–1.31
	PAC + PL	55			4.6			20.9		
Pignata et al, 2015 (MTO-11)[27]	PAC + pazopanib	37	Platinum-resistant recurrent	PFS	6.35	0.42	0.25–0.69	19.1	0.6	0.32–1.13
	PAC	36			3.49			13.7		
du Bois et al, 2014[28]	Pazopanib	472	Pure maintenance	PFS	17.9	0.77	0.64–0.91	NA	1.08	0.87–1.33
	PL	468			12.3			NA		
Sehouli et al, 2016[17]	TOP + sorafenib	86	Platinum-resistant or refractory recurrent	PFS	6.7	0.6	0.43–0.83	17.1	0.65	0.45–0.93
	TOP + PL	86			4.4			10.1		
Herzog et al, 2013[29]	Sorafenib	123	Pure maintenance	PFS	12.7	1.09	0.72–1.63	NA	1.49	0.69–3.23
	PL	123			15.7			NA		

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TABLE 2. *(Continued)*

References	Arms	Size	Patients Enrolled	Primary Endpoint	PFS			OS		
					Median (mo)	HR	HR, 95%CI	Median (mo)	HR	HR, 95%CI
Ledermann et al, 2016 (ICON 6)[30]	TC/GC/C + PL	118	Platinum-sensitive relapsed	PFS	8.7	0.56	0.44–0.72	21	0.77	0.55–1.07
	TC/GC/C + Cediranib + cediranib(m)	164			11			26.3		
Gotlieb et al, 2012[15]	Aflibercept	29	Platinum-resistant relapsed	Time to repeat paracentesis	6.3	NA	NA	16	1.023	0.562–1.863
	PL	26			7.3			12.9		

Bev, Bevacizumab; C, Carboplatin; GC, Gemcitabine + Carboplatin; m, maintenance therapy; NA, not available; PAC, weekly paclitaxel; PL, placebo; PLD, pegylated liposomal doxorubicin; TC, Paclitaxel + Carboplatin; TOP, topotecan.

Overall Survival

Three studies (n = 4142 participants) assessed the risk of death in patients with newly diagnosed ovarian cancer, pooling the data of these studies showed no significant difference in OS when participants were treated with angiogenesis inhibitors and chemotherapy combination treatment compared with chemotherapy alone (HR, 0.95; 95% CI, 0.86–1.05; $I^2 = 0\%$). In contrast, subgroup analysis suggested antiangiogenics-containing combination therapies had a significantly better OS in the patients with a high risk of progression from 2 studies with a total of 1750 participants (HR, 0.84; 95% CI, 0.74–0.96; $I^2 = 0\%$).

Nine studies (n = 3310 participants) assessed the risk of death in the recurrent setting, pooling the data of these studies also found statistically significant lower risk of death in women who received antiangiogenics-containing combination therapies compared with those who received chemotherapy alone (HR, 086; 95% CI, 0.79–0.94; $I^2 = 0\%$).

In addition, further subgroup analysis showed angiogenesis inhibitors had significant survival benefits for both platinum-sensitive recurrent ovarian cancer from 3 trials with a total of 1514 participants (HR, 0.86; 95% CI, 0.76–0.98; $I^2 = 0\%$) and platinum-resistant recurrent ovarian cancer from 4 trials with a total of 661 participants (HR, 0.78; 95% CI, 0.65–0.94; $I^2 = 0\%$).

Conversely, no significant difference in the risk of death was observed in the pure maintenance antiangiogenics therapy who achieved a good response to before chemotherapy (HR, 1.06; 95% CI, 0.88–1.28; $I^2 = 0\%$) based on the results of 3 studies with a total of 1269 patients (Fig. 3a).

The funnel plot for OS revealed almost symmetry (Fig. 4a), and we further assessed publication bias on Egger test ($P = 0.156$), thus indicating no significant publication bias for OS.

Progression-Free Survival

Angiogenesis inhibitors and chemotherapy combination treatment had significantly lower risks of disease progression compared with women with chemotherapy alone in both newly diagnosed setting (HR, 0.83; 95%CI, 0.71–0.97; $I^2 = 75\%$) and the recurrent setting (HR, 0.58; 95% CI, 0.52–0.65; $I^2 = 39\%$). Subgroup analysis for newly diagnosed patients with a high risk of progression indicated the PFS was significantly improved (HR, 0.72; 95% CI, 0.65–0.81; $I^2 = 0\%$). Moreover, further subgroup analysis comparing the benefit on PFS for platinum-sensitive recurrent ovarian cancer (HR, 0.56; 95% CI, 0.48–0.64; $I^2 = 31\%$) and platinum-resistant recurrent ovarian cancer (HR, 0.50; 95% CI, 0.42–0.60; $I^2 = 0\%$) both suggested significantly lower risks of disease progression. We detected no significant heterogeneity in both subgroups.

However, although pazopanib showed a significantly improved PFS (HR, 0.76; 95% CI, 0.64–0.91) from 1 trial,[28] we found no significant improvement for PFS in the pure maintenance angiogenesis inhibitors therapy (HR, 0.80; 95% CI, 0.63–1.01; $I^2 = 37\%$), with no significant between-study heterogeneity (Fig. 3b).

The funnel plot for PFS revealed almost symmetry (Fig. 4b), and we further assessed publication bias on Egger test ($P = 0.185$), thus indicating no significant publication bias for PFS.

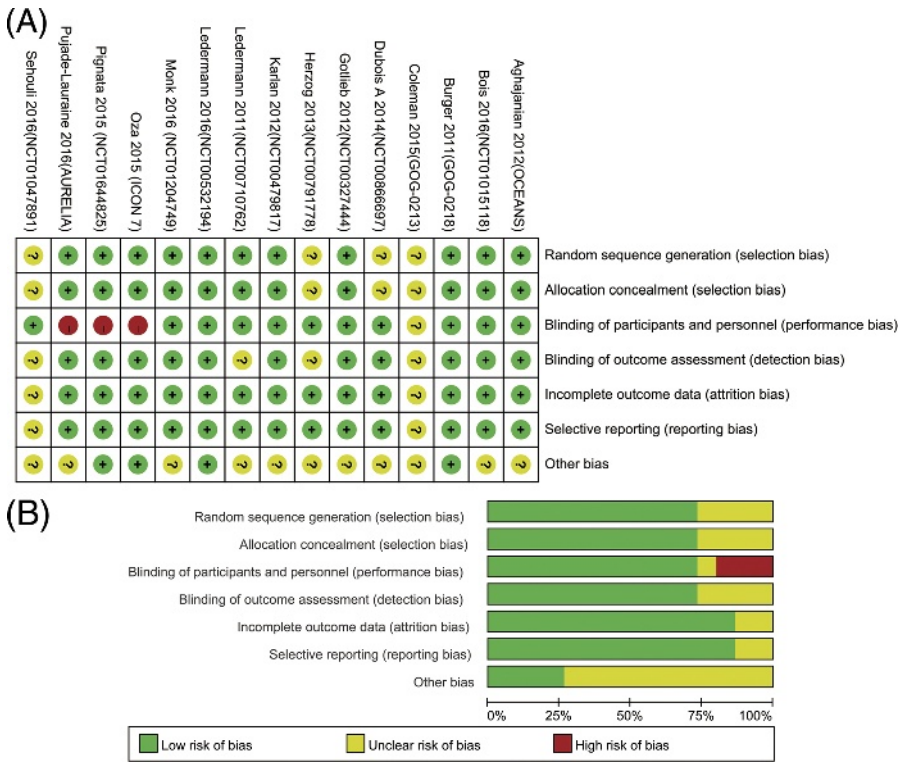

FIGURE 2. Risk of bias graph A, review of authors' judgements about each risk of bias item presented as percentages across all included studies. Risk of bias summary B, review of authors' judgements about each risk of bias item for each included study.

Adverse Events

Supplementary Figure A http://links.lww.com/IGC/A709 presents 7 common adverse events that are potentially associated with angiogenesis inhibitors during treatment. Among this updated analysis, the risks of adverse events (AEs) were significantly increased as follows: gastrointestinal perforation ($G \geq 3$; RR, 2.57; 95% CI, 1.66–3.97; $I^2 = 63\%$), hypertension ($G \geq 3$; RR, 7.60; 95% CI, 2.79–20.70; $I^2 = 74\%$), arterial thromboembolism (RR, 2.27; 95% CI, 1.34–3.84; $I^2 = 0\%$), proteinuria ($G \geq 3$; RR, 4.31; 95% CI, 2.15–8.64; $I^2 = 0\%$), and complication of wound healing (RR, 1.72; 95% CI, 1.12–2.63; $I^2 = 1\%$).We found no significant increased risks for either neutropenia ($G \geq 4$; RR, 1.09; 95% CI, 0.93–1.28; $I^2 = 46\%$) or venous thromboembolism (RR, 1.08; 95% CI, 0.79–1.48; $I^2 = 26\%$).

DISCUSSION

This updated meta-analysis was derived from 3 new RCTs and final data to reassess the efficacy and safety of angiogenesis inhibitors and chemotherapy combination treatment in ovarian cancer. The conclusion is different from the previous meta-analysis, especially in the grouping of statistical analysis. Considering the clinical settings to use angiogenesis inhibitors may play a major role in the treatment benefit, we divided 15 trials into 3 groups.

For newly diagnosed ovarian cancer, the addition of angiogenesis inhibitors to chemotherapy was associated with a significant improvement on PFS with large heterogeneity, but there was no evidence of a benefit on OS. Considering the large heterogeneity, we performed further subgroup analysis in patients with a high risk of progression who were predefined in the ICON7 trial and matched all the recruited patients in the GOG-218 trial, the results of which showed bevacizumab-containing therapy had significant improvement in both PFS and OS, with no significant between-study heterogeneity. Hence, our analysis showed that bevacizumab plus chemotherapy, followed by maintenance bevacizumab therapy, could be considered a front-line treatment option for patients with high-risk features or high-postsurgical tumor burden, with evidence of both PFS and OS benefits for this subgroup. However, because the survival benefit of angiogenesis inhibitors in high-risk patients was concluded from subgroup analysis, the results should be noted as the consistency of patient characteristics and principle of randomization were not ensured.

Although women with advanced epithelial ovarian cancer responded to many available therapeutic agents, almost all die from recurrence, which makes the treatment of recurrent ovarian cancer important. In the present study, antiangiogenics-containing therapies significantly reduced the HR of progression by 42% and risk of death by 14%, compared with chemotherapy alone with no significant between-study heterogeneity. Further analysis of 2 subgroups (ie, platinum-sensitive recurrent ovarian cancer and platinum-resistant recurrent ovarian cancer) both showed improvement on PFS and OS, with no significant between-study heterogeneity. The results were encouraging among women with recurrent ovarian cancer no matter whether responded to previous platinum-containing chemotherapy or not, demonstrating that angiogenesis inhibitors combined with chemotherapy is a great

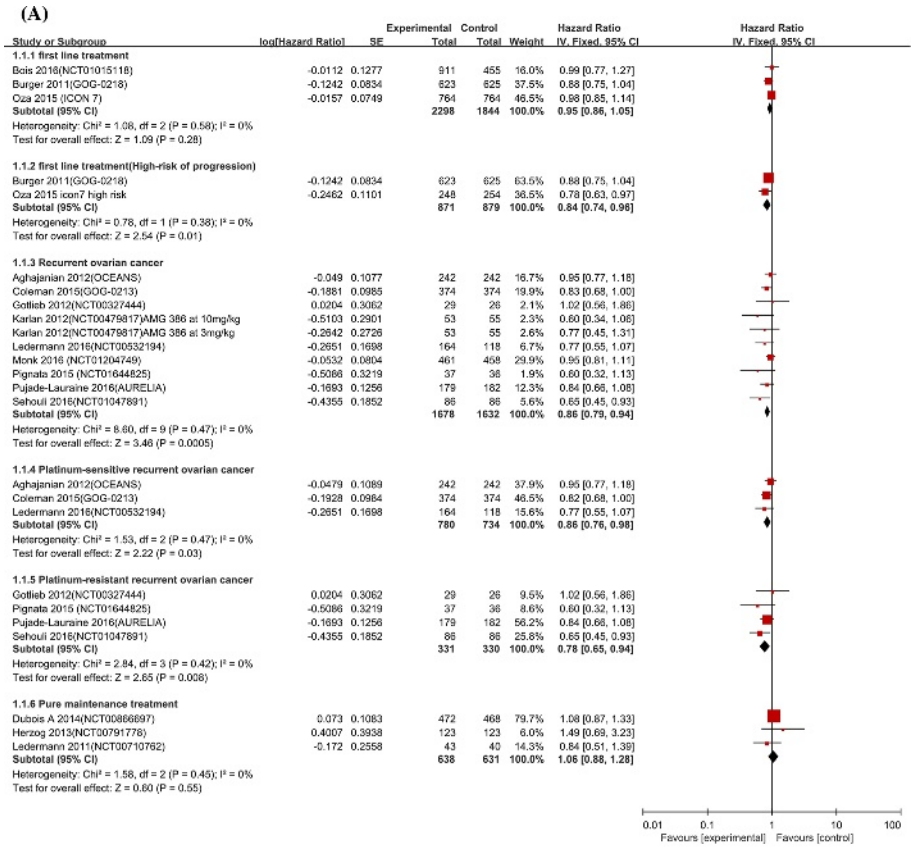

FIGURE 3. Forest plots: A, OS and B, PFS.

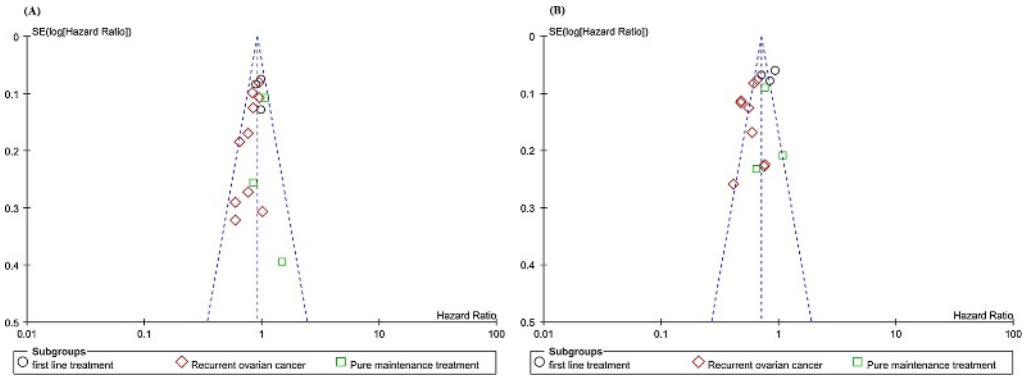

FIGURE 4. Forest plots: A, OS and B, PFS.

treatment option for recurrent ovarian cancer. Among them, bevacizumab, a kind of antiangiogenics by binding VEGF, has demonstrated a significant clinical benefit from several trials, and on the basis of these trials, bevacizumab was approved for first-line and second-line treatment of patients with both platinum-sensitive and platinum-resistant ovarian cancer.[26] However, its activity in patients whose disease relapses after first-line bevacizumab-containing therapy is still unknown. Hence, further studies addressing this issue need to be performed.

Maintenance therapy has been one proposed strategy to improve outcomes, and incorporation of angiogenesis inhibitors had also been of interest. Recently, a number of clinical trials took combined strategies, using angiogenesis inhibitors in the maintenance setting. In the present study, we mainly analyzed the maintenance antiangiogenics monotherapy in the trials, which recruited patients who responded to previous chemotherapy (ie, a Partial Response or Complete Response according to the RECIST criteria in patients with measurable disease). In the trial,[25] BIBF 1120 was not given to treat recurrent disease but to prolong the progression-free interval. It was evaluated after the completion of chemotherapy for relapsed ovarian cancer. The other 2 trials[28,29] were designed to compare pazopanib or sorafenib to placebo as maintenance treatment after first-line therapy with systemic chemotherapy, and pazopanib showed a significant better PFS in the maintenance setting. However, pooled analysis of the 3 studies suggested no significant improvement in either PFS or OS. The lack of statistical significance may be because of lack of statistical power. In addition, more patients in the experience arm required dose modifications and discontinued treatment because of severe AEs, such as severe liver-related toxicity, severe gastrointestinal events, resulting in reduced dose of the planned dose. As a group, both short-term and longer-term adverse effects, the negative impact on quality of life associated with frequent visits to a physician or clinic and the cost may resulting in no significantly clinical benefit. Hence, further study should be performed to select patients who can really benefit from long-term maintenance treatment, particularly those who are at high risk of progression.

Adverse events were more common in the angiogenesis inhibitors-containing arm compared with the control arm, several significantly so (severe gastrointestinal events, severe hypertension, severe proteinuria, arterial thromboembolism, and complication of wound healing). It is necessary to monitor and manage these adverse events during the antiangiogenics therapy to minimize the risks. If severe adverse events such as gastrointestinal events can be controlled, antiangiogenics can be used safely.

This updated meta-analysis included 15 RCTs with 8721 patients, whereas the previous publication contained 12 RCTs with 7775 patients. One additional trial, NCT00327444,[15] to our knowledge, was the first phase 2 study to show the effectiveness of VEGF blockade (aflibercept) in the reduction of malignant ascites for advanced chemoresistant ovarian cancer and recurrent symptomatic malignant ascites. The other 2 additional trials had final results published in abstract form from conference proceedings. Moreover, the most recent meta-analysis divided 12 trials into 3 groups: the bevacizumb group, the VEGFRIs group, the trebananib group. Improvement on PFS was seen in all groups and only the trebananib group demonstrated a significant prolongation on OS. However, to assess the role of clinical setting to use angiogenesis inhibitors in the treatment benefit, we divided 15 trials into 3 groups: first-line setting, the recurrent setting, and pure maintenance setting. Our results indicated that combination treatment with angiogenesis inhibitors and chemotherapy improved PFS and OS in the recurrent setting and high-risk progression subgroup, with no statistically significant improvement in OS for newly diagnosed ovarian cancer. We detected no significant improvement for either PFS or OS in pure maintenance setting.

A limitation of this analysis is clinical heterogeneity across the studies, including the different chemotherapy regimens, the tumor stages, and the length of follow-up. Secondly, there are 2 trials, the data of which have thus far been published only as conference abstracts, and they must be judged as being at high risk of bias until further details are known. Thirdly, although most of the included studies were published in high-impact journals, there were study features that carry potential risk of bias such as pharmaceutical industry funding and open-label design. Fourthly, there are differences in angiogenesis inhibitors (which include VEGF blockade, VEGF-R tyrosine kinase inhibitors, angiopoietin inhibitor) that might dictate an optimal choice for combination with chemotherapy or other biological agents. Finally, issues such as the optimize duration and timing of treatment, the potential tumor or host biologic factors to identify, which patients will benefit most (and perhaps more importantly, those who are not likely to respond), have not been established.

CONCLUSIONS

Together, although there are significant differences of increased risks of adverse events with antiangiogenics therapy, findings from our meta-analysis are relatively promising. Our findings clearly lend support to the use of angiogenesis inhibitors in combination with chemotherapy in the clinical management of patients with newly diagnosed (especially for high-risk patients) or recurrent ovarian cancer. However, no statistically significant clinical benefit was identified in the pure maintenance settings.

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