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Antiangiogenesis therapy in ovarian cancer patients

An updated meta-analysis for 15 randomized controlled trials

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Abstract

Background: Antiangiogenesis therapy has been demonstrated to prolong the free survival with tolerable toxicity. However the efficacy of these drugs in overall survival (OS) remains controversial. This study was designed to assess the overall performance of antiangiogenesis therapy in improving the survival of ovary cancer (OC) patients.

Methods: Electronic database of PubMed, Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched to identify relevant clinical randomized control trial (RCTs) assessing the therapeutic value of antiangiogenesis therapy in OC patients during 2011 to 2017. Additionally, abstracts of annual meetings were also conducted. Only English articles were considered. Progression free survival (PFS), OS, and objective response rate (ORR) were obtained from eligible RCTs. The HRs for time-to-event variables and ORs for dichotomous outcomes with their 95% CIs were used for this meta-analysis. All the statistical analyses were carried out by Stata 11.0 software using a fixed or random-models according to heterogeneity.

Results: A total of 15 RCTs including 9359 patients were recruited into this meta-analysis. Addition of antiangiogenic agents improved PFS (HR = 0.71, 95% CI 0.62–0.81, $P < .001$), OS (HR = 0.92, 95% CI 0.86–0.98, $P = .008$) and ORR (OR = 1.74, 95% CI 1.27–2.39, $P = .001$) compared to placebo or chemotherapy alone in overall analysis. Antiangiogenic agents prolonged both PFS (HR = 0.58, 95% CI 0.52–0.65, $P = .000$) and OS (HR=0.84, 95% CI 0.76–0.92, $P = .000$) in recurrent settings but only PFS in primary settings (HR = 0.88, 95% CI 0.79–0.98, $P = .020$), longer PFS and OS in both platinum-sensitive recurrent patients (HR = 0.56, 95% CI 0.48–0.64, $P = .000$, PFS; HR = 0.86, 95% CI 0.76–0.98, $P = .027$, OS) as well as platinum-resistant recurrent cases (HR = 0.54, 95% CI 0.41–0.71, $P = .000$, PFS; HR = 0.84, 95% CI 0.71–0.98, $P = .029$, OS). Throughout therapy improved PFS (HR = 0.66, 95% CI 0.57–0.76, $P < .001$) and OS (HR = 0.89, 95% CI 0.83–0.96, $P = .001$). However the maintenance therapy of antiangiogenic agents was irrelevant to a longer PFS or OS.

Conclusion: Based on the available studies, antiangiogenic agents play an important role in the survival of OC patients. More randomized controlled trials are needed to reach more convinced conclusion.

Abbreviations: 95% CIs = 95% confidence intervals, HR = Hazard Ratio, OR = Odds ratio.

Keywords: antiangiogenesis, meta-analysis, ovarian cancer, prognosis

1. Introduction

Ovarian cancer is the leading fifth cancer type for estimated deaths in women and the leading cause of gynecologic cancer deaths worldwide, the 5-year survival rate for patients with stage III or IV epithelial ovarian cancer (EOC) remains <40%.[1] Approximately 3 quarters of patients with EOC are diagnosed at advanced stage, for whose the standard first-line treatment involves initial optimal cytoreductive surgery followed by systematic chemotherapy with carboplatin and paclitaxel.[2,3] In spite of the high initial response rates of primary therapy strategy, the majority of patients will ultimately suffer from disease progression and recurrence, require further treatment with chemotherapy, and eventually develop drug resistance and succumb to their disease. In the last decades, no substantial progress was made since much efforts had tried for the treatment of EOC.[4] Attempts to add a third cytotoxic agent was failed to gain any clinical benefit, but resulted in increased adverse events.[5]With the development of modern biology, targeted therapy has become a promising approach to overcome ovarian cancer and within which antiangiogenic therapy has made an amazing antitumor activity.

Angiogenesis, the formation of new vessels from pre-existing vasculature, plays fundamental roles in normal ovarian physiology

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YJ and XS contributed equally to this study.

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as well as in the pathogenesis of ovarian cancer, promoting tumor proliferation and metastasis.[4,6] The poor prognosis of ovarian cancer is closely related to intensive new blood vessels, which make antiangiogenic therapy a promising therapeutic target for ovarian cancer. Antiangiogenic agents exert their antitumor activity via inhibiting the neovascularization and the possible mechanism is increasing the effects of chemotherapy by normalizing tumor vasculature, relieving the tumor hypoxia and enhancing the delivery of cytotoxic drugs. According to difference of mechanism, antiangiogenic agents are classified to 3 groups: VEGF inhibitor (bevacizumab), VEGF-R tyrosine kinase inhibitors (cediranib, pazopanib, sorafenib, nintedanib, and erlotinib) and angiopoietin inhibitors (trebananib).[7] Accumulating evidence has demonstrated that antiangiogenic therapy in patients with EOC is related to a longer progression free survival (PFS) with tolerable degree of toxicity.[8,9] However, the efficacy of these drugs in overall survival (OS) remains controversial. To shed light on a better insight into the clinical benefits and the proper use of antiangiogenesis therapy for ovarian cancer, we performed an update meta-analysis of all eligible randomized control trials (RCTs) on this topic.

2. Material and methods

2.1. Search strategy

A literature searchof PubMed, Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials during 2011 to 2017 was conducted to find the RCTs assessing the efficiency of antiangiogenesis agents in ovarian cancer. The search terms involve "ovarian cancer, antiangiogenic agents, antiangiogenic therapy, trenananib, AMG 386, bevacizumab, Avastin, cediranib, AZD 2171, pazopanib, nintedanib, BIBF 1120, sorafenib, aflibercept, Erlotinib, sunitinib, and RCT." The language was restricted to English only. Additionally, abstracts from the annual meetings of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and European Society of Gynecological Oncology (ESGO) were screened to identify the potentially relevant clinical trials. We also examined the reference lists of recruited articles, previously published reviews and meta-analyses to find potentially eligible studies.

2.2. Trial selection criteria

The inclusion criteria for eligible studies in the meta-analysis were as follows: types of patients: adult women ($>=18$ years old) with pathologically confirmed EOC; types of studies: prospective phase II and phase III randomized clinical trials, published or unpublished, with primary outcomes of PFS or OS and secondary outcome of ORR or toxicity; types of interventions: the experimental arm was antiangiogenic therapy alone or combined with chemotherapy while the placebo or chemotherapy alone was considered as the standard controlled arm; antiangiogenic agents were used as maintenance therapy after chemotherapy or currently with chemotherapy followed by a maintenance period throughout therapy); types of outcome: PFS defined as time from randomization until disease progression, death or date of last follow-up; OS was defined as the time from randomization until death or last follow-up; ORR defined by according to the response evaluation criteria in solid tumors (RECIST).[10] Besides, studies involving the use of other targeted agents are excluded. While the same trials were reported in different papers and meetings, only the most updated or complete report was included. Two independent investigators (JJ and XS) examined all the potential eligible articles and individually selected the studies.

2.3. Data extraction

Two reviewers (JJ and XS) independently extracted the general information and exact data for this meta-analysis, including the first author, antiangiogenic agents, journal, phase, publication year, treatment setting, interventions, number of patients, period of follow-up, median PFS and HR with 95% CI, median OS and HR with 95% CI and ORR.

2.4. Statistical analysis

All statistical analysis of this meta-analysis was performed using Stata, version 11.0 software. Pooled HRs for time-to-event data or pooled ORs for dichotomous data, with two-sided 95% CI and P values were calculated with fixed or random-effect models. Statistical heterogeneity was explored by the Cochran's Q-test and inconsistency (I^2) statistics; value of I^2 over 50% indicate substantial heterogeneity.[11] A fixed-effect model was used if there was no heterogeneity, otherwise, a random-effect model was used.[12] Statistically significant was referred to two-tailed $P<.05$. Forest plot was used for graphical representation of each study and pooled analysis. Publication bias was assessed by Begg's test and Egger's test.[13,14] Additionally, we conducted one-way sensitivity analyses to evaluate the effects of the individual studies by estimating the average HRs in the absence of each study. Subgroup analyses were performed by patient inclusion criteria aiming to provide evidence for gynecologists to choose the optimal antiangiogenic agents for optimal kind of patients with ovarian cancer.

3. Results

A total of 304 potential relevant articles in peer-reviewed journals were screened in our literature search and eventually 15 eligible studies were identified. One additional report presented at 2015 ESGO annual meeting was also included. As a result, 9 phase III trials[8,15–22] and 6 phase II trials[23–28] met the inclusion criteria of this meta-analysis, involving 9359 patients in the pooled analyses. The detailed selection procedure is further presented in Figure s1, http://links.lww.com/MD/C424. Of the included 15 studies, 7 trials evaluated the addition of antiangiogenic agents as first-line therapy[15,16,20–22,27,28] while the other 8 trials evaluated recurrent ovarian cancer,[24,26] including platinum-sensitive recurrent[8,18,19,23] as well as platinum-sensitive recurrent.[17,19,25] 4 trials[21,22,26,27] employed the antiangiogenic agents as a maintenance strategy while the remaining 11 trials applied the throughout strategy. Three groups of antiangiogenic agentswere investigated including the anti-VEGF group (bevacizumab), VEGF-R tyrosine kinase inhibitor (TKI) group (cediranib, pazopanib, sorafenib, nintedanib, erlotinib), and angiopoietin inhibitors group (trebananib). GOG 0218[16] and ICON6[8] were 3-armed trials with patients receiving chemotherapy alone, antiangiogeneic initiation therapy or antiangiogeneic throughout therapy, where we only recruited the chemotherapy alone group and antiangiogeneic throughout therapy group to reduce the heterogeneity. Another RCT[24] was a 3-armed trial with patients receiving chemotherapy alone, or antiangiogeneic throughout therapy with different doses, where we recruited all these 3 groups. The detailed characteristics of all these included studies are summarized in Table 1.

HR and their 95% CI for PFS was available in 14 studies and a random effect was used for PFS analyses due to the significant heterogeneity ($P=.000$, $I^2=83.6\%$). The overall analyses revealed that compared to placebo or chemotherapy alone,

Table 1

Characteristics of eligible trials included in the meta-analysis.

Author (trial) Year/ Phase	Agents/ setting	Stage	No. of pts Con/Int	Median age	Median follow-up Con/Int	Intervention		Median PFS, months		Median OS, months		ORR (%) Con/Int
						Con	Int	Con/Int	HR (95%CI)	Con/Int	HR (95%CI)	
Perren TJ[15] (ICON7) 2011/III	Bev/primary	I–II (9%) III–IV (91%)	764/764	57/57	48.6/48.8	C+P q3w for 6 cycles	C+P+Bev q3w for 5/6 cycles Followed by bev for 12 cycles	17.5/19.9	0.93 (0.83–1.05)	58.6/58	0.99 (0.85–1.14)	48/67
Burger RA[16] (GOG0218) 2011/III	Bev/primary	III or IV	625/623	60/60	17.4/17.4	C+P+PL q3w for 6 cycles Followed by PL for 16 cycles	C+P+Bev q3w for 6 cycles followed by Bev for 16 cycles	10.3/14.1	0.77 (0.68–0.87)	39.3/39.7	0.885 (0.75–1.04)	52/74
Pugade-Lauraine E[17] (AURELIA) 2014/III	Bev/recurrent	NR	182/179	61/62	13.9/13	Single agent chemo until PD	Single agent chemo + Bev until PD	3.4/6.7	0.48 (0.38–0.61)	13.3/16.6	0.85 (0.66–1.08)	11.8/27.3
Aghajanian C[18] (OCEANS) 2012/III	Bev/recurrent	NR	242/242	61/60	56.4/58.2	C+G q3w for 6–10 cycles	C+G+Bev q3w for 6–10 cycles; followed by Bev until PD	8.4/12.4	0.484 (0.388–0.605)	32.9/33.6	0.95 (0.77–1.18)	57.4/78.5
Colemana RL[19] (GOG 0213) 2015/III	Bev/recurrent	NR	374/374	60	NR	C+P	C+P+Bev followed by Bev until PD	10.4/13.8	0.614 (0.522–0.722)	37.3/42.2	0.827 (0.683–1.005)	58.4/78.8
Monk BJ[20] (TRINOVA-1) 2014/III	Tre/recurrent	NR	458/461	59/60	10.1/10.1	P+PL qw until PD	P+Tre (15 mg/kg)qw until PD	5.4/7.2	0.66 (0.57–0.77)	17.3/19	0.86 (0.69–1.08)	30/38
Karlan BY*[25] 2012/II	Tre/recurrent	II–IV	55/53	62/59	14.9/15.4	P qw until PD	P+Tre qw until PD	4.6/7.2	0.81 (0.51–1.3)	20.9/22.5	0.60 (0.34–1.06)	27/37
Karlan BY†[25] 2012/II	Tre/recurrent	II–IV	55/53	62/60	14.9/15.2	P qw until PD	P+Tre qw until PD	4.6/5.7	0.75 (0.49–1.21)	20.9/20.4	0.77 (0.45–1.31)	27/19
Ledermann JA[21] (ICON6) 2016/III	Ced/recurrent	NR	118/164	62/62	19.5/19.5	Platinum-based chemo +PL for 6 cys followed by PL up to 18 months	Platinum-based chemo +Ced for 6 cys followed by Ced up to 18 months	8.7/11.0	0.56 (0.44–0.72)	21/26.3	0.77 (0.55–1.07)	NR
Du Bois A[22] (AGO-OVAR16)2014/III	Paz/primary	II (7%) III-IV (93%)	468/472	57/56	24.3/24.3	Platinum-based chemo ≥5 cys followed by PL until PD	Platinum-based chemo≥ 5 cys followed by Paz until PD	12.3/17.9	0.766 (0.64–0.91)	NR	1.08 (0.87–1.33)	NR
Pignata S[26] (MITO11) 2015/II	Paz/recurrent	IC–IV	36/37	58/56	16.1/16.1	P qw until PD	P qw + Paz until PD	3.49/6.35	0.42 (0.25–0.69)	13.7/19.1	0.60 (0.32–1.13)	25/56
Du Bois A[23] (AGO-OVAR12) 2016/III	Nin/primary	IIB–IV	455/911	58/58	22.4/22.4	C+P+PL for 6 cys followed by PL up to 120 weeks	C+P+Nin for 6 cys followed by Nin up to 120 weeks	16.6/17.2	0.84 (0.72–0.98)	NR	0.99 (0.77–1.27)	NR
Ledermann JA[27] 2011/II	Nin/recurrent	I–IV	40/43	63/60	36 weeks	Second-line chemo followed by PL until PD	Second-line chemo followed by Nin until PD	NR	0.65 (0.41–1.02)	NR	0.84 (0.51–1.39)	NR
Herzog TJ[28] 2013/II	Sor/primary	III–IV	123/123	54.4/56.9	NR	P+C for first-line chemo followed by PL until PD	P+C for first-line chemo followed by Sor until PD	12.7/15.7	1.09 (0.72–1.63)	NR	1.48 (0.69–3.23)	NR
Hainsworth JD[8] 2015/II	Sor/primary	III–IV	42/43	62/63	NR	C+P up to 6 cys	C+P+Sor up to 6 cys followed by Sor totally for 12 months	16.3/15.4		NA/36.5		74/67
Vergote IB[24] 2014/III	Erl/primary	I–IV	415/420	59/59	51/51	Platinum-based chemo for 6–9 cys without PD followed by observation	Platinum-based chemo for 6–9 cys without PD followed by erl for 2 years	12.4/12.7	1.05 (0.9–1.23)	59.1/50.8	0.99 (0.81–1.20)	NR

Bev = bevacizumab, C = carboplatin, Ced = cediranib, chemo = chemotherapy, con = control group, cys = cycles, Erl = erlotinib, G = germcitabine, Int = intervention group, Nin = nintedanib, P = paclitaxel, Paz = pazopanib, PD = disease progression, PL = placebo, Sor = sorafenib, Tre = trebananib.

* Trebananib 10 mg/kg.

† Trebananib 3 mg/kg.

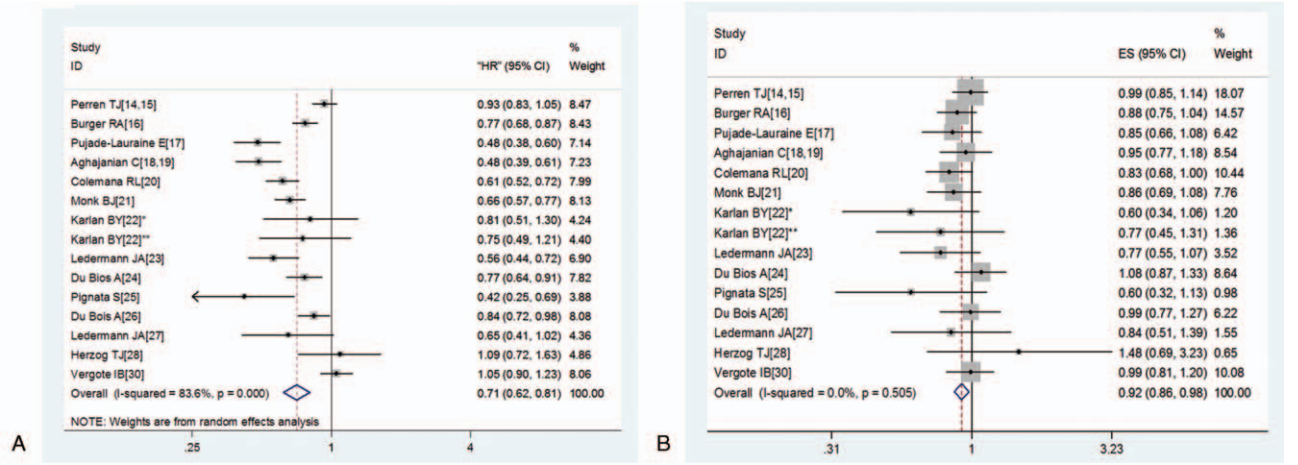

Figure 1. The efficacy of antiangiogenic therapy on PFS (A) and OS (B). OS = overall survival, PFS = progression free survival.

incorporation of antiangiogenic agents was associated with statistical significant improvement in PFS among patients with ovarian cancer (HR = 0.71, 95% CI0.62–0.81, $P = .000$; random effect; Fig. 1A). The Begg's test ($P = .322$) and Egger's test ($P = .202$) revealed that there was no significant publication bias. HR and their 95% CI for OS was available in 14 studies. No heterogeneity ($P = .525$, $I^2 = 0.0\%$) was detected among the studies and a fixed effect was used for OS analyses. The overall analyses revealed that the antiangiogenic therapy was associated with statistical significant improved OS in patients with ovarian cancer (HR = 0.92, 95% CI 0.86–0.98, $P = .008$; fixed-effect; Fig. 1B). Begg's test ($P = .138$) and Egger's test ($P = .166$) revealed that there was no significant publication bias. Additionally, we conducted one-way sensitivity analysis to confirm our results above (Figure s2, http://links.lww.com/MD/C424).

Subgroup analyses based on treatment lines (primary setting vs recurrent setting) were conducted. The results showed an improved PFS in both primary setting (HR = 0.88, 95% CI 0.79–0.98, $P = .020$; randomized-effect; Fig. 2A) and recurrent setting (HR = 0.58, 95% CI 0.52–0.65, $P < .001$; randomized-effect; Fig. 2A). As for OS, we found a statistical significant improvement of OS in patients with recurrent ovarian cancer (HR = 0.84, 95% CI 0.76–0.92, $P < .001$; fixed effect; Fig. 2B). However, OS was not improved in the primary setting (HR = 0.98, 95% CI 0.90–1.06, $P = .620$; fixed-effect; Fig. 2B).

Additionally, we further investigated survival benefit of antiangiogenic agents between platinum-sensitive and platinum-resistant recurrent patients. The results revealed a longer PFS and OS in platinum-sensitive recurrent patients HR = 0.56, 95% CI 0.48–0.64, $P = .000$, randomized-effect, Fig. 3A for PFS; (HR = 0.86, 95% CI 0.76–0.98, $P = .027$, fixed-effect, Fig. 3B for OS) as well as platinum-resistant recurrent cases (HR = 0.54, 95% CI 0.41–0.71, $P = .000$, randomized-effect, Fig. 3A for PFS; HR = 0.84, 95% CI 0.71–0.98, $P = .029$, fixed-effect; Fig. 3B for OS).

Subgroup analyses stratified by treatment strategy (maintenance therapy vs throughout therapy) revealed that throughout therapy of antiangiogenic agents was associated with a statistically significant improved PFS (HR = 0.66, 95% CI 0.57–0.76, $P = .000$; randomized-effect; Fig. 4A) and OS (HR = 0.89, 95% CI 0.83–0.96, $P = .001$; fixed-effect; Fig. 4B). However the maintenance therapy of antiangiogenic agents was irrelevant to a longer PFS or OS (Fig. 4).

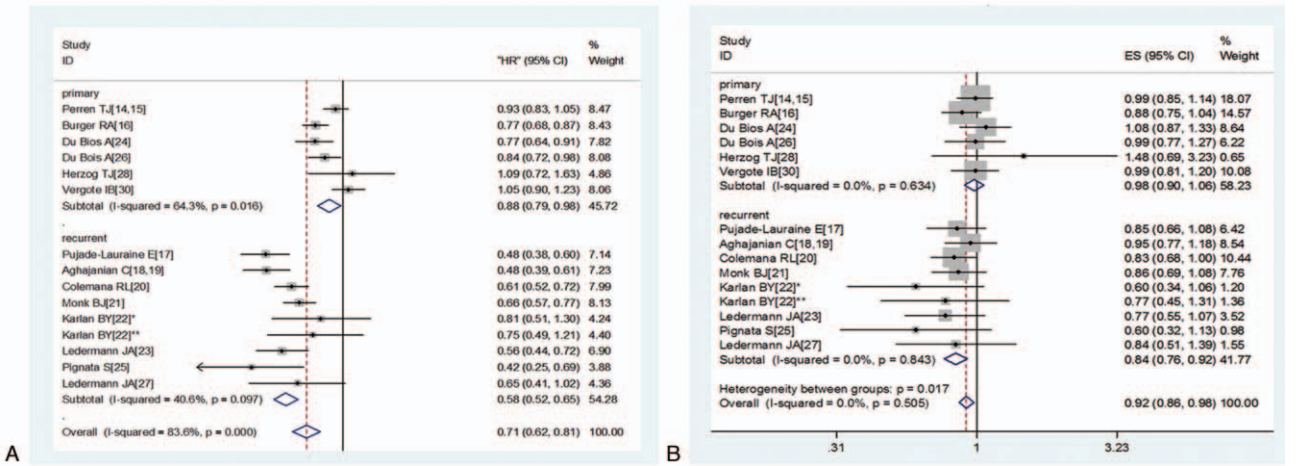

Figure 2. Subgroup analysis based on treatment setting on PFS (A) and OS (B). OS = overall survival, PFS = progression free survival.

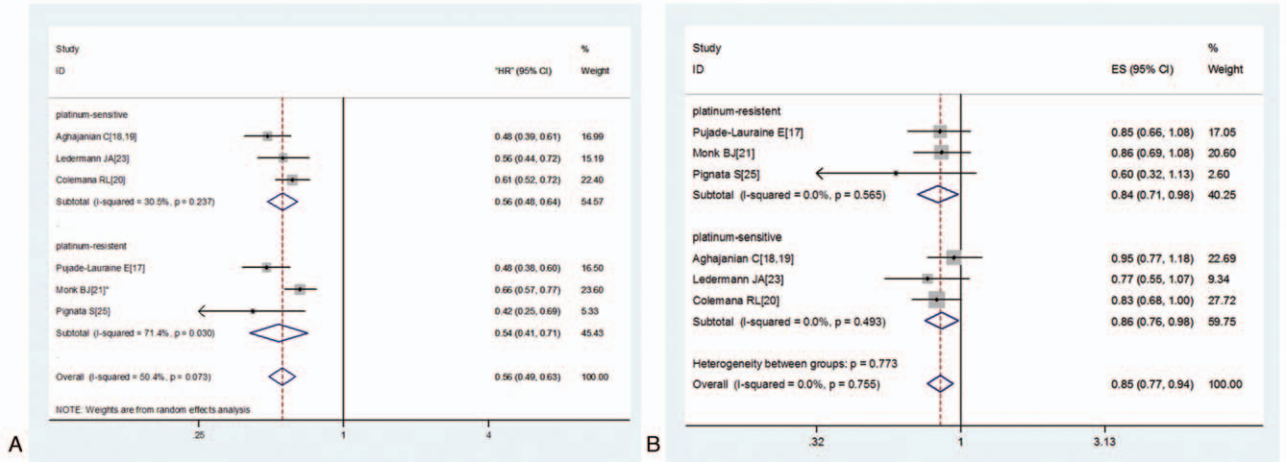

Figure 3. Subgroup analysis based on recurrent pattern on PFS (A) and OS (B). OS = overall survival, PFS = progression free survival.

Seven antiangiogenic agents included were divided into 3 groups according to their functional mechanism. Subgroup analyses stratified by the antiangiogenic agents indicated the incorporation of all 3 kinds of antiangiogenic agents were associated with a statistically longer PFS (Fig. 5A). Otherwise, only anti-VEGF group (bevacizumab) (HR = 0.91, 95% CI 0.84–0.99, $P = .025$, fixed effect; Fig. 5B) and angiopoietin inhibitors group (trebananib) (HR = 0.81, 95% CI 0.67–0.99, $P = .036$; fixed effect; Fig. 5B) demonstrated a longer OS.

A total of 10 trials provided this outcome results, including 3 trials employed antiangiogenic agents as primary therapy while the other 7 trials as recurrent therapy. A random effect was used due to the huge heterogeneity ($P < .001$, $I^2 = 80.0\%$). The pooled OR was 1.74 (95% CI 1.27–2.39; $P = .001$; Figure s3, http://links.lww.com/MD/C424), indicating that the incorporation of antiangiogenic agents was related to a statistically significant improved ORR compared to chemotherapy alone. The subgroup analysis stratified by treatment setting indicated that the addition of antiangiogenic agents in both front-line and recurrent settings led to an improvement on ORR (OR = 1.94, 95% CI 1.23–3.08, *P = .005 for primary setting; OR = 1.69, 95% CI 1.11–2.56,* P = *.014 for recurrent setting; Figure s3, http://links.lww.com/MD/C424).*

4. Discussion

The treatment of ovarian cancer remains a huge challenge for gynecologists. The majority of patients with ovarian cancer will eventually experience relapse and require further therapy. Antiangiogenic therapy has demonstrated survival benefits in ovarian cancer among a couple of RCTs.[8,15–28] However, the results of these benefits are inconsistent and whether incorporate antiangiogenic agents into ovarian cancer patients are still under debate. With the updated data of some trials and the most recent evidences, our present meta-analysis aims to provide further proof for the beneficial effect and the optimal use of antiangiogenic therapy in ovarian cancer. Our study revealed that the incorporation of antiangiogenic agents for ovarian cancer patients obtained a survival benefit as a whole, including a clear longer PFS and OS, as well as an elevated ORR. Besides,

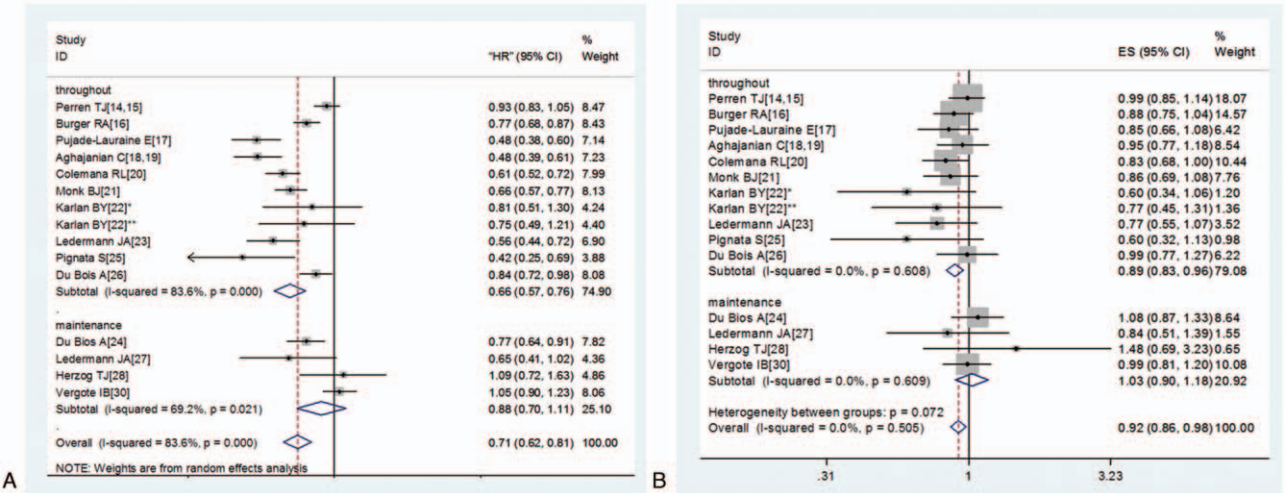

Figure 4. Subgroup analysis based on treatment strategy on PFS (A) and OS (B). PFS = progression free survival.

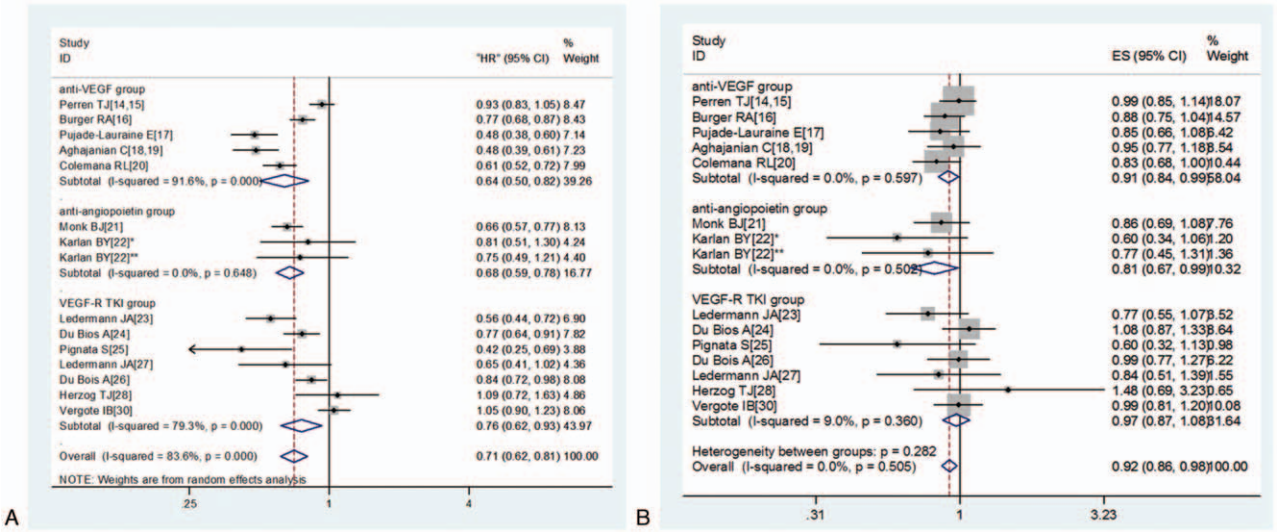

Figure 5. Subgroup analysis based on functional mechanism on PFS (A) and OS (B). OS = overall survival, PFS = progression free survival.

subgroup analyses investigated that the incorporation of antiangiogenic agents gained prolonged PFS in all of the subgroups we studied except for the maintenance therapy group. As for OS, clinical benefit was only seen in recurrent setting subgroup, throughout strategy subgroup, anti-VEGF subgroup and angiopoietin inhibitors subgroup.

Antiangionenic therapyin ovarian cancer exerted encouraging survival benefits in several RCTs. However, its clinical application is still immature and a couple of questions remain controversial. Firstly, survival benefits gained with antiangiogenic therapy always refer to the PFS improvements. It is not appropriate to evaluate the clinical benefit of new drugs only in terms of improvement in PFS. OS is also a crucial study end point. However, to our best knowledge, GOG 0213 was the first phase III RCT employed OS as the primary end point which demonstrated approximately a median of 5 months prolongation of OS in bevacizumab arm compared with control arm (42.2 months vs 37.3 months) without reaching statistical significance (HR: 0.827, 95% CI 0.683–1.005). Therefore, further RCTs are needed to explore the OS benefits and to confirm the PFS benefits regarding to the antiangiogenic therapy in ovarian cancer. Secondly, the optimal timing (primary setting vs recurrent setting) and the proper incorporation strategy (throughout strategy vs maintenance strategy) of the addition of antiangiogenic agents are still under investigated. In this study, we revealed that antiangiogenic therapy used in recurrent setting, both in platinum-sensitive and platinum-resistant recurrent cases, related to extended PFS as well as OS, which was in consistent with Xuyuan Li.[29] In contrast, in newly diagnosed ovarian cancer patients, antiangiogenic therapy gained a longer PFS but not OS. Besides, it's revealed that throughout strategy extended both PFS and OS, while maintenance strategy gained no clinical benefits. Therefore, it seems that throughout strategy for recurrent ovarian cancer patients is the most promising pattern for antiangiogenic therapy. However, our findings need further validation. Finally, the potential bio-markers with optimal sensitivity and specificity for predicting the efficacy and helping stratify the most benefited patients of antiangiogenic therapy are under explored.

Despite bevacizumab brings statistically significant survival benefit in term of PFS and/or OS, the clinical modest benefit, the high cost, increased toxicity especially the fetal adverse events like gastrointestinal perforation, and the growing evidence that only a subset of patients will benefit from the drug, prompted more efforts regarding to select reliable biomarkers helping stratify the most benefited patients.[30,31] Several candidate biomarkers such as mesothelin, fms-like tyrosine kinase-4 (FLT4), α1-acid glycoprotein (AGP), and CA-125 as well as circulating endothelial cells, cell free DNA, miR-378 and its downstream targets were investigated.[32–34] In ICON7, the combined values of circulating Ang1 and Tie2 (Tunica internal endothelial cell kinase 2) concentrations predicted improved PFS in bevacizumab-treated patients in the training set.[35] Using median concentrations as cutoffs, high Ang1/low Tie2 values were associated with significantly improved PFS for bevacizumab-treated patients in both datasets (median, 23.0 months for bevacizumab arm vs. 16.2 months for the standard arm; log rank test $P = .006$). By contrast, in the high Ang1/high Tie2 group, the median PFS for the bevacizumab arm (12.8months) was significantly lower than the median PFS for the standard treatment arm (28.5 months). Besides, the prognostic indices derived from the training set also distinguished high and low probability for progression in the validation set ($P = .008$), generating similar values for HR (0.21 vs. 0.27) between treatment and control arms for patients with high Ang1 and low Tie2 values. In addition, molecular subgroup of high-grade serous ovarian cancer (HGSOC) was also a predictor of outcome following bevacizumab.[36] Using a 63-gene expression signature, 3 major subgroups were identified, including 2 with angiogenic gene up-regulation and one with angiogenic gene repression and immune gene up-regulation. The latter immune subgroup had a superior OS compared to the other 2 subgroups combined [HR = 0.66 (0.46–0.94)], but the addition of bevacizumab conferred a significantly reduce in PFS and OS compared to chemotherapy alone. The challenge ahead is to validate these predictive biomarkers and optimize their use in clinical practice.

Another intriguing and encouraging finding of the present study is that trebananib, a peptide-Fc fusion protein preventing the interaction of Ang1/2 with Tie2 receptor which is distinct from the anti-VEGF/VEGFR agents, showed activity with prolonged PFS and OS in the treatment of recurrent ovarian

cancer.[37,38] Notably, toxicity profile of trebananib is tolerable and different from anti-VEGF/VEGFR agents where the most significant adverse event has been reported to be edema.[39] As one of the possible mechanism of bevacizumab resistance is related to activation or up-regulation of alternate pro-angiogenic pathways within the tumor such as Ang1,[31] a possibility is raised that the combination of trebananib with bevacizumab could hold great promise in enhancing the efficacy of antiangiogenic therapy in ovarian cancer. Trebananib has been further investigated in ongoing trials in both recurrent and front-line settings (TRINOVA-2, NCT01281254; TRINOVA-3, NCT01493505).

This meta-analysis validated the clinical effect of bevacizumab by recruiting the latest data of ICON7 and OCEANS, and the results of an ongoing RCT named GOG0213. Bevacizumab, the most widely studied antiangiogenic agent, has exhibited meaningful clinical benefit in ovarian cancer.[15–19] However, as one of the most active target agents, some questions remain unknown. Recently, results of GOG 0213, a randomized phase III trial of carboplatin and paclitaxel in combination with bevacizumab or not, have been presented at 2015 ESGO annual meeting. Although barely missed statistical significance, the 5-month improvement of OS is thought clinically important which is in contrast to OCEANS, another phase III trial in platinum-sensitive recurrent ovarian cancer patients evaluating carboplatin and gemcitabine with or without bevacizumab, where there was no trend of OS benefit. Here, we raised the question that which is the best chemotherapy regimen in combination with bevacizumab in platinum-sensitive relapsed ovarian cancer and whether carboplatin/paclitexel regimen is superior to carboplatin/gemcitabine regimen. Perspective validation is needed to interpret this issue. Besides, the optimal duration of bevacizumab administration remains controversial. After combination with chemotherapy, bevacizumab was used as maintenance therapy until disease progression or unacceptable toxicity in relapsed cases. In contrast, the length of bevacizumab administration after chemotherapy in front-line cases was 12 (ICON7) or 16 (GOG 0218) months. To date, several prospective trials (BOOST trial, NCT01462890; MITO16/MANGO2b trial; NCT01802749) with this objective are undergoing in front-line setting.

Several limitations must be noted in this meta-analysis. First of all, the standard for assessing the clinical benefit of new agents is unclear. However, it is sure that the simply use of PFS, OS and ORR in our study is not comprehensive and more information including toxicity, quality of life, symptom control and cost-effectiveness are needed. Secondly, great heterogeneity was found in this meta-analysis which probably originated from patients characteristics (sample size, FIGO stage, pathological type, grade), different intervention strategies (front-line or recurrent, throughout or maintenance, as well as different chemotherapy regimens) and antiangiogenic agents. Thirdly, the number of RCTs recruited in our study was small and our subgroup analysis could not exhibited an exactly answer for the controversial questions above.

In the future, using the updated data of these ongoing high-quality clinical trials regarding to antiangiogenic therapy, further analysis should be performed to consolidate the trends observed in our study.

5. Conclusion

Antiangiogenic therapy exhibited a clear clinical benefit in patients with ovarian cancer. Efforts are needed to guide the proper use of antiangiogenic agents and identify ideal biomarkers helping us to select patient subgroups who may obtain more benefit from this therapy.

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Author contributions

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