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ORIGINAL ARTICLE

Systematic evaluation of bevacizumab in recurrent ovarian cancer treatment

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Summary

Purpose: *This study aimed to evaluate the efficacy and safety of bevacizumab in the treatment of recurrent ovarian cancer.*

Methods: *The Cochrane Library, MEDLINE, and EMBASE were searched. Data regarding the use of bevacizumab in recurrent ovarian cancer were collected from randomized controlled trials (RCTs). Data were evaluated with the Cochrane systematic method, and statistical analysis was performed with the RevMan 5.2 software. Two RCTs comprising a total of 845 patients were included.*

Results: *Bevacizumab combined with conventional chemotherapy prolonged the progression-free survival (PFS) (hazard ratio [HR] 0.48; 95% confidence interval [CI], 0.41–0.56), without significantly altering the overall survival (OS) (HR 1.03; 95% CI 0.79–1.33). Adverse events (NCI-CTCAE v.4.0) associated with bevacizumab were ≥ grade 3 hypertension (relative risk [RR] 2.30; 95% CI 1.39–3.83) and bleeding (RR 4.76; 95% CI 1.38–16.37).*

Conclusions: *Bevacizumab prolonged the PFS of patients with recurrent ovarian cancer. Additional high-quality randomized controlled trials are needed to verify these results.*

Key words: *bevacizumab, efficacy, randomized controlled trials, recurrent ovarian cancer, systematic evaluation*

Introduction

Ovarian cancer is the third most common gynecological malignancy, but ranks first in long-term mortality. It is, therefore, the most lethal gynecological malignancy [1]. A major contributing factor to the high mortality rate is the high recurrence rate of ovarian cancer. Approximately 60–70% of the operated ovarian cancer patients treated with first-line platinum and paclitaxel based chemotherapy experience recurrent disease [2,3]. At present, no uniform definition for recurrent ovarian cancer (ROC) exists. The U.S. Gynecologic Oncology Group (GOG) has defined ROC as a recurrent lesion arising >6 months after clinical remission following first-line platinum-based chemotherapy. Patients with ROC have a poor prognosis, with expected median overall survival <3 years [4].

Most patients with ROC develop resistance towards the initial chemotherapy regimen [5]. Yet, there are still few chemotherapy options for platinum-resistant or even refractory disease. The benefit of surgery in oligometastatic disease has yet to be defined. The emergence of molecular targeted therapies, including angiogenesis inhibitors, is promising in ROC management [6]. Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, that demonstrated substantial activity in phase II clinical trials. Particularly, it inhibits tumor growth and ascites formation interfering in the angiogenesis pathway. Further studies have suggested that bevacizumab confers a favorable clinical response with manageable toxicity [7-9]. However, other studies reported severe toxicity, mainly intestinal perforation [10]. Bevacizumab administration and toxicity management caused by this agent pose a financial burden to health services. Studies dealing with bevacizumab cost-effectiveness are therefore needed.

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Table 1. Characteristics of the studies included

Studies	*Participants N(range)*		*Age, years*		*Treatment regimens*		*Outcomes*
[Ref]	*T*	*C*	*T*	*C*	*T*	*C*	
OCEANS [14]	242	242	60 (38-87)	61 (28-86)	G+C+Bev Cycles 1-10: G 1,000 mg/m^2 on days 1 and 8; C AUC 4 mg/ml/min on day 1; Bev 15 mg/kg on day 1, q3w	G+C+PL Cycles 1-10: G 1,000 mg/m^2 on days 1 and 8; C AUC 4 mg/ml/min on day 1; PL 15 mg/kg on day 1, q3w	The median PFS was 12.4 and 8.4 months for the T and C groups, with HR 0.484 (95% CI 0.388 to 0.605;log-rank p<0.0001). The median OS for C and T groups was 35.2 and 33.3 months, respectively.
AURELIA [13]	179	182	62 (25-80)	61 (25-84)	Chemotherapy+ Bev Paclitaxel 80 mg/m^2 days 1, 8, 15, and 22 q4w; or Topotecan 4 mg/m^2 days 1,8, and 15 q4w (or 1.25 mg/m^2, days 1-5 q3w); or PLD 40 mg/m^2 day 1 q4w; Bev 15 mg/kg q3w or 10 mg/kg q2w	Chemotherapy Paclitaxel 80 mg/m^2 days 1, 8, 15, and 22 q4w; or Topotecan 4 mg/m^2 days 1,8, and 15 q4w (or 1.25 mg/m^2, days 1-5 q3w); or PLD 40 mg/m^2 day 1 q4w	The median PFS was 6.7 and 3.4 months for group T and C respectively,with HR 0.48 (95% CI 0.38 to 0.60;log-rank p<0.001).

T: treatment group, C: control group, Bev: bevacizumab,C: carboplatin,G: gemcitabine,PLD: pegylated liposomal doxorubicin, PL: placebo, PFS: progression-free survival, OS: overall survival, HR: hazard ratio, CI: confidence interval

Methods

Inclusion criteria

All patients (any race) were aged >18 years, with histologically proven ROC on the basis of the GOG criteria, and had not received any treatment after relapse.

The treatment arms included in the study comprised of bevacizumab vs conventional chemotherapy, bevacizumab+conventional chemotherapy vs conventional chemotherapy, and bevacizumab+conventional chemotherapy vs placebo+conventional chemotherapy.

The primary outcomes were PFS and quality of life (QoL), while the secondary were OS, toxicities, and adverse events.

Exclusion criteria

Patients were excluded if ROC occurred beyond second-line chemotherapy failure or bevacizumab (or other anti-angiogenesis inhibitor drugs) had been previously administered. Patients with severe circulatory system disease or with liver and kidney dysfunction were also excluded.

Search strategy

The clinical controlled trials database of the Cochrane Library (2013 No. 4), MEDLINE (1990–2013/2014), EMBASE (1990–2013/2014), Chinese Journal Full-text Database (CNKI, 1979–2013/2014), Chinese Biomedical Literature Database (CBM, 1978–2013/2014), and the VIP Chinese Science and Technology Periodicals Database (VIP, 1989–2013.4) were searched by using the English retrieval keywords "bevacizumab," "recurrent or relapsed ovarian cancer," "randomized controlled trial," and "randomized or controlled clinical trial." The Chinese keywords used were "bevacizumab," "recurrent ovarian cancer," and "randomized controlled trial" as appropriate for the database. Relevant full text articles from peer-reviewed publications were retrieved. References within these publications were also assessed. Finally, Chinese and English language literature were collected.

Data extraction and quality assessment

Two authors independently screened each article by original article title and abstract, to exclude duplicate publications and conference abstracts and literature that did not meet the inclusion criteria. Articles that potentially met the inclusion criteria were identified. The full-text of these articles was further screened to ensure they met the inclusion criteria.

Two authors independently extracted data from trials that met the inclusion criteria (Table 1). Data included title, author, country and region, basic information of the studies, baseline conditions and disease status of the patients in 2 groups, experimental design, research time and follow-up time, disease interventions in the experimental group and the control group (including the administration methods, dose, and treatment duration), primary outcomes, secondary

outcomes, the number of patients lost to follow-up and how they were statistically handled.

Quality assessment of the literature was carried out in accordance with the method in Cochrane Reviewer's Handbook 5.1 [11]. Two authors independently assessed the risk of bias in the included literature. The quality items to be assessed were randomization methods, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Any disagreements between the authors were solved through discussion or through a third researcher's opinion.

Statistics

RevMan 5.2 software provided by the Cochrane Collaboration was used for the meta-analysis. Time-related data statistically analyzed the HR using the reversed variance method at the 95% CI.

Count data were used to evaluate the efficacy using RR or odds ratio (OR) at the 95% CI. Heterogeneity was evaluated using the x2 test, and subgroup analysis was performed when possible heterogenetic factors were identified. If subgroups had no statistically significant heterogeneity ($p \geq 0.1$, $I^2 \leq 25\%$), the fixed effect model was then used to perform the meta-analysis of various studies. If statistically significant heterogeneity was identified among subgroups ($p<0.1$, $I^2>25\%$), the underlying causes of heterogeneity were analyzed and subgroup analysis of possible heterogeneity causing factors was performed. For studies with no clinical heterogeneity, but with statistical heterogeneity, the random effect model was applied for the meta-analysis, and the findings were interpreted carefully [12]. If it was impossible to find the source or the heterogeneity between the 2 groups was too large, then descriptive qualitative analysis was performed. Statistical significance was set at $p<0.05$.

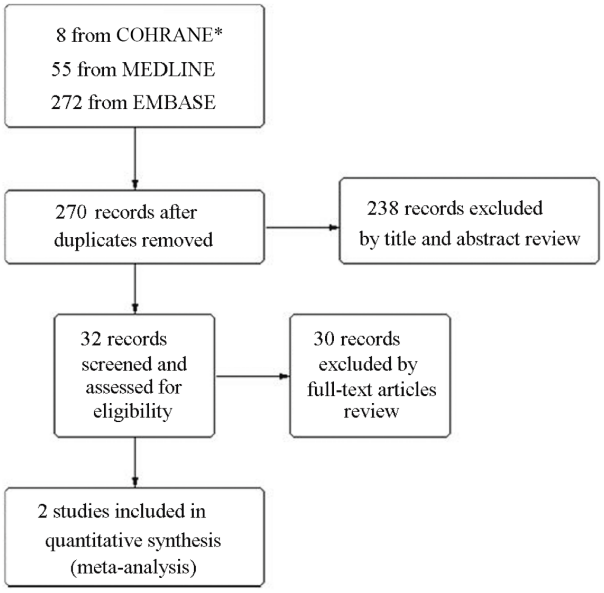


Figure 1. Flow diagram of literature search. *Cohrane Central Register of Controlled Trials

Results

Literature search results and quality evaluation

Initially, 335 articles citing the use of bevacizumab in the treatment of ROC were retrieved; no literature was identified in the CNKI, CBM, or VIP databases. Of the 335 articles, 238 were excluded because of duplicate publication, cross-literature,

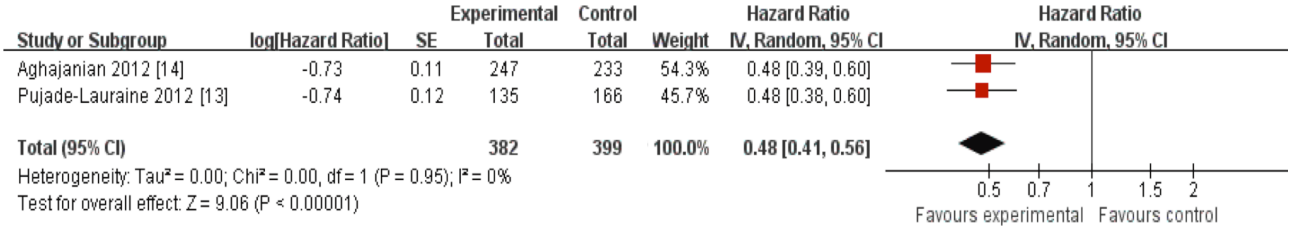


Figure 2. Comparison of progression free survival of chemotherapy+Bev with chemotherapy.

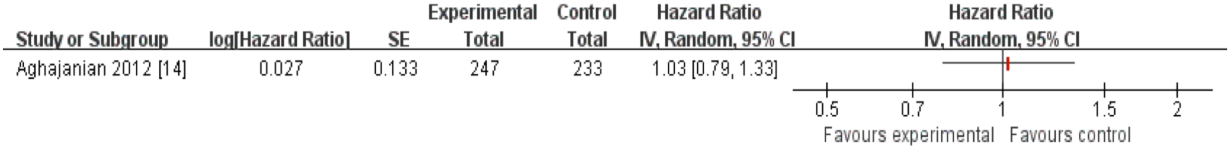
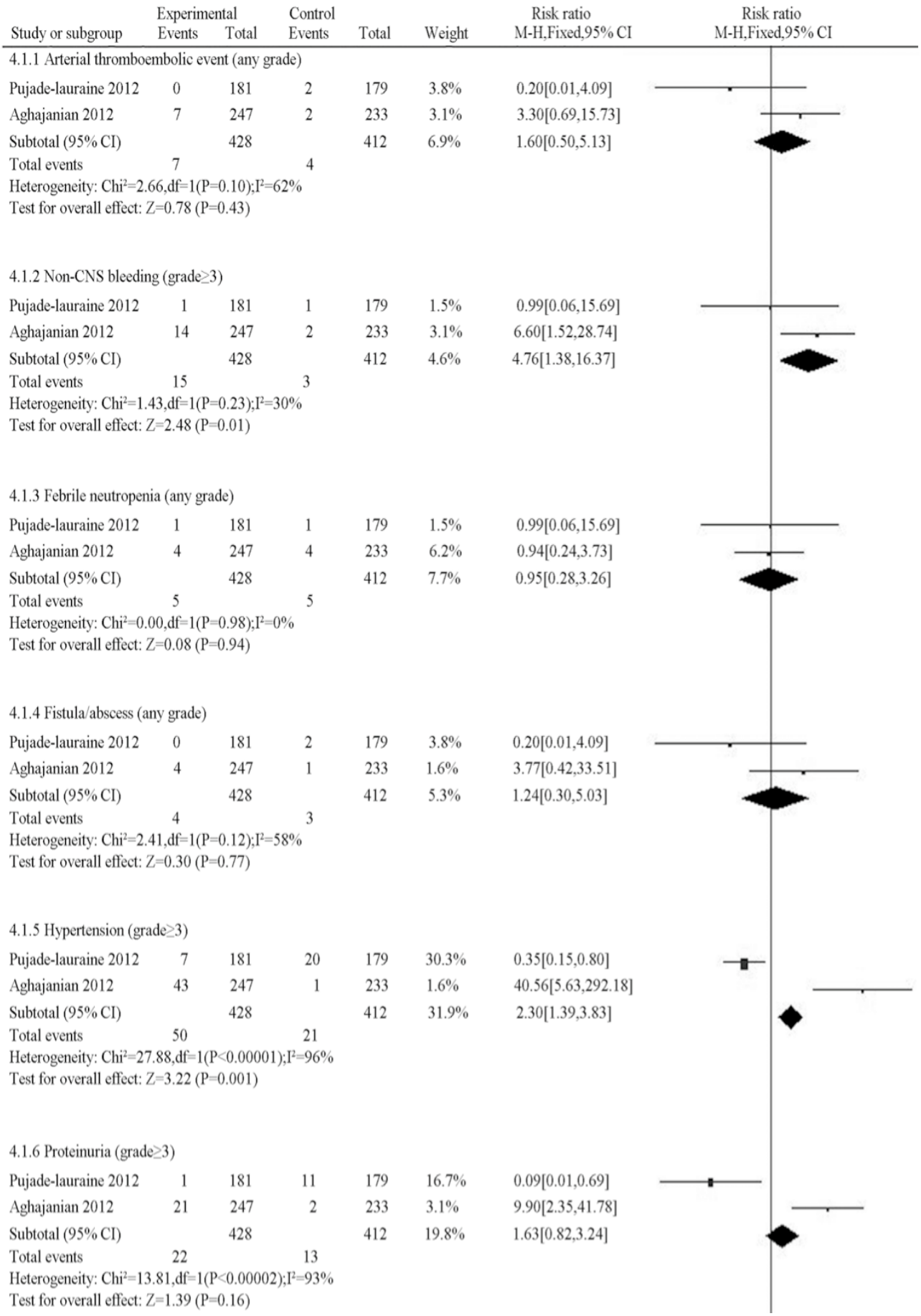


Figure 3. Comparison of overall survival of chemotherapy+Bev with chemotherapy.



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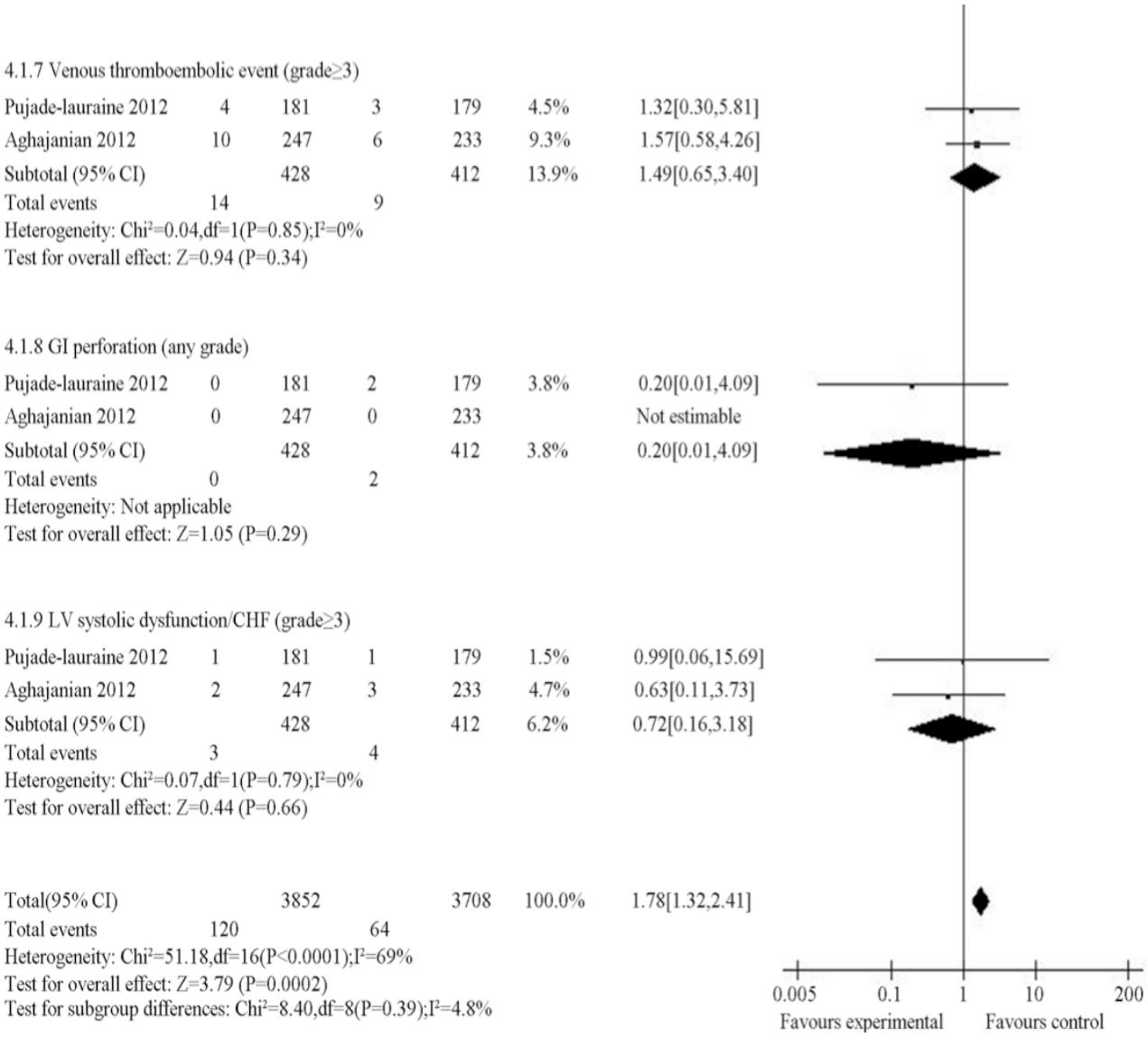

Figure 4. Comparison of adverse events of chemotherapy+Bev with chemotherapy.

and deviation of the inclusion criteria. After initial screening of the article title and the abstract, 32 possibly relevant articles remained. After reading the full-text article and rescreening, 2 RCTs comprising a total of 845 patients were included. Non-randomized clinical trials were also excluded [12,13] (Figure 1). The study sites of the 2 RCTs included were outside China, and the articles were written in English. The schemas and methodological quality assessment results of the included studies are shown in Tables 1 and 2, respectively.

Analysis of results

PFS

The OCEANS trial [14] compared the PFS of patients who received bevacizumab plus gemcitabine and carboplatin and the control group (placebo plus gemcitabine and carboplatin). The median PFS was 12.4 vs 8.4 months for the treatment and control group, respectively (HR=0.48; 95% CI 0.39–0.61; p<0.0001). The median PFS of the bevacizumab plus conventional chemotherapy group in the AURELIA study [13] was 6.7 months, while PFS was 3.4 months in the conventional chemotherapy group (pegylated liposomal doxorubicin/PLD, or topotecan/TOP, or weekly paclitaxel/PAC) (HR=0.48; 95% CI 0.38–0.60; p<0.0001). Meta-analysis of the 2 studies showed that bevacizumab significantly prolonged PFS (HR=0.48; 95% CI 0.41–0.56) (Figure 2), indicating that bevacizumab plus conventional chemotherapy was better than conventional chemotherapy alone.

Neither study assessed the QoL of the study

Table 2. Quality assessment of the studies included

Studies [Ref]	*Random sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
OCEANS [14]	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
AURELIA[13]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

subjects.

OS

Although the obtained OS data of the OCEANS study [14] have yet to mature, the OS of patients in the treatment group was not significantly different from that of patients in the control group (HR 1.03;95% CI 0.79-1.33), suggesting that the addition of bevacizumab did not prolong OS (Figure 3). Patients in the placebo arm did receive bevacizumab at subsequent relapse more frequently than in the other arm, and this could partly explain the lack of OS benefit.

In a subgroup analysis of the AURELIA study, patients treated with weekly paclitaxel had a median OS of 13 months, which was significantly increased to 22 months with the addition of bevacizumab.

Toxicities

Both studies reported a higher incidence of adverse events in the bevacizumab than the control group mainly comprised of ≥grade 3 hypertension (RR 2.30; 95% CI 1.39–3.83) and bleeding (RR 4.76; 95% CI 1.38–16.37). Other adverse reactions reported were arterial thromboembolism (of any grade), non-central nervous system bleeding (≥grade 3), neutropenia (of any grade), fistula or abscess formation (of any grade), proteinuria, venous thromboembolism (≥grade 3), heart dysfunction and intestinal perforation events (Figure 4).

Discussion

Currently, neither international uniformity concerning chemotherapy for ROC nor predictive factors of response to chemotherapy exist. Most medical oncologists administer a chemotherapy regimen for ROC according to their own principles of treatment and therapeutic experience, but efficacy has been limited [15]. Chemotherapy is therefore offered with palliative rather than curative intent in patients with ROC, with QoL being the most important factor considered. Notably, PFS and OS are extended with current therapeutic strategies. At the 2010 conference of Gynecologic Cancer InterGroup, an expert consensus on the endpoint indicators of ovarian cancer clinical trials was reached. PFS was the agreed valid endpoint indicator for platinum-sensitive ROC because it reflects tumor shrinkage and disease control in the treatment study process [16].

Molecular-targeted therapy normally targets an abrupt molecular pathway using antibodies and ligands that specifically bind to target molecules in order to block or inhibit the critical factors or kinases which drive tumor occurrence and growth. The goal is to restore cell growth and angiogenesis inhibition with high specificity and low toxicity [17]. Normally, angiogenesis only occurs during embryonic development and tissue-repair. Abnormal angiogenesis is therefore one of the central pathological changes in tumors, and it is a critical process of tumor invasion and metastasis [18]. The co-expression of VEGF and its receptors in malignant solid tumors, in combination with a paracrine/autocrine signaling, makes it an ideal target for anti-cancer therapies [19]. Bevacizumab is a recombinant humanized monoclonal antibody that competitively binds to the VEGF receptors, inhibiting the proliferation of endothelial cells and thus inhibiting angiogenesis. In various tumor models, including ovarian cancer, bevacizumab inhibits VEGF activity impeding tumor growth and metastasis [20]. The vascular structure and function of ovarian cancer is different from the normal ovarian tissue, appearing as a twisted and disordered vascular network with increased permeability and filled in with immature endothelial cells [18]. This abnormal phenomenon of structure and function makes ovarian cancer greatly dependent on VEGF [21], suggesting that the strategy of anti-VEGF targeted treatment towards ovarian cancer is feasible.

The above meta-analysis showed that, compared to conventional chemotherapy drugs alone, the addition of bevacizumab could prolong PFS indicating that bevacizumab is effective to a certain extent. However, studies showed that serious adverse reactions, primarily severe hypertension and bleeding, were more common among patients treated with bevacizumab than in those who received placebo. Other adverse reactions, such as

neutropenia and thrombosis, were not significantly different between the bevacizumab and control groups, and they were well tolerated by the patients. Therefore, additional large-scale and long-period RCTs are required to assess the safety of bevacizumab.

In addition, phase II clinical trials have confirmed that treatment with conventional chemotherapy plus bevacizumab is effective against ROC. Burger et al. [7] performed a phase II clinical trial to evaluate the efficacy and tolerability of bevacizumab alone in the treatment of refractory and recurrent epithelial ovarian cancer and primary peritoneal cancer. The study included 62 patients with a mean age of 57 years. The treatment schedule was intravenous injection of 15 mg/kg of bevacizumab every 21 days, and it was stopped when PFS reached 6 months. In this study, the median PFS was 4.7 months, and the median OS 17 months. Thirteen patients (21%) had remission of clinical symptoms; 4 patients (6.5%) experienced grade 3–4 gastrointestinal toxicity without any intestinal perforation event. Six patients (9.7%) had ≥ grade 3 hypertension. It was therefore concluded that bevacizumab was an effective, well-tolerated agent for ROC, making it a second- or third-line treatment choice for ovarian or peritoneal cancer.

A phase II clinical trial performed by Cannistra et al. [22] evaluated the efficacy and safety of bevacizumab in platinum-resistant epithelial ovarian and serous peritoneal carcinoma. The study included 44 patients with a mean age of 59.5 years. The treatment comprised intravenous injection of 15 mg/kg bevacizumab every 21 days. The median PFS and OS were 4.4 and 11 months, respectively. Remission of the clinical symptoms was observed in 7 patients (16%), while 5 patients (11%) had intestinal perforation events. These results indicated that bevacizumab had some anti-tumor activity in platinum-resistant epithelial ovarian and serous peritoneal carcinoma.

Another phase II clinical trial was performed by Garcia et al. [9], evaluating the antitumor activity and safety of bevacizumab with low-dose metronomic oral administration of cyclophosphamide. Seventy patients were included with an average age of 60 years. The study treatment comprised intravenous injection of bevacizumab (10 mg/kg, q2 weeks) and oral administration of cyclophosphamide (50 mg/d) biweekly. Clinical remission was observed in 17 patients (24%), and 56% of the patients achieved a 6-month PFS. However, 4 patients (6%) experienced intestinal perforation. The experimental results suggested that bevacizumab combined with cyclophosphamide was clinically effective in the treatment of ROC.

Owing to the failure to find "gray literature", the language limitations, and the lack of communication with authors of other studies, we did not find non-English language published or unpublished reports, leading to possible existence of a selection bias. Secondly, we only included 2 RCTs comprising 845 patients; therefore, the efficiency of the statistical tests used here might be low. The statistical strength of the evidence obtained might be poor, with possible bias; extrapolated conclusions need, therefore, to be accepted with caution. Well-designed RCTs with high methodological quality are needed to prove the efficacy and safety of bevacizumab in the treatment of ROC. Patients' QoL and cost-effectiveness parameters should also be evaluated in these studies.

In summary, bevacizumab appears to have some effect in the treatment of ROC. However, owing to the lack of sufficient high-quality evidence obtained by RCTs to support this conclusion, the efficacy of bevacizumab has not been fully elucidated. Additional large, high-quality multi-center RCTs, with strict adherence to allocation concealment and blinding and long term follow-up are needed to fully evaluate the efficacy of bevacizumab in ROC.

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