Original Article

Bevacizumab combined with platinum-based chemotherapy in primary or relapsed ovarian cancer patients: Meta-analysis and literature to review

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Abstract

Introduction: Earlier, patients with advanced ovarian cancer were treated with a combination of cytoreductive surgery and platinum-based chemotherapy, which had significant outcomes in the past until an increase in relapse and resistance to treatment, which led to the use or development of bevacizumab (a vascular endothelial growth factor inhibitor) in the treatment of primary or relapsed ovarian cancer. **Method and Methodology:** This study includes five-phase three randomized controlled clinical trials designed to study the impact of bevacizumab in combination with platinum-based chemotherapy compared with platinum-based chemotherapy alone. **Results:** This study demonstrated significant improvement in the progression-free span but no improvement in overall survival in the treatment group when compared with the control group. Also, adverse effects reported with combination therapy were tolerable and easily manageable by decreasing the infusion rate or by decreasing the frequency of infusion.

Keywords: Bevacizumab, chemotherapy, meta-analysis, ovarian cancer, platinum based

Introduction

Epithelial ovarian cancer leads to 15,000 deaths in the United States annually,[1] making it the fifth leading cause of cancer death in females. It has the highest mortality rates among all the gynecological cancers.[2] Considering the biology of the disease, most of the patients are usually diagnosed at an advanced stage.[3] Previously, patients with advanced ovarian cancer were treated with cytoreductive surgery in combination with platinum-based chemotherapy. This regimen showed a good initial response, but most of the patients receiving the treatment usually relapsed which led to the trials of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, in the treatment of primary or relapsed ovarian tumor.[4-6] VEGF and angiogenesis are significant promotors of ovarian cancer progression; hence, VEGF inhibitors were considered in the treatment of primary and relapsed ovarian cancer patients.[7,8]

Materials and Methods

This meta-analysis was conducted according to Cochrane Collaboration guidelines and reported as per Preferred Reporting

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Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The findings are summarized in the PRISMA flow chart. Three authors (MM, MZ, and ET) performed a systematic literature search using databases such as MEDLINE (via PubMed), Embase, and Cochrane Library using the medical search terms and their respective entry words with the following search strategy: "bevacizumab, platinum-based, chemotherapy, primary, relapsed, ovarian cancer and literature". Additionally, unpublished trials were identified from the clinicaltrials.gov website and references of all pertinent articles were also scrutinized to ensure the inclusion of all relevant studies. The search was completed on November 1, 2021, and we only included studies available in English. Four authors (MM, MZ, ET, and PM) independently screened the search results in a two-step process based on predetermined inclusion/exclusion criteria. First 756 articles were evaluated for relevance on the title and abstract level, followed by a full-text screening of the final list of 200 articles. Any disagreements were resolved by discussion or a third-party review, and a total of five articles were included in the study. The following eligibility criteria were used: original articles reporting the efficacy of bevacizumab with platinum-based chemotherapy in the treatment of primary and relapsed ovarian cancer as compared to control groups receiving platinum-based chemotherapy. All articles emphasizing the importance of bevacizumab with platinum-based chemotherapy in the treatment of primary or relapsed ovarian cancer were included in the study. Only five articles met the selection criteria for eligibility. All qualifying studies were nationwide inpatient or pooled clinical trial data. The reasons for the exclusion of the other 55 articles were irrelevant ($n = 25$), duplicate ($n = 16$), reviews ($n = 7$), and poor data reporting ($n = 7$). Out of the five included studies, all five studies showed improvement in progression-free survival with combination therapy when compared with control. Three studies supported improvement in overall survival with combination therapy, while two studied favored overall survival with only platinum-based control therapy. Four studies showed a correlation between adverse effects including hypertension, proteinuria, arterial and venous thromboembolism, wound healing complications, posterior reversible leukoencephalopathy syndrome (PRES), and Gastrointestinal (GI) events, while three studies showed a correlation between adverse effects including neutropenia, bleeding, and congestive heart failure.

The primary endpoint was progression-free survival at 12 months, while secondary endpoints include overall survival and adverse effects including hypertension, proteinuria, arterial and venous thromboembolism, wound healing complications, PRES, congestive heart failure, neutropenia, bleeding, and GI events. Data on baseline characteristics and clinical outcomes were then extracted and summary tables were created. Summary estimates of the clinical endpoints were then calculated with risk ratio (RR) and 95% confidence intervals using the random-effects model. Heterogeneity between studies was examined with the Cochran's Q-based I2 statistic, which can be defined as low (25% to 50%), moderate (50% to 75%), or high (>75%). Statistical analysis was performed using Comprehensive Meta-analysis software (CMA version 3.0, Bio stat Inc).

Results

A total of 5 studies including 4648 patients (2641 in combined bevacizumab and platinum-based chemotherapy treatment group, while 2007 patients in sole platinum-based chemotherapy control group) were included in the study. All five studies included were randomized control phase-3 clinical trials conducted to observe the efficacy of bevacizumab when combined with platinum-based chemotherapy in patients with primary and relapsed ovarian cancer. The mean age was 63 years in both treatment and control groups. Further details on study and participant characteristics, primary and secondary outcomes, and adverse effects are summarized in Tables 1-3, respectively. No evidence of publication bias was found [PRISMA flow chart].

The primary outcome of progression-free survival at 12 months was witnessed in 33.4% of patients included in the treatment group as compared to 22.9% observed in the control group. There was a significant difference in favor of the treatment as compared to the control group [RR = 1.56 (95% CI: 1.09 to 2.24; $P = 0.020$)] [Table 2 and Figure 1].

The secondary outcome of overall survival at 12 months was observed in 76.7% of patients in the treatment group as compared to 73.02% observed in the control group. There was no significant difference witnessed in the treatment group as compared to the control group [RR = 1.04 (95% CI: 0.96 to 1.12; $P = 0.34$)] [Table 2 and Figure 2].

| Table 1: Study characteristics including in our meta-analysis						
Study	Trial name	Publication year	Design	Country	Treatment group	Control group
Lauraine *et al.*	Aurelia trial	2014	Phase 3 randomized control trial	China, USA, and Europe	Bevacizumab with platinum-based chemotherapy	Platinum-based chemotherapy
Aghajanian *et al.*	Oceans trial	2015	Phase 3 randomized control trial	USA, Japan, Korea	Bevacizumab with platinum-based chemotherapy	Platinum-based chemotherapy
Burger *et al.*	GOG-0218 trial	2011	Phase 3 randomized control trial	China, USA, and Europe	Bevacizumab with platinum-based chemotherapy	Platinum-based chemotherapy
Perren *et al.*	ICON-7 trial	2011	Phase 3 randomized control trial	USA	Bevacizumab with platinum-based chemotherapy	Platinum-based chemotherapy
Pignata *et al.*	MITO16b/ MANGO–OV2/trial	2021	Phase 3 randomized control trial	Italy, Germany, France, and USA	Bevacizumab with platinum-based chemotherapy	Platinum-based chemotherapy

Table 2: Primary and secondary outcomes including in our meta-analysis

Study	Trial name	Treatment/Control group	Progression-free span (PFS) at 12 months	Overall survival in 12 months
Lauraine *et al.*	Aurelia trial	Treatment group	18 (10.5%)	106 (59.3%)
		Control group	8 (4.5%)	98 (54%)
Aghajanian *et al.*	Oceans trial	Treatment group	-	226 (91.5%)
		Control group	-	222 (95.3%)
Burger *et al.*	GOG-0218 trial	Treatment group	473 (38%)	869 (69.6%)
		Control group	199 (32%)	442 (70.7%)
Perren *et al.*	ICON-7 trial	Treatment group	585 (77%)	678 (88.7%)
		Control group	464 (61%)	652 (85%)
Pignata *et al.*	MITO16b/ MANGO–OV2/trial	Treatment group	83 (41%)	151 (74.4%)
		Control group	35 (17%)	122 (60.1%)
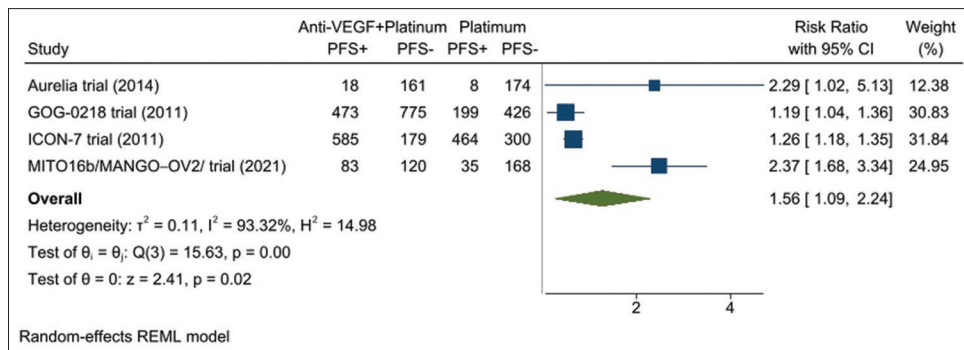
Figure 1: Progression-free span. The risk ratio above 1 indicates higher PFS event rates in the anti-VEGF + Platinum group compared to the Platinum group
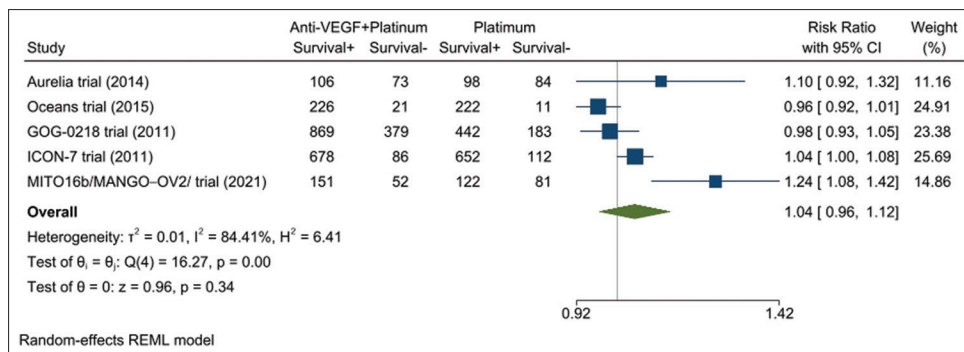
Figure 2: Overall survival. The risk ratio above 1 indicates higher survival rates in the anti-VEGF + Platinum group compared to the Platinum group

In total, 33% of patients in the treatment group receiving bevacizumab with platinum-based chemotherapy developed hypertension as compared to only 21.68% of patients in the control group receiving platinum-based chemotherapy. Overall RR of 2.77 with confidence interval of 95% was noted, which was statistically significant confirming higher hypertensive events in patients receiving bevacizumab along with platinum-based chemotherapy when compared with the control [Table 3 and Figure 3].

In total, 12.6% of patients in the treatment group developed proteinuria as compared to 1.48% in the control group receiving platinum-based chemotherapy. An overall RR of 5.44 with the confidence interval of 95% was noted which was statistically significant confirming higher proteinuria incidence in patients receiving combination treatment therapy [Table 3 and Figure 4].

In total, 4.26% of patients in the treatment group receiving bevacizumab with platinum-based chemotherapy developed arterial and venous thromboembolism as compared to 3.28% of patients in the control group receiving platinum-based chemotherapy. An overall RR of 1.20 with the confidence interval of 95% was noted, which was statistically significant confirming a higher incidence of arterial and venous thromboembolism in patients receiving combination therapy as compared to the control [Table 3 and Figure 5].

In total, 2.2% of patients in bevacizumab with the platinum-based chemotherapy treatment group developed wound healing complications as compared to 1.2% of patients in the control group receiving platinum-based chemotherapy. An overall RR of 1.42 with the confidence interval of 95% was noted, which was

Table 3: Adverse effects included in our meta-analysis

| Study	Trial name	Treatment/Control group	HTN*	Proteinuria	AVTE*	WHD*	PRES*	CHF*	GI events*	Neutropenia	Bleeding
Lauraine *et al.*	Aurelia trial	Treatment group	13 (7%)	3 (1.7%)	9 (5%)	0 (0%)	1 (0.5%)	1 (0.6%)	15 (8.4%)	-	2 (1.1%)
		Control group	2 (1.1%)	0 (0%)	8 (4.4%)	0 (0%)	0 (0%)	1 (0.5%)	2 (1.1%)	-	2 (1.0%)
Aghajanian *et al.*	Oceans trial	Treatment group	104 (42%)	49 (20%)	17 (6.8%)	2 (0.8%)	2 (0.8%)	2 (0.8%)	18 (7.3%)	52 (21%)	16 (6.5%)
		Control group	20 (8.5%)	8 (3.4%)	7 (3%)	0 (0%)	0 (0%)	2 (0.7%)	3 (1.3%)	51 (22%)	4 (1.7%)
Burger *et al.*	GOG-0218 trial	Treatment group	239 (19%)	14 (1.1%)	81 (6.5%)	40 (3.2%)	2 (0.2%)	-	33 (2.6%)	769 (62%)	23 (1.8%)
		Control group	43 (6.8%)	4 (0.6%)	40 (6.5%)	17 (2.7%)	0 (0%)	-	7 (1.1%)	347 (55%)	5 (0.8%)
Perren *et al.*	ICON-7 trial	Treatment group	-	-	-	-	-	-	-	-	-
		Control group	-	-	-	-	-	-	-	-	-
Pignata *et al.*	MITO16b/MANGO–OV2/trial	Treatment group	197 (97%)	82 (40.4%)	6 (3%)	14 (7%)	0 (0%)	2 (1%)	168 (82.7%)	147 (72%)	-
		Control group	186 (92%)	7 (3.4%)	5 (2.5%)	7 (3.5%)	0 (0%)	1 (0.5%)	92 (45%)	130 (64%)	-

*HTN=Hypertension, AVTE=Arterial and venous thromboembolism, WHD=Wound healing complications, PRES=Posterior reversible leukoencephalopathy syndrome, CHF=Congestive Heart Failure, GI events=including perforation, obstruction, and fistula formation
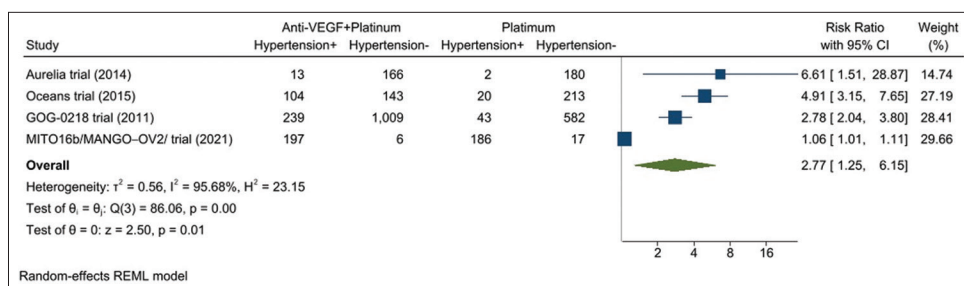
Figure 3: Hypertension. The risk ratio above 1 indicates higher hypertension event rates in the anti-VEGF + Platinum group compared to the Platinum group
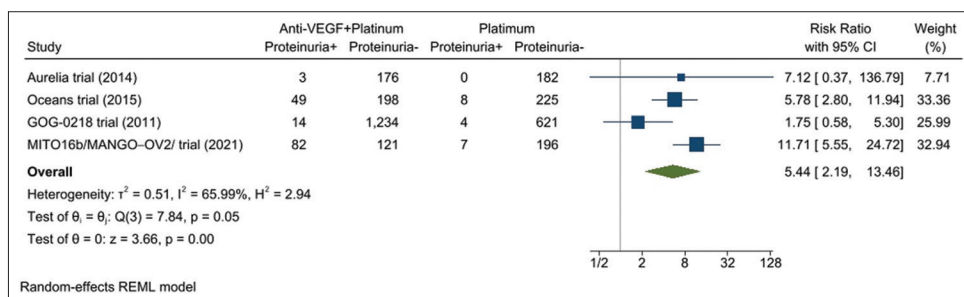
Figure 4: Proteinuria. The risk ratio above 1 indicates higher proteinuria event rates in the anti-VEGF + Platinum group compared to the Platinum group
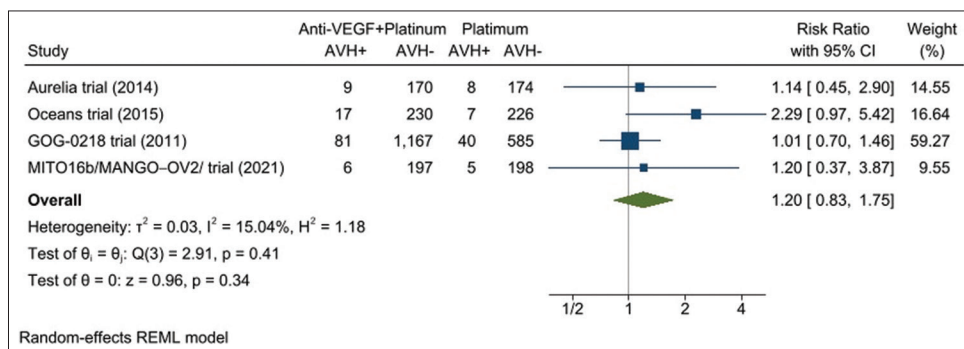
Figure 5: Arterial and venous thromboembolism. The risk ratio above 1 indicates higher Arterial and Venous thromboembolism (AVH) event rates in the anti-VEGF + Platinum group compared to the Platinum group

statistically significant confirming a higher incidence of wound healing complications in patients receiving combination therapy as compared to their control [Table 3 and Figure 6].

In total, 0.3% of patients in the treatment group receiving bevacizumab with platinum-based chemotherapy developed PRES as compared to no cases reported with platinum-based

chemotherapy. An overall RR of 3.31 with a confidence interval of 95% was noted, which was statistically significant confirming a higher incidence of reversible posterior leukoencephalopathy syndrome in the treatment group as compared to the control [Table 3 and Figure 7].

In total, 0.48% of patients in the treatment group receiving bevacizumab with platinum-based chemotherapy developed congestive heart failure as compared to 0.34% of patients in the control group receiving platinum-based chemotherapy. An overall RR of 1.21 with a confidence interval of 95% was noted, which was statistically significant confirming a comparatively higher incidence of congestive heart failure in the treatment group as compared to the control group [Table 3 and Figure 8].

In total, 20.2% of patients in bevacizumab with the platinum-based chemotherapy treatment group developed GI events including
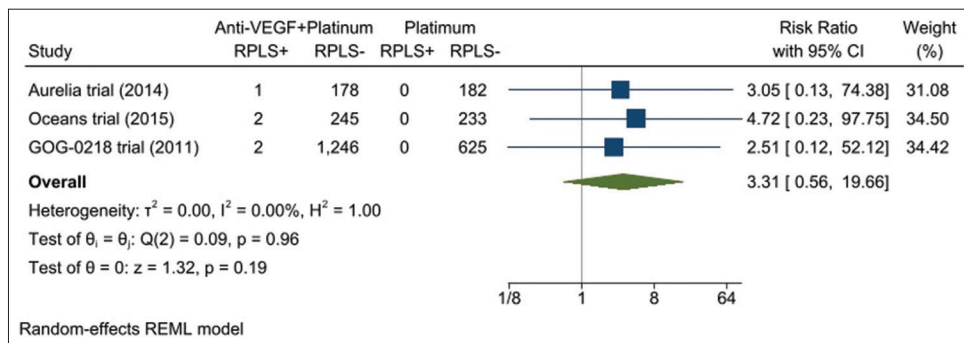
gastritis, fistula, or perforation as compared to 9.7% of patients in the control group receiving platinum-based chemotherapy. An overall RR of 2.85 with a confidence interval of 95% was noted, which was statistically significant confirming higher GI events including fistula, gastritis, or perforation in treatment as compared to the control group [Table 3 and Figure 9].

In total, 31% of patients in bevacizumab with the platinum-based chemotherapy treatment group developed neutropenia as compared to 28.2% of patients in the control group receiving platinum-based chemotherapy. An overall RR of 1.1 with a confidence interval of 95% was noted, which was statistically significant confirming higher neutropenia events reported in patients in the treatment group as compared to the control [Table 3 and Figure 10].

In total, 1.88% of patients in the treatment group receiving a combination of bevacizumab with platinum-based chemotherapy
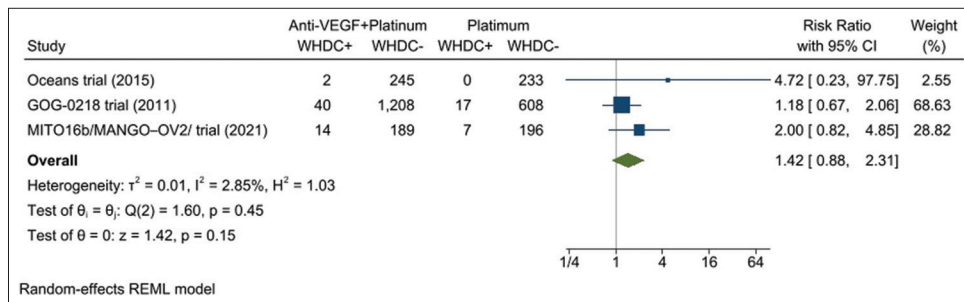
Figure 6: Wound healing disruption/complications. The risk ratio above 1 indicates higher Wound healing disruption/complications (WHDC) event rates in the anti-VEGF + Platinum group compared to the Platinum group

Figure 7: Reversible posterior leuco-encephalopathy syndrome. The risk ratio above 1 indicates higher Reversible posterior leuco-encephalopathy syndrome (RPLS) event rates in the anti-VEGF + Platinum group compared to the Platinum group
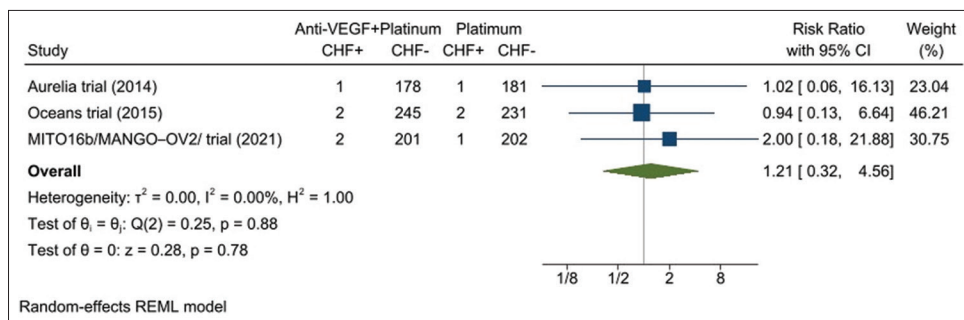
Figure 8: Congestive heart failure. The risk ratio above 1 indicates higher CHF event rates in the anti-VEGF + Platinum group compared to the Platinum group

developed bleeding as compared to 0.7% of patients in the control group receiving platinum-based chemotherapy. An overall RR of 2.53 with a confidence interval of 95% was noted, which was statistically significant confirming higher bleeding rates in patients receiving combination therapy as compared to the control [Table 3 and Figure 11].

Discussion

It is well known that angiogenesis is key to solid tumor growth. VEGF is an angiogenetic factor known to promote the progression of different cancers including ovarian cancer. Antiangiogenetic drugs like bevacizumab, an anti-VEGF monoclonal antibody, has been studied in the treatment of diverse cancer types.[9] Bevacizumab is approved in different settings in the treatment of metastatic colorectal cancer, renal cell carcinoma, glioblastoma, nonsmall cell lung cancer, and metastatic hepatocellular cancer. In ovarian cancer, VEGF

blockade have been found to inhibit tumor growth and malignant ascites formation[10,11] This has led to several studies including the use of bevacizumab in ovarian cancer.

In this meta-analysis, we pooled the results from five phase III randomized controlled clinical trials studying the efficacy of a combination of bevacizumab and platinum-based chemotherapy agents in primary and relapsed ovarian cancer. We used efficacy data available from phase III trials of bevacizumab in advanced ovarian cancer: GOG-0218, ICON7, OCEANS, AURELIA, and MITO161B/MANGO-OV2.[12-16] Bevacizumab was included in the front-line treatment of ovarian cancer patients in GOG-0218[12] and ICON7[13] trials. OCEANS, AURELIA, and MITO16B/MANGO-OV2 all studied the use of bevacizumab in patients with recurrent ovarian cancer. To our knowledge, this study includes the largest pool of patients evaluating the use of bevacizumab in primary and relapsed ovarian cancer.
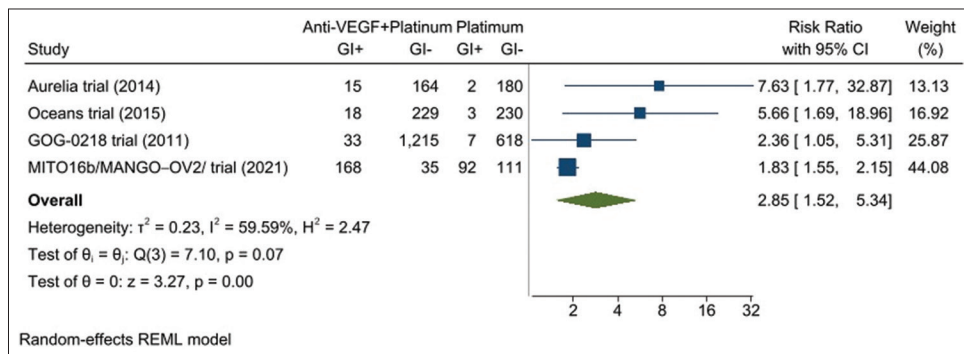
Figure 9: GI events including fistula, perforations. The risk ratio above 1 indicates higher GI event rates in the anti-VEGF + Platinum group compared to the Platinum group
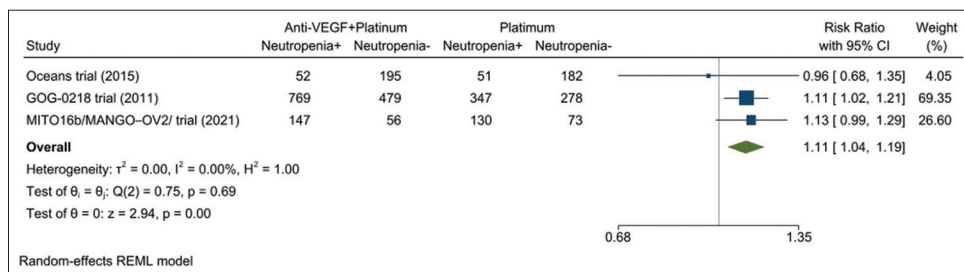
Figure 10: Neutropenia. The risk ratio above 1 indicates higher neutropenia event rates in the anti-VEGF + Platinum group compared to the Platinum group
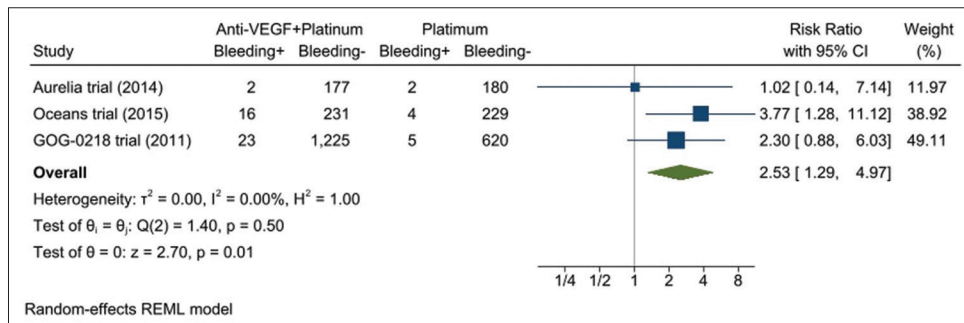
Figure 11: Bleeding. The risk ratio above 1 indicates higher bleeding event rates in the anti-VEGF + Platinum group compared to the Platinum group

PRISMA flow chart

Identification

Records identified from a total of 756 articles → Records removed *before screening:* N = 556

Screening

Records screened (*n* = 200) → Records excluded (*n* = 0)

Reports sought for retrieval (*n* = 60) → Reports not retrieved (*n* = 140)

Reports assessed for eligibility (*n* = 60) → Reports excluded: Irrelevant (*n* = 25), Duplicate (*n* =16), Reviews (*n* = 7), Poor data reporting (*n* = 7)

Studies included in review (*n* = 5) Reports of included studies (*n* = 5)

PRISMA flow chart

Results from our meta-analysis confirm that the addition of bevacizumab to platinum-based chemotherapy regimens provides meaningful benefits for women with primary and relapsed ovarian cancer in terms of progression-free survival at 12 months. PFS at 12 months was noted in 33.4% of patients in the combination group compared to 22.9% in the control group. This was a statistically significant difference in favor of the treatment group [RR = 1.56 (95% CI: 1.09 to 2.24; $P = 0.020$)]. Substantial benefit in terms of progression-free survival has also been proven in other cancers with the use of bevacizumab. Bevacizumab has shown improvement in PFS in patients with metastatic breast cancer as well when compared with the platinum-based chemotherapy group.[17]

In our study, no statistically significant improvement in overall survival at 12 months was seen in the bevacizumab group. The detection of differences in overall survival was affected in some of the included studies. For example, in the GOG-0218 trial, the potential to detect a difference in survival was limited by a lack of control for multiple subsequent regimens, including crossover to bevacizumab or other anti-VEGF drugs.[12] Overall survival difference was not detected in the AURELIA study as a crossover to bevacizumab was allowed from the control group and 40% of patients were initially assigned to the control group. Patients in the standard chemotherapy alone group also received bevacizumab at the time of progression.[15] In the ICON7 study, while there was no difference in overall survival reported between both groups but in the subgroup of patients at high risk for progression, overall survival was 36.6 months in the bevacizumab group when compared with 28.8 months in the control group.[13]

The lack of overall survival in our study contrasts with evidence supporting the use of bevacizumab in metastatic, persistent, and recurrent cervical carcinoma. In the GOG 240 trial, a statistically significant improvement in Overall Survival (OS) was found in patients who received combination therapy compared to the control group (median, 16.8 versus 13.3 months, respectively; hazard ratio0.77, 98% CI 0.62–0.95).[18]

An issue previously unaddressed by prior studies is the activity of bevacizumab in ovarian cancer patients whose disease reoccurred after first-line bevacizumab-containing therapy. This has been well described in other cancers. For instance, in metastatic colorectal cancer, improved OS was noted in patients who had received first-line bevacizumab-containing regimens.[19] This meta-analysis is unique in that it includes results from MITO16B/MANGO-OV2, which studied patients with platinum-sensitive recurrent ovarian cancer already treated with bevacizumab during the first-line therapy. Results from MITO16B/MANGO-OV2 support the use of bevacizumab in patients with platinum-sensitive recurrent ovarian cancer already treated with bevacizumab during first-line therapy.[16]

Our meta-analysis adds to robust evidence demonstrating the PFS benefit of the addition of bevacizumab and chemotherapy in primary or recurrent ovarian cancer. However, we also studied adverse effects associated with the use of bevacizumab in these settings. Hypertension, proteinuria, arterial and venous thromboembolism, bleeding, and wound healing complications were more frequent in the treatment group when compared to the control group. Gastrointestinal events like gastritis, fistula, or perforation occurred at a higher rate in patients in the bevacizumab group. Of note, AURELIA trial was designed to reduce the risk of GI perforations by excluding patients with clinical symptoms of bowel obstruction, evidence of rectosigmoid involvement, or bowel involvement on computer tomography.[15] PRES syndrome, though a rare adverse event, only occurred in the patients receiving bevacizumab during their treatment course.

There are some limitations in this meta-analysis. There was some heterogeneity between the five randomized controlled trials included in this study. AURELIA and MANGO/MITOV were open-label studies with potential bias since PFS was determined by investigators.[15,16] In addition, some of the studies included in our meta-analysis did not provide data on quality of life. As a result, we are unable to report on the quality of life in patients who received bevacizumab.

In conclusion, our study supports the use of bevacizumab in addition to platinum-based chemotherapy in primary or relapsed ovarian cancer. Significant improvement in PFS was seen with the use of bevacizumab. However, overall survival benefit was not noted, and bevacizumab significantly increased the occurrence of adverse events which can be prevented by reducing the frequency of bevacizumab infusions. This study will have an impact on our reader in a way that if any patient with epithelial ovarian cancer whether primary or relapsed comes to the office or gets admitted to the hospital, instead of treating them with conventional treatment, a combination of VEGF inhibitor with

platinum-based chemotherapy should be used to treat epithelial ovarian cancer in order to prevent its relapse with minimal occurrence of manageable adverse effects.

Disclosure and declaration statement

There were no human, and animal subjects included in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There were no financial or nonfinancial conflicts noticed or witnessed among all the authors of the submitted projects.

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