Comparative efficacy and safety of low-dose vs. high-dose bevacizumab in ovarian cancer: a systematic literature review and indirect treatment comparison

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Introduction

- Bevacizumab (BEV) is widely used in treating solid tumor malignancies, but there is limited evidence directly comparing different doses, particularly in ovarian cancer.
- The ICON7 trial[1] investigated low-dose (7.5 mg/kg every three weeks [Q3W]) BEV with carboplatin and paclitaxel versus carboplatin and paclitaxel alone, whereas the GOG 0218 trial[2] studied high-dose (15 mg/kg Q3W) BEV in the same comparison.
- In Canada, low-dose BEV is funded in the front-line setting in all provinces except Prince Edward Island and Québec.[3-5]

Objective

This study indirectly compared the efficacy and safety of low-dose vs. high-dose BEV in ovarian cancer using available clinical trial data.

Methods

Systematic Literature Review

- A systematic literature review (SLR) was conducted searching Embase, MEDLINE®, and CENTRAL up to September 18, 2023.
- Randomized controlled trials (RCTs) evaluating BEV against any therapy or control in adults with fallopian tube, primary peritoneal, or ovarian cancer were included.
- Outcomes of interest were survival, response, and safety outcomes.

Indirect Treatment Comparison

- A comprehensive feasibility assessment was conducted before performing the indirect treatment comparison (ITC) to evaluate the feasibility of a quantitative analysis.[6]
- The feasibility assessment identified heterogeneities across trials in treatment (e.g., number of treatment cycles, line of treatment, maintenance therapy) and disease characteristics (e.g., disease stage, ovarian cancer type).
- A total of 13 analyses were completed. The primary analysis included all six trials. To address heterogeneities, sensitivity analyses were conducted to validate the reliability of the primary analysis, and subgroup analyses were performed to examine treatment effects based on cancer stage.
- ITCs were conducted using the Bucher method, which is suitable for a "simple star" network involving three treatment nodes.[7]
- For direct comparisons with multiple studies or subpopulations, random-effects (RE) pairwise meta-analysis was used to combine estimates into a single relative treatment effect.
- Risk ratios (RRs) were calculated for binary outcomes, and hazard ratios (HRs) were calculated for survival outcomes. For presentation, log-transformed RRs and HRs with their 95% confidence intervals were back-transformed using the exponential function.
- All analyses were conducted using the 'metafor' package in R version 4.3.1,[8] employing RE models with restricted maximum likelihood estimators for tau.
- Statistical significance was evaluated using a 5% type I error rate, and the null hypothesis of equality between treatments was tested in each analysis.

Results

Study Selection

- The SLR search identified a total of 3,938 records. Following study selection, 126 publications representing 28 unique RCTs were included in the SLR (**Figure 1**).
- Finally, based on network connectivity through a common comparator, six RCTs were eligible to be included in the ITC (**Figure 2**).

Results (continued)

Figure 1: Study selection process.

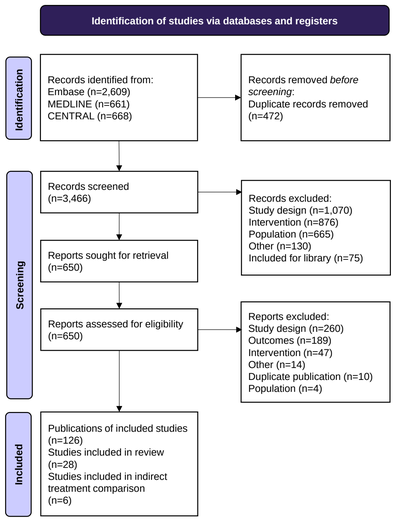
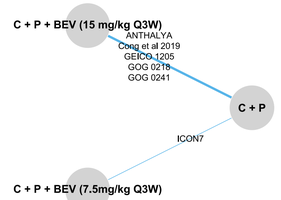


Figure 2: Global network of included studies.



BEV, bevacizumab, C, carboplatin, P, paclitaxel, Q3W, every 3 weeks. Note: In GOG 0218 the comparator arm was carboplatin + paclitaxel + placebo.

Study Characteristics

- The ITC included six RCTs (sample size: 24-1,528 patients). Five trials evaluated high-dose BEV and one evaluated low-dose BEV, all in combination with carboplatin + paclitaxel. The common comparator across trials was carboplatin + paclitaxel alone (n=5) or with placebo (n=1; GOG 0218) (**Table 1**).
- Trials mainly included stage III (n=4) or stage II-III (n=1) ovarian cancer patients, though one trial did not report cancer stage.
- Variations were noted in treatment duration, line of treatment, disease stage, and histologic subtype.

Table 1: Study characteristics of included studies

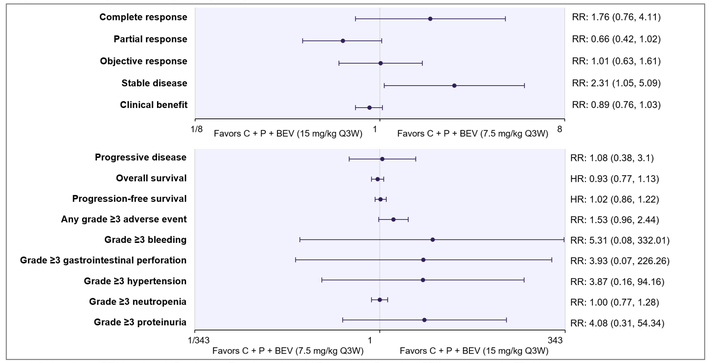
Trial	Phase	Blinding	Country	Setting	Sample Size	Intervention	Comparator	Line of Treatment	Disease Stage (%)	Histology (%)
ANTHALYA[9]	II	Open-label	France	Multi-center	95	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel (post-operative: + BEV)	1L	IIIC: 69.5% IV: 30.5%	Serous: 95.2% Other: 3.1% Endometrioid: 0.9% Serous/Endometrioid: 0.9%
Cong 2019[10]	NR	NR	China	Single center	164	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel	≥2L	NR	NR
GEICO 1205[11]	II	Open-label	Spain	Multi-center	68	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel (post-operative: + BEV)	1L	IIIC: 66.2% IV: 33.8%	Serous: 78.0% Adenocarcinoma: 17.6% Endometrioid: 4.5%
GOG 0218[2]	III	Double-blind	Multi-national	Multi-center	1,248	High-dose BEV + carboplatin + paclitaxel + placebo	Carboplatin + paclitaxel + placebo	1L	III: 74.3% IV: 25.7%	Serous: 84.8% Other: 8.7% Clear cell: 2.8% Endometrioid: 2.8% Mucinous: 0.9%
GOG 0241[12]	III	Open-label	Multi-national	Multi-center	24	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel	1L	Recurrence after stage I: 12.3% II: 33.6% III: 45.9% IV: 8.4%	Mucinous (unconfirmed): 59.4% Mucinous (confirmed): 40.6%
ICON7[1]	III	Open-label	Multi-national	Multi-center	1,528	Low-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel	1L	I/IIA: 9.3% II: 9.2% III: 2.1% IIIA: 3.6% IIIB: 5.9% IIIC: 56.9% IV: 13.2%	Serous: 69.0% Clear cell: 8.4% Endometrioid: 7.7% Other: 7.1% Mixed: 5.8% Mucinous: 2.3%

1L, first line; 2L, second line; BEV, bevacizumab; NR, not reported.

Primary Analyses

- Primary analyses showed no significant differences between low-dose vs. high-dose BEV for partial response (risk ratio [RR] [95% confidence interval]: 0.66 [0.42, 1.02]), complete response (RR: 1.76 [0.76, 4.11]), objective response rate (RR: 1.01 [0.63, 1.61]), progressive disease (RR: 1.08 [0.38, 3.10]), clinical benefit (RR: 0.89 [0.76, 1.03]), overall survival (hazard ratio [HR]: 0.93 [0.77, 1.13]), progression-free survival (HR: 1.02 [0.86, 1.22]), any grade ≥3 adverse event (RR: 1.53 [0.96, 2.44]), or specific grade ≥3 adverse events (**Table 2**).
- However, a significant difference was found for stable disease, with higher rates for low-dose BEV compared to high-dose BEV (RR: 2.31 [1.05, 5.09]).

Figure 2: Forest plots of the primary analysis results.



*, statistical significance; BEV, bevacizumab; C, carboplatin; CI, confidence interval; HR, hazard ratio; P, paclitaxel; Q3W, every three weeks; RR, risk ratio.
Note: Clinical benefit was a composite outcome of complete response, partial response, and stable disease.
Note: Objective response was a composite outcome of complete response and partial response.

Sensitivity and Subgroup Analyses

- Sensitivity (**Table 3**) and subgroup analyses (results not shown) confirmed the findings from the primary analyses.
- The only significant difference was found for stable disease, with higher rates for low-dose BEV, in a sensitivity analysis adjusted for histology (RR: 2.38 [1.06, 5.34]).

Table 3: Summary table of the sensitivity analysis results

Outcome	Estimate (95% CI)						
	Sensitivity analysis 1†		Sensitivity analysis 2‡	Sensitivity analysis 3§		Sensitivity analysis 4¶	
	A	B		A	B	A	B
Complete response	RR: 2.39 (0.17, 34.11)	Equivalent to sensitivity analysis 1A	-	RR: 1.74 (0.74, 4.09)	Equivalent to sensitivity analysis 3A	Equivalent to primary analysis A	Equivalent to primary analysis A
Partial response	RR: 0.47 (0.05, 4.24)	Equivalent to sensitivity analysis 1A	-	RR: 0.66 (0.43, 1.04)	Equivalent to sensitivity analysis 3A	Equivalent to primary analysis A	Equivalent to primary analysis A
Stable disease	RR: 1.54 (0.07, 33.11)	Equivalent to sensitivity analysis 1A	-	RR: *2.38 (1.06, 5.34)	Equivalent to sensitivity analysis 3A	Equivalent to primary analysis A	Equivalent to primary analysis A
Progressive disease	-	-	-	Equivalent to primary analysis A	Equivalent to primary analysis A	Equivalent to primary analysis A	Equivalent to primary analysis A
Clinical benefit	RR: 0.80 (0.23, 2.83)	Equivalent to sensitivity analysis 1A	-	RR: 0.89 (0.76, 1.03)	Equivalent to sensitivity analysis 3A	Equivalent to primary analysis A	Equivalent to primary analysis A
Objective response	RR: 0.76 (0.17, 3.39)	Equivalent to sensitivity analysis 1A	RR: 1.35 (0.95, 1.91)	RR: 1.04 (0.61, 1.76)	Equivalent to sensitivity analysis 3A	RR: 0.81 (0.59, 1.10)	Equivalent to sensitivity analysis 4A
OS hazard ratio	-	Equivalent to primary analysis B	-	-	Equivalent to primary analysis B	-	Equivalent to primary analysis B
PFS hazard ratio	-	Equivalent to primary analysis B	-	-	Equivalent to primary analysis B	-	Equivalent to primary analysis B
Any grade ≥3 adverse event	RR: 1.34 (0.67, 2.69)	Equivalent to sensitivity analysis 1A	RR: 1.66 (0.80, 3.43)	Equivalent to sensitivity analysis 2	Equivalent to sensitivity analysis 2	Equivalent to sensitivity analysis 1A	Equivalent to sensitivity analysis 1A
Grade ≥3 bleeding	Equivalent to primary analysis A	Equivalent to primary analysis A	-	-	-	Equivalent to primary analysis A	Equivalent to primary analysis A
Grade ≥3 gastrointestinal perforation	Equivalent to primary analysis A	Equivalent to primary analysis A	-	-	-	Equivalent to primary analysis A	Equivalent to primary analysis A
Grade ≥3 hypertension	Equivalent to primary analysis A	Equivalent to primary analysis A	-	-	-	Equivalent to primary analysis A	Equivalent to primary analysis A
Grade ≥3 neutropenia	-	Equivalent to primary analysis B	-	-	Equivalent to primary analysis B	-	Equivalent to primary analysis B
Grade ≥3 proteinuria	-	Equivalent to primary analysis B	-	-	Equivalent to primary analysis B	-	Equivalent to primary analysis B

*, statistical significance; C, carboplatin; CI, confidence interval; HR, hazard ratio; OS, overall survival; P, paclitaxel; PFS, progression-free survival; RR, risk ratio.
† Sensitivity analysis 1 restricted to trials with six treatment cycles of C + P and front-line treatment.
‡ Sensitivity analysis 2 restricted to trials with the majority of patients having stage IIIC ovarian cancer.
§ Sensitivity analysis 3 restricted to trials with similar types of ovarian cancer (i.e., excluding mucinous ovarian cancer).
¶ Sensitivity analysis 4 excluded trials where all patients received bevacizumab maintenance therapy after surgery (comparison only in pre-operative setting).
Note: Clinical benefit was a composite outcome of complete response, partial response, and stable disease.
Note: Objective response was a composite outcome of complete response and partial response.
Note: : Analysis A did not allow trials with placebo in addition to treatment, whereas Analysis B did. No separate analyses (i.e., analysis A/analysis B) were conducted for sensitivity analysis 2, as this analysis set would include the same trials based on reported outcomes and lead to equivalent results.

Conclusions

- **This ITC found no significant differences between low- (7.5 mg/kg Q3W) and high-dose (15 mg/kg Q3W) BEV in response, survival, or safety outcomes, except for a higher stable disease rate with low-dose BEV. However, when stable disease was included as part of the broader composite outcome of clinical benefit (which encompassed partial response and complete response in addition to stable disease), there was no significant difference, suggesting limited clinical relevance.**
- **Study limitations included the small number of studies, treatment and patient heterogeneity, and restriction to BEV combinations with platinum-based chemotherapy, although sensitivity and subgroup analyses addressed some of these limitations.**
- **The findings highlight the absence of consistent superiority between low- and high-dose BEV, indicating that dose selection may not significantly impact clinical outcomes in ovarian cancer treatment.**
- **While further studies with a larger evidence base are needed, these results could inform clinical decisions and reimbursement in Canada, where only low-dose BEV is funded in the front-line setting.**

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References

1. Perren TJ, et al. NEJM. 2011;365(26):2484-2496p.
2. Tewari KS, et al. J Clin Oncol. 2019;37(26):2317-2328.
3. Canadian Agency for Drugs and Technologies in Health. 2015. https://www.cadth.ca/sites/default/files/pcodr/pcodr_bevacizumab_avastin_oc-fn_rec.pdf
4. Canadian Agency for Drugs and Technologies in Health. 2018. https://www.cadth.ca/sites/default/files/pcodr/pcodr_provfund_avastin-oc.pdf
5. Régie de l'assurance maladie. 2024. https://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/find-out-whether-a-drug-covered?m=bevacizumab
6. Cope S, et al. BMC Med. 2014;1293.
7. Wells GA, et al. 2009. https://www.cadth.ca/sites/default/files/pdf/H0462_itc_tr_e.pdf
8. Viechtbauer W. J. Stat. Softw. 2010;36(3):1 - 48.
9. Rouzier R, et al. Eur J Cancer. 2017;70133-142.
10. Cong J, et al. J BUON. 2019;24(3):1003-1008.
11. Garcia Eury Y, et al. Int J Gynecol Cancer. 2019;29(6):1050-1056.
12. Gore M, et al. Gynecol Oncol. 2019;153(3):541-548.