Directness and quality of evidence of bevacizumab combined with chemotherapy for platinum-resistant, recurrent ovarian cancer in the AURELIA trial

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Introduction

According to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group, one of the factors that can decrease the quality of evidence and strength of recommendations in clinical practice is "indirectness" [1] (Table 1). Direct evidence refers to research that directly compares the interventions of interest in specific populations and measures appropriate outcomes that are important to patients [2]. Conversely, indirect comparisons between agents that have not been directly compared in a single clinical trial may be made by inappropriately combining different data sets. Defining a comparison or patients or interventions as indirect depends on an understanding of whether biological or social factors are sufficiently different that one might expect substantial differences in the magnitude of effect.

Effective control of platinum-resistant disease presents a particular challenge in ovarian cancer and could be justifiably considered an unmet need. The median overall survival (OS) for women with platinum-resistant ovarian cancer is approximately 12 months, and the overall response rate (ORR) for single-agent therapies is in the range of 10% to 15%, with median response durations of approximately 3 to 4 months [3-6]. Thus, careful selection of the target population is needed to identify patients who might achieve benefit with acceptable toxicity. A careful description of beneficial and negative clinical outcomes is also important for justifying the use and acceptance of a new regimen for treating a disease in which palliation is currently the main goal.

Given the challenging population, justification for adoption of a new standard of care requires evidence that is "direct", avoiding the issues of "indirectness" described above. Two recent publications [7-8] presenting the results of studies investigating the use of bevacizumab combined with chemotherapy for platinum-resistant, recurrent ovarian cancer provide some insight into this issue.

Table 1. Factors that can decrease the quality of evidence (according to GRADE Working Group) (modified from [1])

Limitations in study design and/or execution (risk of bias)
Inconsistency (heterogeneity) of results
"Indirectness" of evidence (treatments of interest not directly compared with each other in a single trial, patient population studied differs from that in which treatments are being used, the intervention tested may differ from the intervention of interest or be tested in a non-usual setting or regimen, outcomes may differ from those of primary interest)
Lack of precision in results (meaning that the clinical action would differ if the upper *versus* the lower boundary of the confidence interval represented the truth)
Publication bias

Summary of the two publications

In the AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) trial, patients had histologically-confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within 6 months of completing ≥4 cycles of platinum-based therapy [7]. Strict exclusion criteria were implemented to reduce the risk of gastrointestinal perforation, which was previously report-

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ed at a high incidence in patients receiving bevacizumab for heavily pretreated ovarian cancer. Chemotherapy was selected by investigators from pegylated liposomal doxorubicin (PLD), weekly paclitaxel, or topotecan. Patients were randomly assigned to single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal. Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone. The primary endpoint was progression-free survival (PFS) by RECIST. Secondary endpoints included ORR, OS, safety, and patient-reported outcomes (PROs).

A sample size of 332 patients was planned, providing 80% power to detect a PFS hazard ratio (HR) of 0.70 with two-sided log-rank testing at α=0.05 after 247 PFS events, assuming a median PFS of 4.0 months with chemotherapy (CT) and 5.7 months with bevacizumab + chemotherapy (BEV-CT). At the recommendation of the Independent Data Monitoring Committee (IDMC), the sample size was increased to ≥360 patients, with primary analysis planned after 290 PFS events based on an HR of 0.72 and 80% power. The recommendation of the IDMC in January 2011 followed review of the PFS event rate in the CT arm only (without preliminary review of treatment effect) and the overall treatment discontinuation rate. PROs were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Ovarian Cancer Module 28 (EORTC QLQ-OV28) and Functional Assessment of Cancer Therapy–Ovarian Cancer symptom index (FOSI) at baseline and every two or three cycles (8/9 weeks) until disease progression. The primary PRO hypothesis was that more patients receiving BEV-CT than CT would achieve at least a 15% (≥15-point) absolute improvement on the QLQ-OV28 abdominal/gastrointestinal symptom subscale (items 31-36) at week 8/9. Patients with missing week 8/9 questionnaires were classified as unimproved.

The PFS HR value after PFS events in 301 of 361 patients was 0.48 (95% confidence interval [CI]=0.38–0.60; unstratified log-rank p=0.001). Median PFS was 3.4 months with CT *versus* 6.7 months with BEV-CT. RECIST ORR was 11.8% *versus* 27.3%, respectively (p=0.001). The OS HR was 0.85 (95% CI=0.66–1.08; p=0.174) and median OS was 13.3 *versus* 16.6 months, respectively. Grade ≥2 hypertension and proteinuria were more common in BEV-CT recipients, and the rate of gastrointestinal perforation in this group was 2.2%.

Baseline quality of life (QoL) questionnaires were available from 89% of 361 randomised patients. A higher proportion of BEV-CT than CT recipients achieved a ≥15% improvement in abdominal/gastrointestinal symptoms (primary PRO endpoint) at week 8/9 (21.9% *vs* 9.3%, difference of 12.7%; 95% CI=4.4–20.9; p=0.002). Mixed-Model Repeated-Measures analysis covering all timepoints also favored BEV-CT (difference of 6.4 points, 95% CI=1.3–11.6; p=0.015). More BEV-CT than CT patients achieved a ≥15% improvement in FOSI at week 8/9 (12.2% *vs* 3.1%, difference of 9.0%; 95% CI=2.9–15.2%; p=0.003). Sensitivity analyses provided similar results and conclusions.

According to the authors, the AURELIA study showed that bevacizumab has beneficial effects beyond prolongation of PFS, including greater improvements in abdominal/gastrointestinal symptoms and other aspects of QoL, supporting a role for adding bevacizumab to chemotherapy for the treatment of women with platinum-resistant ovarian cancer.

Methodological comment

The quality of evidence (i.e. our confidence that the reported estimates of effect are accurate) may decrease when substantial differences exist between the population, intervention, or outcomes of interest [2]. Thus, results may be considered to be "indirect" when patients in a clinical study differ from those in which we are interested. Patients enrolled onto AURELIA were selected on the basis of having received no more than two prior lines of chemotherapy and not having platinum-refractory disease. In addition, patients could not have a history of bowel obstruction, clinical signs of bowel obstruction, or evidence of bowel involvement on computed tomography. Thus, those patients with the greatest need for symptom improvement and response, and who therefore might derive the greatest benefit from a bevacizumab-containing combination, might also be the ones who are at greatest risk for serious toxicity. Therefore, if this regimen is to be considered in symptomatic patients with platinum-resistant disease, it would be important to adhere to similar eligibility criteria as those used in AURELIA.

Study endpoints are another element that may differ from those of primary interest. For example, surrogate outcomes might be used that are not themselves important, but are measured based on a assumption that changes surrogate endpoint reflect changes in another important outcome. OS is recognized as the most reliable and ethically acceptable outcome in the clinical development of cancer drugs, but this endpoint was neither planned as a primary endpoint of the AURELIA study nor shown to be improved by BEV-CT. Nevertheless, for symptomatic patients with platinum-resistant disease, it is difficult to ignore the possibility that bevacizumab combined with either weekly paclitaxel, PLD, or topotecan might confer

important benefit, despite the absence of an OS advantage. When OS data are not available to assist in making treatment decisions, it is even more crucial that PFS and the PROs included in a study are of sufficient quality to provide confidence that the estimates of the effect are correct. The strengths and weaknesses of PFS and PROs have been previously discussed in this journal [9-10], and it is well known that both of these endpoints require blinding to be properly maintained; unfortunately, the AURELIA study had an open-label design. This lack of blinding introduces a potential source of bias to the PFS endpoint, especially given that the study design allowed for crossover to single-agent bevacizumab for patients progressing in the CT arm. The open-label design may have also influenced the PRO endpoints, given that patients were aware of whether or not they were receiving bevacizumab. In other words, patients who knew that their regimen contained bevacizumab may have been unintentionally biased toward reporting more favorable PROs, partly because they were receiving what they perceived might be a more effective regimen. An unavoidable imbalance in the percentage of patients with missing PRO assessments between the two treatment arms was also observed, possibly biasing the PRO results in favor of the bevacizumab group, essentially making PRO assessment a surrogate of disease progression rather then a pure metric of symptom improvement.

References

1. Brozek JL, Akl EA, Alonso-Coello P, et al.; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64(5):669-77.
2. Guyatt GH, Oxman AD, Kunz R, et al.; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol. 2011;64(12):1303-10.
3. Cannistra SA. Cancer of the ovary. N Engl J Med. 2004;351:2519-29.
4. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001;19:3312-22.
5. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2007;25:2811-8.
6. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol. 1997;15:2183-93.
7. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32(13):1302-8.
8. Stockler MR, Hilpert F, Friedlander M, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol. 2014;32(13):1309-16.
9. Di Maio M, Daniele G, Piccirillo MC. Impact on health-related quality of life of the addition of bevacizumab to first-line chemotherapy for ovarian cancer. Cancer Breaking News 2013;1(1):33-5.
10. Daniele G, Di Maio M, Piccirillo MC. Independent radiologic review of the Gynecologic Oncology Group Study 0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer: methodological comment. Cancer Breaking News 2014;2(1):35-7.