

Emerging Role for Bevacizumab in Combination With Chemotherapy for Patients With Platinum-Resistant Ovarian Cancer

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Since bevacizumab was first reported to have single-agent activity in ovarian cancer,^{1,2} multiple studies have sought to establish whether combining bevacizumab with chemotherapy might improve the outcome of patients with newly diagnosed or recurrent disease. In the article that accompanies this editorial, Pujade-Lauraine et al³ report the results of AURELIA, a randomized trial comparing the effectiveness of chemotherapy combined with bevacizumab (investigator's choice of once-per-week paclitaxel, pegylated liposomal doxorubicin [PLD], or topotecan) to that of chemotherapy alone in recurrent platinum-resistant ovarian cancer. In a companion article, Stockler et al⁴ report the results of patient-related outcomes (PROs) in AURELIA, evaluating abdominal/GI PROs in patients receiving chemotherapy combined with bevacizumab as compared with chemotherapy alone.

AURELIA is the fourth randomized phase III study of bevacizumab in ovarian cancer. Two of the prior trials, Gynecologic Oncology Group (GOG) 218⁵ and International Collaborative Ovarian Neoplasm 7 (ICON7),⁶ examined bevacizumab together with chemotherapy followed by bevacizumab maintenance therapy in the setting of newly diagnosed ovarian cancer.^{5,6} The third trial, OCEANS, studied the combination of bevacizumab together with carboplatin and gemcitabine chemotherapy followed by bevacizumab maintenance therapy in the setting of platinum-sensitive, recurrent disease.⁷ Like each of these three studies, AURELIA observed a statistically significant benefit in progression-free survival (PFS) with the addition of bevacizumab to chemotherapy, with an absolute 3.3-month improvement in median PFS from 3.4 months in the chemotherapy-alone arm to 6.7 months in the chemotherapy plus bevacizumab arm (hazard ratio, 0.48; 95% CI 0.38 to 0.60; $P < .001$). This margin of benefit is similar to those reported in the GOG 218, ICON7, and OCEANS studies, which suggests a remarkable consistency in the observed effects of combining bevacizumab with chemotherapy in several different settings in ovarian cancer. However, as with the other randomized phase III studies, no overall survival (OS) benefit was observed in the chemotherapy plus bevacizumab arm in AURELIA. Similar to the OCEANS trial, the combination of bevacizumab and chemotherapy in AURELIA also significantly improved the overall response rate (ORR) from 11.8% to 27.3% ($P = .001$), as assessed by RECIST criteria. No new safety signals were observed in the chemotherapy plus

bevacizumab arm, with the incidence of \geq grade 2 hypertension and proteinuria being similar to that of other studies. The incidence of \geq grade 2 GI perforation was 2.2% in the chemotherapy plus bevacizumab arm compared with 0% in the chemotherapy-alone arm; again, this is consistent with the findings of other studies. Interestingly, the incidence of hand-foot syndrome and peripheral sensory neuropathy was greater in the chemotherapy plus bevacizumab arm compared with chemotherapy alone, which most likely relates to the longer duration of time that patients received either PLD or paclitaxel in the combination arm (because patients remained on chemotherapy for a longer period of time without disease progression). The incidence of treatment-related death was 2.8% in each arm.

Importantly, AURELIA also studied PROs as a separate preplanned end point and found that more patients in the chemotherapy plus bevacizumab arm achieved a $\geq 15\%$ improvement in abdominal/GI symptom PROs (as assessed by the Quality of Life Questionnaire–OV28 abdominal/GI symptom subscale) at week 8 or 9 (21.9% v 9.3%; $P = .002$).⁴ This may represent an underestimate of the PRO improvement with chemotherapy plus bevacizumab, given that only 65% of patients in this trial had sufficient symptoms at baseline for a difference to be detectable. It is noteworthy that AURELIA is the first study incorporating bevacizumab in ovarian cancer to report an improvement in PROs. In the setting of platinum-resistant ovarian cancer, in which therapy is palliative, improvement in PROs is of potential importance even in the absence of an OS benefit. In contrast, in the studies incorporating bevacizumab into first-line and subsequent maintenance treatment, GOG 218 did not demonstrate an improvement in PROs, and ICON7 demonstrated a slight worsening in PROs.^{8,9} Perhaps it is not surprising that PROs were not improved and were possibly compromised by introducing bevacizumab into the first-line setting, where most patients experience relatively few disease-related symptoms once chemotherapy begins, and when the magnitude of median PFS prolongation with bevacizumab is modest. In the relapsed setting, OCEANS did not include a PRO end point.⁷

Although the results reported in these studies add to our experience with bevacizumab in ovarian cancer, interpreting the data from these reports is not straightforward. AURELIA differs from GOG 218 and OCEANS in that it is an open-label study without a placebo

control. This may have introduced the possibility of bias in the PFS end point, especially given that the study design allowed for crossover to single-agent bevacizumab for those patients progressing on the chemotherapy-alone arm.¹⁰ Additionally, the presence of crossover to bevacizumab monotherapy in the control arm may have affected the ability to observe an OS benefit, given that at the time of the final OS analysis, 40% of patients in the chemotherapy-alone arm had received subsequent bevacizumab. This raises the possibility that using bevacizumab sequentially as monotherapy (after progression on chemotherapy alone) might yield equivalent OS compared with combination chemotherapy plus bevacizumab in this disease setting. The open-label design may have also influenced the PRO end points, given that patients were aware of whether or not they were receiving bevacizumab. In other words, patients who had knowledge that their regimen contained bevacizumab may have been unintentionally biased toward reporting more favorable PROs, partly because they were receiving what they perceived to be a possibly more effective regimen.

Another important limitation in interpreting PROs in the study reported by Stockler et al⁴ involves an unavoidable imbalance in the percentage of patients with missing PRO assessments between the two treatment arms. In particular, patients who experienced early disease progression were not always assessed for PROs at week 8 or 9, which resulted in a greater number of missing PRO assessments in the control compared with the experimental arm (Appendix Table A2 in Stockler et al⁴). How such missing data should be handled in PRO analyses is a subject of much debate.¹¹ In the AURELIA trial, missing PRO data were scored as PRO nonresponders, under the assumption that patients who had disease progression and therefore did not complete the PRO assessment likely did not experience an improvement in PROs. Although this may be valid for many patients, it is also possible that some patients with disease progression might not have experienced worsening of symptoms at the time of their removal from protocol therapy and might even have experienced improvement in PROs (related, for instance, to the use of corticosteroids as antiemetics during chemotherapy, to more effective pain management, or to other unknown reasons). Taking this into account, it is possible that the greater percentage of patients with missing data in the control arm might bias the PRO results in favor of the bevacizumab group, essentially rendering PRO assessment a surrogate of disease progression as opposed to a pure metric of symptom improvement. In this regard, it is interesting that by excluding missing data from the PRO analysis, the effect size in PRO benefit between the bevacizumab-containing arm and the chemotherapy-alone arm decreased and became nonstatistically significant (Fig 2 in Stockler et al).⁴ These considerations notwithstanding, the fact that the direction of PRO benefit still favors the bevacizumab arm, even when missing PRO data are excluded from the analysis, suggests that PROs may in fact be improved through the combined use of bevacizumab with chemotherapy in the platinum-resistant setting.

Effective control of platinum-resistant disease presents a particular challenge in ovarian cancer and could be justifiably considered an unmet need. The median OS for women with platinum-resistant disease is approximately 12 months, and the ORR for single-agent therapies is in the range of 10% to 15%, with median response durations of approximately 3 to 4 months.¹²⁻¹⁵ Given this difficult-to-treat population, what criteria should be used to justify a new standard of care? For the first time in the relapsed setting, AURELIA provides us with a constellation of findings that deserve careful consideration,

namely improvement in PROs, median PFS, and ORR. 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. However, if this approach is to be considered, careful patient selection will be critical to identify those who might derive benefit with acceptable toxicity. 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. These criteria were designed to reduce the risk of bowel perforation with bevacizumab, which has been previously reported to occur in up to 11% of patients who fulfilled less stringent eligibility criteria.² 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. Consequently, 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.

Treatment guidelines for the use of bevacizumab in ovarian cancer differ worldwide. In the United States, bevacizumab is not currently approved by the US Food and Drug Administration for any indication in ovarian cancer. Nonetheless, it has been included in the National Comprehensive Cancer Network (NCCN) guidelines as an acceptable agent in combination with carboplatin and gemcitabine in platinum-sensitive relapse.¹⁶ Similarly, the National Institute for Health and Care Excellence in the United Kingdom does not presently recommend bevacizumab for use in either newly diagnosed or recurrent ovarian cancer.^{17,18} In contrast, the European Medicines Agency has approved bevacizumab in combination with carboplatin and paclitaxel, along with subsequent maintenance single-agent bevacizumab, for patients with newly diagnosed ovarian cancer as well as bevacizumab in combination with carboplatin and gemcitabine in platinum-sensitive relapse.¹⁹ This lack of consensus reflects uncertainty regarding the proper end points to use in approving a new regimen in ovarian cancer. Clearly, improvement in OS for patients with platinum-resistant disease would represent a generally agreed upon criterion for approval of a new regimen, but this goal has been difficult to achieve thus far. However, short of improvement in OS, AURELIA raises the possibility that an improvement in PROs, taken together with an improvement in both PFS and ORR, might be sufficient to justify the acceptance of a new regimen in a disease setting in which palliation is an important goal. In our view, it is not unreasonable to consider such evidence supportive of a role for the chemotherapy plus bevacizumab combination in carefully selected patients with symptomatic, platinum-resistant disease, at the same time recognizing that the data to support a PRO benefit are suggestive rather than definitive.

Important questions remain about when and in which setting antiangiogenic therapy will result in the most benefit in patients with ovarian cancer. In the first-line setting, the data to support use of bevacizumab in conjunction with chemotherapy, followed by bevacizumab maintenance, are not compelling. Despite a modest improvement in PFS in GOG 218 and ICON7, neither OS nor PROs were

improved, and the cost-benefit analysis of this approach is not favorable.²⁰ Whether there is a subset of patients with suboptimally debulked disease who derive benefit from the use of bevacizumab in the first-line setting remains to be formally proven.⁶ In the recurrent ovarian cancer setting, however, especially for patients with symptomatic, platinum-resistant disease, a greater case can be made to justify the use of bevacizumab in combination with chemotherapy based on AURELIA. Nonetheless, it remains unknown whether patients with platinum-resistant disease might derive the same benefit from the sequential use of bevacizumab monotherapy after chemotherapy failure rather than the use of initial combination therapy as used in AURELIA. Likewise, it is reasonable to ask whether a similar benefit could be observed by using single-agent bevacizumab as the initial strategy for platinum-resistant disease, reserving cytotoxic chemotherapy as a second step in management. Finally, it remains unclear whether those patients who receive bevacizumab in the newly diagnosed setting (not a US Food and Drug Administration–approved indication) will derive the same benefit from adding bevacizumab to chemotherapy at the time of subsequent platinum-resistant relapse (only 7% of the patients in AURELIA had received prior antiangiogenic therapy). The lack of answers to these important questions does not detract from the contributions of Pujade-Lauraine et al³ or those of Stockler et al,⁴ which suggest that even in the absence of an OS advantage, an aggregate metric comprised of PROs, PFS, and ORR might have value in assessing the promise of a new regimen, especially in the context of suboptimal treatment options for patients with platinum-resistant disease.

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