Editorial Commentary

Among patients with advanced ovarian carcinoma, who benefits from bevacizumab the most?

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Comment on: You B, Purdy C, Copeland LJ, *et al*. Identification of Patients With Ovarian Cancer Experiencing the Highest Benefit From Bevacizumab in the First-Line Setting on the Basis of Their Tumor-Intrinsic Chemosensitivity (KELIM): The GOG-0218 Validation Study. J Clin Oncol 2022;40:3965-74.

Keywords: Advanced ovarian cancer; bevacizumab; KELIM score; maintenance therapy

Submitted Feb 21, 2023. Accepted for publication Mar 06, 2023. Published online Mar 28, 2023.
doi: 10.21037/atm-23-903
View this article at: https://dx.doi.org/10.21037/atm-23-903

The results of ICON 7 and GOG 218 significantly impacted how metastatic ovarian carcinoma is managed (1,2). The investigators of these trials had shown that adding bevacizumab to the standard platinum-based chemotherapy in newly diagnosed advanced epithelial ovarian cancer resulted in a statistically significant improvement in progression-free survival (PFS). Subsequently, bevacizumab was approved for patients with stage III and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by maintenance bevacizumab after the initial cytoreductive surgery.

In ICON 7, PFS at 36 months was 20.3 months with standard therapy, in comparison to 21.8 months with standard therapy plus bevacizumab [hazard ratio (HR), 0.81; 95% CI: 0.70–0.94; P=0.004]. Also, the benefit of adding bevacizumab was the greatest for patients with a high risk of progression, where the estimated median PFS was 10.5 months with standard therapy, as compared with 15.9 months with bevacizumab (HR, 0.68; 95% CI: 0.55–0.85; P<0.001). High-risk disease was defined as International Federation of Gynecology and Obstetrics (FIGO) stage III >1 cm or IV or suboptimally debulked surgery. Oza *et al.* reported the final overall survival results of the ICON 7 trial which revealed that in a specific predefined high-risk population that involved patients with stage IV disease and those with unoperated or sub-optimally debulked (>1 cm) stage III disease, derived a benefit in OS with the addition of bevacizumab with a median OS of 39.3 *vs.* 34.5 months, an absolute difference 4.8 months; P=0.03 (3).

In the GOG 218 trial, the median PFS after adding bevacizumab in the frontline and maintenance therapy setting was an additional four months, from 10.3 to 14.1 months (HR, 0.72; 95% CI: 0.63–0.82). The final survival analysis of GOG 0218 did not show benefit in OS with bevacizumab in the whole population but hinted at a potential OS gain in patients with a stage IV disease (median OS: 42.8 *vs.* 32.6 months; HR, 0.75; 95% CI: 0.59 to 0.95) (4).

Considering the data mentioned earlier from ICON 7 and GOG 218, the question has been, which patients will most likely benefit from the addition of bevacizumab where the cost and the potential side effects are justified? Identifying patients who should be prescribed adjuvant and maintenance bevacizumab treatment is a matter of debate. Hence, reliable biomarkers are required to predict the potential effect of bevacizumab in metastatic ovarian carcinoma.

Several indicators for tumor chemosensitivity have been

reported. You *et al.* developed a marker for tumor intrinsic chemosensitivity based on the results of the CHIVA trial, named the KELIM score (rate of ELIMination of CA-125 constant K). It is a kinetic parameter that uses a minimum of 3 CA-125 values in the first 100 days of chemotherapy to model CA-125 clearance. A higher KELIM score reflects a faster CA-125 elimination rate and higher chemosensitivity. It is an independent prognostic factor for complete cytoreduction and predict subsequent platinum-resistant recurrence (5). Subsequently, Colomban *et al.* assessed the prognostic role of KELIM among the ICON 7 cohort. There was no survival benefit with the addition of bevacizumab in the low-risk group irrespective of the KELIM value. In the high-risk disease group with a favorable standardized KELIM Score >1 there was no OS benefit with the addition of bevacizumab (46.6 *vs.* 48.2 months, log-rank P=0.70). Only those with an unfavorable standardized KELIM score >1 derived a benefit from the addition of bevacizumab (median OS 29.7 *vs.* 20.6 months, log-rank P=0.10). Nevertheless, the survival advantage provided by the addition of bevacizumab was not sufficient to reach similar survivals with those of high-risk disease with a favorable KELIM score (6).

In October 2022, You *et al.* published a GOG 218 validation study in the *Journal of Clinical Oncology*. The authors perform an external validation analysis to address the prognostic value of the KELIM score regarding the impact of bevacizumab on PFS and OS in GOG 218. The primary purpose was to confirm an OS advantage with bevacizumab among high-risk disease with an unfavorable KELIM, as shown by Colomban *et al.* in the post hoc analysis of the ICON 7 trial. The result of multivariate analysis showed that the KELIM score, disease stage, quality of the debulking surgery, histologic grade and ascites have an independent impact on OS and PFS. In the whole population with an unfavorable KELIM score, there was a PFS and OS advantage with bevacizumab-concurrent-maintenance (arm 3) compared with the placebo (arm 1). The median PFS gain was 3.7 months (HR, 0.70) and the median OS benefit was 4.5 months (HR, 0.87). This PFS and OS advantage were not identified in patients with a favorable KELIM score. However, the maximum benefit was shown in patients with high-risk disease and unfavorable KELIM score (median PFS: 9.1 *vs.* 5.6 months; HR, 0.64; median OS: 35.1 *vs.* 29.1 months; HR, 0.79). Again, patients with high-risk disease but extremely chemo-sensitive disease represented as favorable KELIM score did not exhibit benefit from the addition of bevacizumab (7).

Since the approval of bevacizumab in management of epithelial ovarian cancer in the last decade, there has been rapid development in treating ovarian cancer. Additionally, integrating PARP inhibitors in the standard of care has transformed the landscape of ovarian cancer management. It is evidently now that the "one-size fit all' approach does not apply any more. HRD (Homologous recombination deficiency) testing has become a routine investigation offered to all epithelial ovarian cancers, as it has direct impact on prognosis and most importantly on maintenance therapy. Therefore, having a reliable biomarker that predict response to the various treatment options is essential in the modern practice to individualize treatments, that may include early surgical intervention or modifying the systemic therapy.

Treatment with antiangiogenic agents is costly and can have considerable side effects including hypertension, anemia, GI perforation and fistulas. One potential solution for optimizing the treatment is to identify useful biomarkers that aid in selecting patients most likely to benefit from such therapy. Utilizing the KELIM score in managing ovarian carcinoma is beneficial to individualize the treatment plan and potentially utilize anti-angiogenic therapy for appropriate patients. Bais *et al.* retrospectively assessed potential tumor biomarkers from patients in the GOG-218 study. The marker that showed the strongest association with clinical benefit was microvascular density (MVD). The effects of bevacizumab treatment on both PFS and OS were greater in patients with higher MVD in tumor sections. Patients with tumors having the highest MVD are expected to derive the greatest benefit from anti-angiogenic therapy (8). MVD as a biomarker for bevacizumab needs to be addressed in future trials. Li *et al.* reported data on nicotinamide N-methyltransferase (NNMT) overexpression in ovarian cancer. NNMT is an S-adenosylmethionine-dependent enzyme, which plays a vital role in the biotransformation and detoxification of many drugs and xenobiotic compounds. NNMT overexpression has been linked with tumor aggressiveness. NNMT over-expression was associated with higher tumor stage, grade, mesenchymal molecular subtype, and worsening OS. Bevacizumab significantly improved OS in low NNMT expression but did not have an impact on high expression of NNMT (9). Kommoss *et al.* investigated the molecular subtyping of ovarian cancer as predictive of response to bevacizumab. Proliferative and mesenchymal

ovarian cancer subtypes had the greatest benefit from bevacizumab, with a prolongation in PFS and a trend toward greater OS. Patients with proliferative tumors who received bevacizumab had a prolongation in PFS of 10.1 months compared with the standard control arm (HR 0.45, P=0.0015). In the mesenchymal subtype, there was non-statistically significant prolongations in PFS of 8.2 months, P=0.41 (10).

In current practice, following many positive phase III trials, PARP inhibitors have an important role in maintenance therapy in ovarian cancer. Following the publication of the PAOLA-1 trial which showed a significant PFS particularly in HRD positive tumors, including BRCA mutation negative patients it would be worth validating the KELIM score in this cohort.

In conclusion, bevacizumab has been proven to be effective in ovarian cancer management when added to standard chemotherapy. Identifying the group of patients who get the most benefit from the drug is key to managing these cancers. Currently, the most agreed parameter for bevacizumab use is the high disease burden. The KELIM score which has been validated in the ICON 7 and GOG 218 trials showed that an unfavorable KELIM score with high-risk advanced disease had a significant benefit from bevacizumab. A combination of high disease burden with other parameters such has the KELIM score may help in the decision of using bevacizumab in advanced epithelial ovarian cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-903/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Babaier A, Ghatage P. Among patients with advanced ovarian carcinoma, who benefits from bevacizumab the most? Ann Transl Med 2023;11(10):367. doi: 10.21037/atm-23-903

