Editorial Commentary

Bevacizumab as adjunct to chemotherapy for chemoresistant ovarian cancer

Gerhard Hamilton

Department of Vascular Surgery, Medical University of Vienna, Vienna, Austria

Correspondence to: Gerhard Hamilton, PhD. Department of Vascular Surgery, Medical University of Vienna, Vienna A-1090, Austria.
Email: gerhard.hamilton@meduniwien.ac.at.

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

Comment on: Lee JY, Park JY, Park SY, *et al.* Real-world effectiveness of bevacizumab based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA): a Korean Gynecologic Oncology Group study (KGOG 3041). Gynecol Oncol 2019;152:61-7.

Submitted Dec 26, 2019. Accepted for publication Feb 18, 2020.
doi: 10.21037/tcr.2020.02.75
View this article at: http://dx.doi.org/10.21037/tcr.2020.02.75

Ovarian cancer (OC) still has a dismal prognosis due to a high propensity for metastasis, late detection and chemoresistance. The current therapy for OC is extended tumor-reductive surgery, followed by chemotherapeutic treatment comprising platinum-based drugs and taxanes, applied in different schedules. Such first-line chemotherapy yields high responses with up to >75% overall response rates (ORR) but most of the patients relapse early and long-term survival is limited to a 10–30% subpopulation. Therefore, accessory drugs have been tried in hope to improve the progression-free survival (PFS) and overall survival (OS) by targeting different pathways which support the cancer growth. Bevacizumab (BV) represents a humanized monoclonal antibody which is directed to vascular endothelial growth factor (VEGF) and which has been the first targeted therapeutic administered for OC. This antibody impairs tumor vascularization and inhibits neoangiogenesis, especially altering frequency, dimensions and permeability of the vessels (1). The effect of BV as adjunct to standard chemotherapy for platinum-sensitive and platinum-resistant recurrent OC patients have been investigated in phase III trials. In conclusion, these randomized trials proved a statistically significant prolongation of PFS but not on OS. However, addition of BV reduced abdominal symptoms in recurrent OC patients such improving the quality of life (2). However, BV in combination with chemotherapy resulted in increased adverse events such as bleeding, hypertension thromboembolism, proteinuria, and gastrointestinal events among others.

In particular, for the so-called AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) study, patients were randomly assigned to single-agent chemotherapy (pegylated liposomal doxorubicin/PLD, weekly paclitaxel, or topotecan) alone or with administration of BV (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, severe adverse events, or decision to withdraw (3). Following progression with chemotherapy alone crossover to single-agent BV was selected by approximately 40% of the patients. The median PFS was 3.4 months with chemotherapy alone *vs.* 6.7 months with BV-supplemented therapy yielding a PFS hazard ratio (HR) of 0.48 (95% CI, 0.38 to 0.60; P<0.001) in 301/361 patients. ORR according to RECIST criteria was 11.8% *vs.* 27.3%, respectively (P=0.001). However, the median OS of 13.3 *vs.* 16.6 months resulting in a HR of 0.85 (95% CI, 0.66 to 1.08; P<0.174) showed no significant effect of BV. Grade ≥2 hypertension and proteinuria were more common with BV. The PFS HRs for the three chemotherapeutic agents tested were 0.46 for paclitaxel (10.4 *vs.* 3.9 months), 0.57 for PLD cohort (5.4 *vs.* 3.5 months), and 0.32 for topotecan (5.8 *vs.* 2.1 months). A better ORR was achieved in patients treated with the paclitaxel-BV combination in (53.3% *vs.* 30.2%) or with BV-topotecan (17.0% *vs.* 0.0%) *vs.* BV and PLD (13.7% *vs.* 7.8%). However, the best chemotherapy combination for BV could not be established because none of the three regimens was randomized.

Quality of life assessment revealed that the part of

patients experiencing ≥15% improvement in abdominal and GI symptoms scores after 8 or 9 weeks of therapy was greater in the BV-chemotherapy cohort than the chemotherapy cohort (21.9% *vs.* 9.3%; P=0.002) (4). In respect to the three different chemotherapeutics, the melioration was 25.0% *vs.* 13.0% for paclitaxel, 20.0% *vs.* 8.8% for topotecan and 21.1% *vs.* 6.8% for PLD. Additionally, in 113 patients (31%) bearing ascites, paracentesis was carried out for 9 (8%) in the chemotherapy group and 1 (2%) in the BV-chemotherapy group indicating control of ascites in the BV group. Comparatively, the AURELIA trial showed a 3.3 months improvement in PFS which is comparable to results found in other similar trials (ICON7, OCEANS and GOG218) thus corroborating a significant role BV combined with chemotherapy for different cohorts of OC patients (5). Disappointingly, no prolongation of OS was observed (13.7 months) in the BV arm in comparison to the typical OS of approximately 12 months in patients with platinum-resistant OC. Nevertheless, based on the results from AURELIA, the FDA and the European Commission have approved the use of BV in combination with chemotherapy for platinum-resistant OC. For future development, the use of BV beyond progression (BBP) may constitute a new therapeutic approach for the treatment of OC in patients with unfavorable prognosis (6). BBP has been demonstrated to improve OS in recurrent colorectal cancer and of PFS in recurrent breast and lung cancer patients.

BV therapy in combination with paclitaxel/docetaxel, was questioned by Tomao *et al.* for a higher toxicity than for regimens with other chemotherapeutic drugs (7). However, the AURELIA trial authors reinforced the paclitaxel scheme as an effective and low-toxicity regimen in a weekly schedule in relapsed OC patients, compared with PLD or topotecan (8). In the light of a lack of improvements in OS by BV-chemotherapeutics combinations the cost-effectiveness of such therapies was questioned. For example, the addition of BV to single-agent chemotherapy treatment was regarded not to be cost-effective in a Canadian patient population (9). From a health economic perspective, the cost-effectiveness ratio (ICER) of BV were rated as relatively high and more acceptable only for first-line treatment of stage IV OC patients (10).

The "real-world effectiveness of BV based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA)" study evaluated the efficacy of BV with chemotherapy for platinum-resistant OC patients from 27 institutions in a real-world setting (11). All patients had been treated with BV in combination with either weekly paclitaxel, pegylated liposomal doxorubicin/PLD or topotecan for 2nd- or 3rd-line therapy in a routine clinical setting. Of the 391 recruited patients, 259 (66.2%) were treated with BV-PLD, 94 (24.0%) with BV-topotecan, and 38 (9.7%) with BV-weekly paclitaxel. With all chemotherapeutics-BV combinations the median PFS was 6.1 months. In particular, the BV-PLD group revealed a median PFS of 5.4 months, the weekly paclitaxel group 8.3 months and the topotecan group 7.0 months. The overall median OS was 22 months and, in detail, enumerated to 21 months for the PLD group, to 21 months for the weekly paclitaxel group and to 25 months for the topotecan group. Adverse events from BV-supplemented combinations counted for the withdrawal of 29 patients (7.4%). The BV-PLD group had significantly less grade ≥3 adverse events, especially in respect to hematologic toxicities, compared to the other drug combinations (35.8% *vs.* 52.6% and 51.1%, respectively, P=0.012). Thus, it was concluded that for Korean OC patients the efficacy and side effects of BV-chemotherapeutics combinations are consistent and comparable with the results of the AURELIA trial in a real-world setting.

Acquisition of a sufficient supply of vessels is essential for tumors beyond a specified size and this process is a characteristic feature of solid tumors. This tumor vascularization and neoangiogenesis is triggered by proangiogenic factors mainly through tissue hypoxia-regulated overexpression of VEGF. Thus, tumor growth may be impaired by antiangiogenic therapy but the clinical efficacy of this approach alone exhibit limited or only transient anticancer effects in patients due to resistance and rescue circuits. Paradoxically, such therapeutic efforts may promote the selective survival of hypoxic and highly invasive cancer cells in the center of the tumor mass. Accordingly, invasion and metastasis are elevated in preclinical tumor models in response to the inhibition of VEGF (12). Clinically, administration of an anti-VEGF antibody is expected to decrease the tumor burden initially but may trigger hypoxia, invasion and metastasis at the same time thus making afterwards a complete tumor response less likely. Furthermore, an abnormal and suppressed tumor vasculature is expected to limit the delivery of drugs to tumor areas and to impair the efficacy of chemotherapy. The tumor vessel normalization hypothesis purports that a low dose of anti-angiogenic therapy can transiently restore the normal vessel function of the irregular vascular supply and improve the anticancer drug delivery (1). This

effect could be the explanation of the increased PFS and unimproved OS in patients treated with anti-angiogenic BV in combination with chemotherapeutics as compared to chemotherapy alone (13).

In conclusion, the real-world patients study REBECA corroborates the finding of the original AURELIA phase III trial demonstrating prolonged PFS and, possibly, improved quality of life in response to BV-chemotherapy combinations. Selection of the patients expecting to gain the highest benefit from such combinations is difficult due to the lack of predictive biomarkers. Anti-angiogenic therapy with BV in combination with chemotherapy may be not sufficient to improve survival in advanced chemoresistant OC patients and inhibition of additional effectors may be required to improve outcomes. New means for antiangiogenic therapy are under investigation and are expected to offer the possibility of treating OC with orally bioavailable molecularly targeted therapy (14,15).

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.02.75). The author has no conflicts of interest to declare.

Ethical Statement: The author is 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.

References

1. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9.
2. 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;32:1309-16.
3. 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;32:1302-8.
4. Bamias A, Gibbs E, Khoon Lee C, et al. Bevacizumab with or after chemotherapy for platinum-resistant recurrent ovarian cancer: exploratory analyses of the AURELIA trial. Ann Oncol 2017;28:1842-8.
5. Rossi L, Verrico M, Zaccarelli E, et al. Bevacizumab in ovarian cancer: A critical review of phase III studies. Oncotarget 2017;8:12389-405.
6. Shoji T, Eto H, Sato T, et al. A new therapeutic strategy for recurrent ovarian cancer-bevacizumab beyond progressive disease. Healthcare (Basel) 2019. doi: 10.3390/healthcare7030109.
7. Tomao F, Papa A, Rossi L, et al. Angiogenesis and antiangiogenic agents in cervical cancer. Onco Targets Ther 2014;7:2237-48.
8. Pujade-Lauraine E, Hilpert F, Poveda A. Reply to F. Tomao et al. J Clin Oncol 2014;32:3580.
9. Ball G, Xie F, Tarride JE. Economic evaluation of bevacizumab for treatment of platinum-resistant recurrent ovarian cancer in Canada. Pharmacoecon Open 2018;2:19-29.
10. Neyt M, Vlayen J, Devriese S, et al. First- and second-line bevacizumab in ovarian cancer: a Belgian cost-utility analysis. PLoS One 2018;13:e0195134.
11. Lee JY, Park JY, Park SY, et al. Real-world effectiveness of bevacizumab based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA): a Korean Gynecologic Oncology Group study (KGOG 3041). Gynecol Oncol 2019;152:61-7.
12. Rosell R, Pedraz-Valdunciel C. Are neutralising anti-VEGF or VEGFR2 antibodies necessary in the treatment of EGFR-mutated non-small-cell lung cancer? Lancet Oncol 2019;20:1617-8.
13. Jayson GC, Hicklin DJ, Ellis LM. Antiangiogenic therapy--evolving view based on clinical trial results. Nat Rev Clin Oncol 2012;9:297-303.
14. Qin S, Li A, Yi M, et al. Recent advances on anti-

angiogenesis receptor tyrosine kinase inhibitors in cancer therapy. J Hematol Oncol 2019;12:27.
15. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci 2019. [Epub ahead of print].

Cite this article as: Hamilton G. Bevacizumab as adjunct to chemotherapy for chemoresistant ovarian cancer. Transl Cancer Res 2020;9(4):2157-2160. doi: 10.21037/tcr.2020.02.75

