Editorial Commentary

Bevacizumab combined with chemotherapy in platinum-resistant ovarian cancer: beyond the AURELIA trial

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Although ovarian cancer accounts for a small percentage of the total malignancies that affect women, ovarian cancer remains the most lethal gynecological malignancy, leading to over 14,000 deaths in the last year (1). Non-specific symptoms such as lower abdominal pain, early satiety, urinary frequency, constipation, and abdominal distension characterize the insidious onset of this disease (2), In fact, 4 out of 5 women diagnosed with ovarian cancer are diagnosed only after the cancer has already reached its advanced stages, having spread throughout the abdomen or into the retroperitoneal space (1,3). Due to this, less than one-third of patients with ovarian cancer discovered in the advanced stages (stage 3 or 4) survive longer than 5 years after diagnosis (3).

For years, the standard of care for ovarian cancer has been cytoreductive surgery followed by platinum-based chemotherapy. Up to 80% of women with ovarian cancer will initially respond to platinum-based chemotherapy, but most women will ultimately relapse and develop drug resistance to these platinum-based agents (4). A rise in serum CA-125, new tumor growth on imaging, or worsening physical exam findings generally herald the recurrence of ovarian cancer (4). If the recurrence occurs in fewer than 6 months from the completion of the primary platinum-based therapy, patients are described as having platinum-resistant recurrent ovarian cancer (5). Re-initiation of platinum-based chemotherapeutic monotherapy in ovarian cancer that has recurred in less than 6 months from the completion of the first treatment has a probability of <10% for a clinically significant treatment response (2).

Due to the dismal response expected from multiple cycles of platinum-based chemotherapeutics, many second-line therapies have been tested to evaluate for efficacy, tolerability, and cost effectiveness. The most active second-line agents used in patients with platinum-resistant recurrent ovarian cancer include paclitaxel, topotecan, gemcitabine, and pegylated liposomal doxorubicin (PLD) (6). Response rates for second-line cytotoxic monotherapy have ranged from 10–35%, with a high likelihood of recurrence within in months after treatment initiation (2). Using multiple cytotoxic agents for platinum-resistant recurrent ovarian cancer are typically avoided as cumulative toxicity increases without a demonstrable increase in efficacy (6).

Given these findings, many trials in the last few years have explored different drug targets for patients with platinum-resistant epithelial ovarian, fallopian tube, and primary peritoneal cancer. One such target is the vascular endothelial growth factor (VEGF) targeted by the humanized recombinant monoclonal antibody bevacizumab (BEV). BEV reduces the formation of new blood vessels, including their number, density, diameter, and permeability in cancer cells (7). Furthermore, due to its unique mechanism of action, it behaves in a synergistic way when combined with conventional chemotherapeutics, and it carries with it a different set of toxicities (7).

To this day, there have been five large-scale phase III randomized controlled trials testing the effects of BEV in patients with either newly diagnosed ovarian cancer,

recurrent platinum-sensitive ovarian cancer, or recurrent platinum-resistant ovarian cancer (GOG-0218, ICON7, OCEANS, GOG-0213, and AURELIA) (6,8-11). In the GOG-0218 and ICON7 trials, BEV was administered to women receiving a new diagnosis of epithelial ovarian cancer who were at high risk for disease progression, either secondary to initial diagnosis at an advanced stage of the disease or disease characterized by a very aggressive histology (8,9). Results of these trials demonstrated a significant extension of progression-free survival (PFS) when patients were given carboplatin and paclitaxel combined with BEV versus carboplatin and paclitaxel combined with placebo. Even when the BEV dose was cut in half in the ICON7 trial, patients continued to have a significant improvement in PFS.

The OCEANS and GOG-0213 trials tested the effects of BEV when given to patients who had a recurrence of ovarian cancer greater than 6 months after completion of the last platinum-based chemotherapy regimen (platinum-sensitive) (10,11). Each trial tested a different cytotoxic agent in addition to the standard platinum-based chemotherapeutic. The OCEANS trial tested carboplatin and gemcitabine combined with BEV versus combined with placebo, and the GOG-0213 trial tested carboplatin and paclitaxel combined with BEV versus combined with placebo. Both trials showed an increase in PFS when patients had BEV added to the above-mentioned chemotherapy regimen, but neither trial was able to show a significant difference in OS.

The AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) trial was the first phase III randomized controlled trial to combine BEV with standard chemotherapy for women with platinum-resistant ovarian cancer. BEV was tested in combination with PLD, paclitaxel, or topotecan in patients with recurrent ovarian cancer within 6 months after the end of at least four platinum-based chemotherapy cycles (6). Many exclusion criteria were used to limit high-risk patients from exposure to BEV. Specifically, patients treated with more than two previous regimens of chemotherapy, patients with refractory tumor, or patients with gastrointestinal fistulas, perforations, obstruction, abscesses, or involvement of the intestine by tumor spread were excluded from the trial. This trial revealed a significant increase of 3.3 months in PFS when BEV was added to all subgroups of chemotherapeutics. Given these results, the Food and Drug Administration (FDA) of the United States and the European Commission approved the use of BEV for recurrent platinum-resistant ovarian cancer (12).

Although the AURELIA trial revealed promising results, there were many exclusion criteria that prevented certain women from participating. For these reasons, Lee *et al.* created an observational study, REBECA (Real-world effectiveness of BEV based on AURELIA in platinum-resistant recurrent ovarian cancer), to test the effectiveness of the findings published by the AURELIA trial (12). Specifically, a similar sized cohort of Korean women was studied to establish the safety profile of BEV, the effectiveness of treatments, and to determine the optimal chemotherapy partner for BEV. This retrospective study included women from large, unselected, general clinical practice populations of varying ages. The combination of paclitaxel-BEV produced the longest median PFS when compared to topotecan-BEV and PLD-BEV. Importantly, this trial revealed that BEV is effective in a general clinical population with a similar safety profile established by AURELIA (12).

The AURELIA and REBECA trials now illustrated with two different cohorts of women the safety and effectiveness of treating platinum-resistant recurrent ovarian cancer with chemotherapeutics combined with BEV. Further analysis of the AURELIA trial revealed some important characteristics of the trial that may have influenced the reporting of the OS. In an exploratory analysis of each subgroup in the AURELIA trial, it is seen that the risk of death is reduced in patients receiving BEV either at onset of disease recurrence after crossover from the chemotherapy alone arm or when patients received BEV upfront when randomized into a chemotherapy-BEV combined treatment arm (13). In fact, 40% of patients randomized to the chemotherapy alone arm ended up receiving BEV after disease progression, and this fact likely contributed to the lack of OS seen in the AURELIA trial (13).

Further analysis of the patient characteristics in the AURELIA trial may reveal additional variables not originally thought to influence the OS in women with platinum-resistant ovarian cancer. Sostelly *et al.* found that ascites and tumor kinetics metrics are strongly associated with OS in women with platinum-resistant ovarian cancer (5). The presence of ascites at baseline is a well-known poor prognostic factor for women with ovarian cancer. Women with ovarian cancer in this advanced stage may be more responsive to anti-VEGF therapy such as BEV, and they may require long-term maintenance therapy with it after the completion of cytotoxic therapy (14). The measurement of tumor shrinkage at week 8 by computed tomography

(CT) scan after treatment initiation was also found to be predictive of OS in women with platinum-resistant ovarian cancer (5). Using these two variables may help clinicians accurately predict long-term treatment responses and help predict OS in these patients.

The AURELIA trial was powered to detect differences in PFS in women who were taking chemotherapy and BEV versus chemotherapy alone. It was not powered to detect differences in OS. Recently, three meta-analyses have been performed to determine which patients, if any, are likely to have improved OS when taking BEV in combination with chemotherapy for ovarian cancer (15-17). In newly diagnosed ovarian cancer in low risk patients, the addition of BEV to standard chemotherapy did not improve PFS or OS (15). In high risk of progression patients (International Federation of Gynecology and Obstetrics stage III or IV or >1.0 cm of residual disease after debulking surgery) or patients with recurrent disease, BEV in combination with paclitaxel and carboplatin showed increased PFS and OS. BEV did not show significant benefit in a pure maintenance setting (17).

Although the combination of BEV with other chemotherapeutics has shown an increase in PFS and OS in certain patients, there are many other characteristics about BEV that must be considered. By analyzing the AURELIA trial, Wysham *et al.* showed that adding BEV to the standard chemotherapy regimen will cost over $400,000 per quality adjusted life year (QALY) and gain only 0.15 QALYs (18). Therefore, to be cost effective, BEV must be reduced to 20% of its current cost (18). Furthermore, the use of BEV has been associated with a number of adverse events including hypertension, arterial thromboembolism, proteinuria, and complications of wound healing (17,19). Although rare, GI perforation is the most feared complication with a 50% mortality rate when this occurs in the setting of recurrent ovarian cancer (20). Due to these risks, the FDA limits the number of cytotoxic agents used prior to BEV therapy to two (20).

When considering the use of BEV, it is important to consider multiple aspects of the patient's care to include ovarian cancer type, extent of spread, previous cytotoxic treatments, cost effectiveness, potential symptom relief, and potential adverse effects. BEV has shown significant promise in the prolongation of PFS in patients with high risk of progression or recurrent ovarian cancer, including freedom from regular paracentesis in one group of patients with malignant ascites (21). Furthermore, with the recent meta-analyses studying the landmark randomized controlled trials with the use of BEV combination therapy, we see BEV may also lead to improvements in OS in addition to PFS (15-17). In a large-scale survey of women with ovarian cancer, it was seen that patients are more willing to accept higher toxicities of therapy for a greater OS improvement, but not for attainment of PFS (22). Therefore, a knowledge of each patient's history and preferences may help guide clinicians to make the right choice when deciding to initiate BEV or other targeted therapy for ovarian cancer.

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