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Ovarian Cancer and Antiangiogenic Therapy: Caveat Emptor

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Platinum and taxane-based chemotherapy after surgical cytoreduction remains the mainstay of treatment for advanced ovarian malignancies, with median progression-free survival (PFS) ranging from 17 to 30 months and median overall survival (OS) ranging from 36 to 65 months depending on the volume of postcytoreductive disease.[1] Furthermore, adding additional cytotoxic agents to first-line therapy has not had an impact on outcome.[2] Given the therapeutic limitations of conventional chemotherapy, recent investigations have explored molecularly guided therapies to target pathways of oncogenesis.

Angiogenesis is recognized as a hallmark of several types of tumors, including ovarian cancer.[3] One of the most important cytokines responsible for tumor-mediated angiogenesis is vascular endothelial growth factor (VEGF), which is secreted by tumor cells and binds to the VEGF receptor (VEGFR) that is present on normal endothelial cells, stimulating new blood vessel formation.[4,5] Thus, efforts to block this pathway, either by inhibiting VEGF or its receptor, have emerged as attractive strategies for cancer treatment.[6,7]

Approaches to manipulation of the VEGF pathway include extracellular interference with VEGF itself, as well as intracytoplasmic inhibition of the tyrosine kinase domain of the VEGFR.[7] The most investigated antiangiogenic agent to date is the humanized monoclonal antibody to VEGF, bevacizumab, which prevents binding of VEGF to its receptor and thereby inhibits angiogenesis.[7] More recently, small-molecule tyrosine kinase inhibitors, which interact with the cytoplasmic domains of VEGFR, have been investigated clinically.[7] Pazopanib is a multitargeted tyrosine kinase inhibitor that inhibits several tyrosine kinase receptors including VEGFR, platelet-derived growth factor receptor, and fibroblast growth factor receptor, all of which modulate signaling through angiogenic, proliferative, or cell survival pathways.[7,8] Early clinical trials have demonstrated promising single-agent activity of pazopanib in recurrent ovarian cancer.[9]

To date, four phase III randomized clinical trials testing bevacizumab in ovarian cancer have been published. The first, Gynecologic Oncology Group (GOG) protocol 218, was a three-arm placebo-controlled study investigating the addition of bevacizumab 15 mg/kg to standard carboplatin and paclitaxel chemotherapy in first-line, adjuvant treatment of advanced-stage epithelial ovarian carcinoma (EOC).[10] The 1,873 enrolled patients were treated either with standard chemotherapy alone, standard chemotherapy with concurrent bevacizumab followed by placebo maintenance, or standard chemotherapy with concurrent and maintenance bevacizumab every 21 days for up to 16 doses.[10] Patients who were treated with concurrent and maintenance bevacizumab experienced a significantly prolonged PFS when compared with chemotherapy alone (14.1 *v* 10.3 months; hazard ratio [HR], 0.717; 95% CI, 0.625 to 0.824; $P = .001$).[10] Although the PFS advantage was encouraging, this benefit did not translate into an OS or quality of life (QOL) advantage.[10] A substantial crossover to bevacizumab (> 40%) occurred during this trial, thereby confounding OS analysis.[6]

The second trial of first-line bevacizumab, International Cooperative Group for Ovarian Neoplasia study 7 (ICON-7), compared standard carboplatin and paclitaxel chemotherapy alone or the same chemotherapy with concurrent bevacizumab followed by 12 cycles of maintenance bevacizumab at 7.5 mg/kg in 1,528 patients with early-stage, high-risk (clear cell histology or grade 3) and stages IIB to IV EOC.[11] As was observed with GOG 218, a statistically significant improvement in PFS was reported in the bevacizumab arm compared with standard chemotherapy (19 *v* 17.3 months; HR, 0.81; 95% CI, 0.70 to 0.94; $P = .0041$).[11] Unfortunately, this PFS advantage again did not translate into an OS benefit.[11] Post hoc subgroup analysis in patients at high risk for recurrence (patients with suboptimally cytoreduced stage III and stage IV disease) demonstrated an even larger 5.4-month improvement in PFS and a 9.4-month median OS advantage (30.3 *v* 39.7 months; $P = .0072$), which seems somewhat counterintuitive.[11] Final analysis of the ICON-7 data was presented at the 2013 European Cancer Congress.[12] In the poor-prognosis group, 332 of 502 patients died (174 in the control arm; 158 in the bevacizumab arm), with an improvement of 4.8 months in restricted mean survival time from 34.5 to 39.3 months (log-rank $P = .03$; proportional hazards test = 0.007).[12]

Two additional phase III trials were undertaken to assess the effects of bevacizumab in platinum-sensitive and platinum-resistant recurrent EOC, respectively. The Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease (OCEANS), a phase III, randomized, placebo-controlled trial, evaluated bevacizumab in the treatment of 484 patients with platinum-sensitive recurrent disease, comparing gemcitabine and

carboplatin chemotherapy every 3 weeks with and without bevacizumab (15 mg/kg for six to 10 cycles), with bevacizumab or placebo continued as maintenance until disease progression.[13] The bevacizumab arm demonstrated a 4-month improvement in median PFS compared with chemotherapy alone (12.4 *v* 8.4 months, respectively; HR, 0.484; 95% CI, 0.388 to 0.605; $P < .001$).[13] Interim survival analysis at 235 deaths revealed a median OS advantage of almost 2 months favoring the placebo arm, but this difference was not statistically significant.[13] As with GOG 218, a proportion of patients on the control arm (31%) ultimately received bevacizumab after progression, confounding interpretation of the OS analysis.[13]

The Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer (AURELIA) trial was an open-label, randomized, phase III trial of standard monotherapy (pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel) with or without bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression in 361 patients with platinum-resistant, recurrent EOC.[14] Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone.[14] The bevacizumab-containing arms experienced a significantly improved PFS compared with monotherapy (6.7 *v* 3.4 months, respectively; HR, 0.48; 95% CI, 0.38 to 0.60; $P < .001$).[14] A similar benefit was observed for median OS, although the study was underpowered to detect OS differences (16.6 months *v* 13.3 months for bevacizumab compared with standard chemotherapy, respectively; HR, 0.85; 95% CI, 0.66 to 1.08; $P = .174$).[14] Once again, the planned postprogression crossover to bevacizumab (which occurred in 40% of patients) likely resulted in confounding of the OS results.[14]

In the article that accompanies this editorial, du Bois et al[15] present initial results of a phase III, placebo-controlled trial, Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom trial 16 (AGO-OVAR 16), evaluating pazopanib maintenance after standard paclitaxel and carboplatin chemotherapy in 940 patients with stage II to IV EOC. Like the trials discussed previously, this investigation used PFS from random assignment as its primary end point. In contrast to GOG 218[10] and ICON-7,[11] random assignment in this trial occurred after completion of at least five cycles of primary chemotherapy in patients without evidence of disease progression, thereby selecting for patients with relative chemosensitivity by excluding the 15% to 20% of patients who were intrinsically resistant to primary therapy. Patients randomly assigned to receive maintenance pazopanib experienced a 5.6-month improvement in PFS compared with the placebo group (HR, 0.77; 95% CI, 0.64 to 0.91; $P = .0021$), although at the time of this report, no OS advantage had been observed.

Given the results of the previous trials, it is possible, if not likely, that these data will have a similar loss of benefit when data matures and OS is assessed. Furthermore, the higher numbers of patients discontinuing therapy in the pazopanib group suggest a probable dilution of treatment effect at final analysis. In this investigation, a startling one third of the patients in the pazopanib arm discontinued treatment because of adverse events, whereas only 5.6% of patients in the placebo arm did so.[15] This increased incidence in adverse effects compares unfavorably with the modest toxicity rates reported in trials using bevacizumab, further attenuating the clinical benefit that can be inferred. The unfavorable benefit-to-risk profile of pazopanib revealed by the second planned interim analysis, in addition to the early HR for OS of 1.076 (95% CI, 0.868 to 1.333; $P = .4985$), prompted GlaxoSmithKline to withdraw its application for the approval of pazopanib maintenance after first-line therapy for EOC in the European Union and to unequivocally forgo seeking such approval elsewhere.[16] Despite the positive PFS results reported by this and other phase III trials in EOC, development of pazopanib in the maintenance setting will undoubtedly falter. Appropriate clinical trial end points remain a matter of debate, and this issue seems more pertinent in light of the overall disappointing results of multiple trials targeting angiogenesis in ovarian cancer.

In each of the published phase III trials, including the study by du Bois et al,[15] the incorporation of antiangiogenic therapy in the first-line or salvage treatment of EOC resulted in a statistically significant PFS advantage that failed to translate into a meaningful improvement in OS.[10,11,13-15] OS has always served as the gold standard end point for efficacy of any new treatment, yet this objective is difficult to attain because of the requirements of large trial size with long follow-up and the inherent inability to control for postprogression therapies and crossover. Indeed, the reported rates of crossover were substantial in the aforementioned bevacizumab phase III trials, ranging from 31% to over 40%.[10,11,13,14]

Although it is tempting to blame crossover for dilution of the survival advantages seen with bevacizumab, its true effect is difficult to estimate. An analogous conundrum occurred with incorporation of paclitaxel into the treatment of ovarian cancer. GOG 111 was a phase III, randomized trial comparing cisplatin combined with either cyclophosphamide or paclitaxel in the adjuvant treatment of 386 patients with suboptimally cytoreduced EOC.[17] The cisplatin-paclitaxel doublet experienced both a significant PFS benefit of 18 months versus 13 months ($P < .001$) as well as a significant OS benefit of 38 months versus 24 months ($P < .001$) when compared with the cisplatin-cyclophosphamide doublet.[17] When the trial was conducted, paclitaxel was not commercially available, so crossover did not occur. The replication European intergroup trial recruited 680 patients with broader selection criteria and administered paclitaxel as a 3-hour instead of a 24-hour infusion.[18] At a median follow-up of 38.5 months and despite a high rate of crossover (48%) to paclitaxel at progression, patients receiving the paclitaxel regimen still experienced a longer PFS (median, 15.5 *v* 11.5 months; log-rank $P < .001$) and a longer OS (median, 35.6 *v* 25.8 months; log-rank $P = .0016$) compared with those receiving the cyclophosphamide regimen.[18] The high rate of crossover had little effect on survival, given that the PFS and OS curves from the two studies are nearly superimposable.

Thus, it may not always be correct to ascribe lack of survival differences to crossover, and we should consider that other factors might influence the diminishing survival benefit reported in these antiangiogenic trials. One theory suggests that bevacizumab reduces peritumoral edema, converting an apparent response into a pseudoresponse that results in no real reduction in tumor burden.[19] Clearly, molecularly targeted therapies have generated a paradox whereby our preferred surrogate end points are not well correlated with the putative gold standard. Ocana et al[20] asserted that clinically meaningful differences in end points such as OS and QOL should dictate whether a study be considered positive. The authors did not entirely proscribe the use of surrogate end points; rather, they advocated that alternative metrics, such as PFS, be used

only when they are predictive of the gold standards of improvements in OS and QOL.[20] In a recently published Society of Gynecologic Oncology white paper, Herzog[21] tackled this issue by evaluating multiple clinical end points in ovarian cancer investigations. The consensus statement proposed four clinically relevant end points that were aimed at simplified interpretation of clinical trials: statistically significant improvement in OS in any setting, statistically significant improvement in PFS when supported by positive patient-reported outcome and/or health-related QOL data, statistically significant improvement in PFS alone when the clinical magnitude of effect is meaningful (eg, in first-line or platinum-sensitive disease), and statistically significant improvement in response rate or clinical benefit rate in settings in which effective options are limited (eg, in heavily pretreated platinum-resistant disease or relatively chemoresistant primary tumors). The authors opined that a large PFS benefit alone should be adequate evidence for regulatory approval of a new agent.

All five of the phase III trials discussed here demonstrated highly significant PFS advantages without OS benefits.[10,11,13-15] The paradigm shift proposed by Herzog et al[21] would likely recommend regulatory approval of both bevacizumab and pazopanib in primary treatment of advanced EOC. But preliminary data that were presented at the American Society of Clinical Oncology Annual Meeting this year call this position into question, especially in light of the Hippocratic oath that implores physicians to do no harm. Gourley et al[22] identified a molecular signature within a subset of 284 high-grade serous cancers from the ICON-7 trial in which antiangiogenic therapy might actually confer a worse PFS (HR, 1.73; 95% CI, 1.12 to 2.68; $P = .048$) and OS (HR, 2.00; 95% CI, 1.11 to 3.61; $P = .022$) when compared with chemotherapy alone. Specifically, these investigators discovered a 63-gene signature that identified an immune subgroup (41% of the ICON-7 high-grade serous specimens analyzed) that had superior PFS (HR, 0.47; 95% CI, 0.32 to 0.71; $P < .001$) and OS (HR, 0.45; 95% CI, 0.26 to 0.79; $P = .005$) when compared with the two proangiogenic subgroups combined, but which incongruously showed a decrement in survival when treated with bevacizumab.[22] Although these provocative data require further validation, they raise the possibility that the use of antiangiogenic agents may affect disease behavior in ways that are not fully predicted by preclinical models.

The assumptions recently voiced by many with respect to the addition of targeted therapies to standard cytotoxic regimens seem to be that these therapies add minimal additional toxicity to cytotoxic therapy and therefore should not require such stringent outcome parameters for approval. Yet the increased toxicity that has been observed with some antiangiogenic agents, as seen in the study reported by du Bois et al,[15] coupled with the possibility that their use may not benefit (and could harm) a subset of patients, should raise caution regarding the indiscriminant use of surrogate end points such as PFS for drug approval. Perhaps the putative gold standard of OS, especially when combined with QOL metrics, should be embraced once again. Alternatively, molecular separation of tumors may allow for identification of patients who are most likely to benefit from these targeted therapies, or the corollary, for selective withholding of targeted therapies from those who are most likely to be harmed. Until we better understand and define the important aspects of tumor biology that may govern effects of targeted therapies, it is premature to claim victory for the addition of these new agents to standard therapy for advanced ovary cancer solely on the basis of significant improvement in PFS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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