Evolving Concepts in the Management of Newly Diagnosed, Epithelial Ovarian Cancer

review article

Evolving Concepts in the Management of Newly Diagnosed Epithelial Ovarian Cancer

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INTRODUCTION

Clinical research over the last 30 years has delivered meaningful improvements in progression-free survival (PFS), overall survival (OS), and quality of life for women with epithelial ovarian cancer (EOC), as highlighted in Figure 1.[1-3] However, EOC remains a highly lethal disease because of peritoneal dissemination at diagnosis, rapid development of chemotherapy resistance, and evasion of host immune response. Minor reductions in disease-specific mortality over the last decade are more likely attributable to the use of oral contraceptives, changes in parity, and the recent expansion of risk-reducing surgery among women from high-risk genetic backgrounds, together with a reduction in long-term hormone replacement, reducing the incidence of EOC.[4-6]

Primary treatment generally incorporates surgical cytoreduction and chemotherapy with a combination of carboplatin and a taxane (paclitaxel or docetaxel), achieving clinical complete remission in more than 80% of women. Prior research focused on optimization of conventional chemotherapy (dose-intensity, dose density, incorporation of different agents), timing of cytoreductive surgery, use of regional (intraperitoneal [IP]) drug administration, and extended maintenance with cytotoxic chemotherapy during remission. With the possible exception of IP drug administration and the use of a dose-dense once-per-week schedule of paclitaxel, none of these carefully conducted, historical phase III trials established a new standard of care.

In parallel with other cancers, there has been an explosion of data related to the etiology, clinical biology, and molecular characteristics of EOC.[7-9] We now understand that EOC is a broad categorization encompassing tumors originating from the fallopian tube, ovarian surface, and cellular rests within the peritoneal cavity, including endometriosis and synchronous tumors involving the endometrial cavity. The ovaries are a favored site of tumor growth, with over 80% bilateral involvement, and large adnexal tumors are often the dominant clinical and pathologic findings, even if the tumor originated from microscopic foci within the fallopian tube or other sites.

High-grade serous carcinoma (HGSC) is the most common histology, followed by endometrioid, clear cell (CCC), low-grade serous, and mucinous carcinomas. In addition, carcinosarcoma (or mixed Müllerian tumor) is now recognized to be an aggressive clonal epithelial malignancy with focal mesenchymal differentiation, attributed to epithelial-to-mesenchymal transition. Each histology has been associated with characteristic molecular features in terms of loss of specific tumor suppressor genes, defects in high-fidelity DNA repair, and activation of signal transduction or downstream pathways. However, unlike in other cancers, reproducible driver mutations are uncommon, limiting the success of therapeutics targeting classic oncogenic signal transduction pathways.

In HGSC and CC carcinoma, there is frequent activation of hypoxia-driven proangiogenic pathways, which trigger increased production of vascular endothelial growth factor (VEGF), and this is largely responsible for capillary leak resulting in increased interstitial pressure, ascites, and pleural effusions. These VEGF-mediated effects are amenable to targeting using conventional chemotherapy, anti-VEGF monoclonal antibodies (bevacizumab), or small-molecule VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs).

In HGSC, as a consequence of homologous recombination deficiency (HRD) and replication stress, there is an opportunity for treatment with inhibitors of poly (ADP-ribose) polymerase (PARP). In addition, DNA mismatch repair and microsatellite instability have been described in a minority of endometrioid and clear cell tumors, but they are uncommon in HGSC, and it is unusual to identify high mutation burden scores in EOC, limiting the activity of single-agent immune checkpoint inhibitors.

ADJUVANT THERAPY FOR EARLY-STAGE DISEASE

The importance of accurate surgical staging is recognized,[10-13] together with the hope that detection of occult metastatic disease could be enhanced with high-resolution functional imaging and/or intraoperative molecular probes to guide surgical interventions. However, the clinical biology of HGSC is characterized by early peritoneal dissemination, and a majority of recurrences with seemingly early-stage disease result from HGSC. In contrast, nonserous tumors (CC, endometrioid, and mucinous) are more

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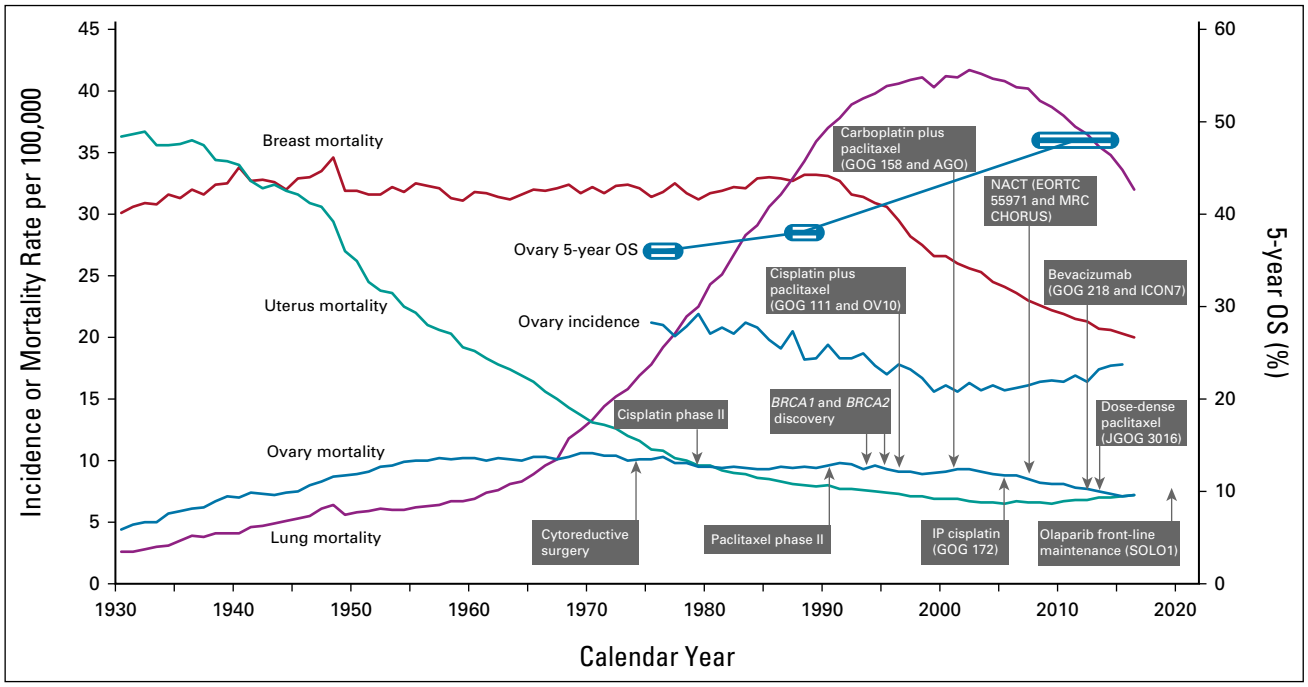

FIG 1. Trends in long-term outcomes in relation to key clinical trials and discoveries. Improvements in US 5-year overall survival (OS) are likely multifactorial, related to diagnostic modalities, access to supportive care, and treatment interventions for primary and recurrent disease. Landmark ovarian cancer discoveries and trial results are plotted along the ovarian cancer mortality curve. US mortality rates from 1930 to present day for breast, uterine (cervix and corpus combined), lung (including bronchus), and ovarian cancers (including fallopian tube and peritoneal) demonstrate a modest downward trend for women with ovarian cancer beginning approximately 2005, which may reflect changes in use of oral contraceptives and hormonal therapy, documentation of high-risk families, and implementation of risk-reducing surgery. US ovarian cancer incidence (1975 onward) also trended downward during this time period. Data adapted.[1-3] AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; MRC CHORUS, Medical Research Council Chemotherapy Or Upfront Surgery; EORTC, European Organisation for Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; ICON7, International Collaborative Ovarian Neoplasm study 7; IP, intraperitoneal; JGOG, Japanese Gynecologic Oncology Group; NACT, neoadjuvant chemotherapy; OS, overall survival; SOLO1, Study of Olaparib maintenance therapy in Ovarian cancer after first-line therapy.

commonly diagnosed in early stages, less likely associated with occult peritoneal implants, and more likely to be cured with primary surgery. These differences are perhaps most clearly illustrated in a retrospective analysis of GOG (Gynecologic Oncology Group) 157, which compared three versus six cycles of adjuvant chemotherapy.[14] In HGSC, improved recurrence-free survival was demonstrated with six cycles, and it is reasonable to recommend six cycles for women with seemingly early-stage HGSC. Among nonserous tumors, no difference was observed between three versus six cycles, although this study was not designed to assess a noninferiority end point.

- Women with seemingly early-stage HGSC should generally receive six cycles of adjuvant chemotherapy.
- The role of adjuvant chemotherapy in early-stage nonserous EOC remains to be established. It should be individualized in accordance with histology, risk factors, adequacy of surgical staging, comorbidities, and likelihood of response to platinum-based chemotherapy. If adjuvant therapy is administered, three to six cycles are generally recommended and can be considered as tolerated.

TIMING AND SCOPE OF CYTOREDUCTIVE SURGERY

With improved diagnostics, high-resolution cross-sectional and functional imaging, and advanced surgical skills, it is reasonable to expect a modest shift toward lower tumor burden at diagnosis and higher rates of optimal (microscopic) primary cytoreductive surgery (PCS). However, approximately 40% of women will continue to present with malnutrition, bowel dysfunction, extensive upper abdominal or extraperitoneal disease, large-volume ascites, advanced age, and associated comorbidities. Many of these patients will receive neoadjuvant chemotherapy (NACT) with consideration of interval cytoreductive surgery, on the basis of outcomes from multiple randomized trials in high-risk disease.

The goal of cytoreductive surgery remains the complete resection of macroscopic disease. Of note, a large retrospective analysis of primary surgery suggests that long-term benefits associated with complete cytoreduction are more apparent among women with low disease burden scores at diagnosis.[15] Patients with complete cytoreduction and high disease burden scores had outcomes similar to those of patients with suboptimal (macroscopic) cytoreduction. As

such, the impact of aggressive primary surgery in women with high disease burden remains to be established, pending results from TRUST (Trial on Radical Upfront Surgery in Advanced Ovarian Cancer).[16]

Triage of patients for PCS or NACT with consideration of interval cytoreductive surgery can be challenging because of imaging studies, which may under- or overestimate the extent of invasive or metastatic disease. Validated models can predict the likelihood of achieving complete primary cytoreduction on the basis of clinical factors.[17] Other models have incorporated laparoscopic assessment of disease burden.[18,19] In addition, molecular markers related to transforming growth factor β pathway activation and invasive mesenchymal biology can predict for a lower likelihood of achieving complete cytoreduction, but they are not yet sufficiently robust to drive surgical decisions,[20] and we await the emergence of models that integrate molecular and clinical factors.

- Although efforts to refine the integration of surgery and chemotherapy are important, the practical limitations of conventional chemotherapy and surgery in the setting of advanced disease are well recognized, and additional strategies are needed to substantially improve long-term outcomes for a majority of patients.

PRIMARY CHEMOTHERAPY

The development of cisplatin was pivotal in the evolution of early chemotherapy regimens for EOC, although complicated by significant hematologic and nonhematologic toxicities. Two phase III trials demonstrated improved OS with a combination of cisplatin and paclitaxel (as a 24-hour infusion) compared with cisplatin and cyclophosphamide[21,22] at a time when investigational paclitaxel was in limited supply and not available outside a clinical trial. Substitution of carboplatin for cisplatin and use of a 3-hour outpatient paclitaxel infusion reduced nonhematologic toxicity and improved overall tolerability, while maintaining therapeutic efficacy.[23-25]

Historical questions remain regarding the advantage of combination regimens compared with sequential single-agents (eg, carboplatin followed by paclitaxel at progression), especially in higher-risk or frail elderly populations.[26,27] However, combinations of paclitaxel with carboplatin are unusual, maintaining the capability to safely administer full doses of both drugs on a 21-day schedule, which has been attributed, in part, to a platelet-sparing effect of paclitaxel on carboplatin-mediated thrombocytopenia.[28] In patients age older than 70 years, a number of studies have demonstrated an association between frailty scoring systems, such as comprehensive geriatric assessment,[29] instrumental activities of daily living,[30] or geriatric vulnerability score,[31] and completion of chemotherapy, development of toxicity, or OS. The EWOC-1 (Elderly Women Ovarian Cancer) study is a prospective randomized study that is currently investigating the extent of benefit and toxicity resulting from the addition of paclitaxel to single-agent carboplatin in vulnerable patients defined by a geriatric vulnerability score greater than 3.

Carboplatin is largely cleared through the kidneys, and achieving a targeted area under the curve (AUC) of concentration × time depends on the glomerular filtration rate (GFR). GFR is no longer usually measured but instead imputed on the basis of the estimated creatinine clearance (CrCl) using an established formula, which relies on a spot measure of serum creatinine. This has proven to be problematic, because most formulae were derived from male patients with near-normal renal function using older methods to standardize creatinine measurements. In addition, women with advanced-stage ovarian cancer typically have reduced nonphysiologic creatinine levels because of decreased muscle mass, malnutrition, decreased distal tubal reabsorption, and other factors, compounded by changes in laboratory reporting on the basis of traceable standards with isotope dilution mass spectrometry (IDMS), which tends to lower reported creatinine values, generating false high estimated CrCl, with risk of carboplatin overdosage. Current US recommendations cap the estimated CrCl to reduce risk; we await better validated methods using IDMS.[32,33]

After a number of international phase III trials involving more than 12,000 women, there is no prospective evidence that higher platinum dose-intensity (with or without hematopoietic growth factor support) extended cycles of chemotherapy, maintenance chemotherapy, incorporation of a third cytotoxic agent, or substitution of cytotoxic agents will improve long-term outcomes for unselected patients with HGSC.[34-40] These limitations of conventional cytotoxic chemotherapy have largely been attributed to the rapid emergence of drug resistance to platinum compounds, natural products, and nucleoside analogs through multiple independent cellular pathways. As such, standard-dose carboplatin and paclitaxel remains a well-tolerated and effective primary treatment regimen and is consistently recommended as a reference arm for trials in advanced-stage disease by the Gynecologic Cancer InterGroup.[41]

Questions remain regarding optimal dose selection, management of hematologic toxicity, and use of granulocyte colony-stimulating factors. In a retrospective analysis of patients enrolled in a phase III trial with advanced-stage disease, dose modification was associated with a reduction in PFS and OS, but also with confounding variables such as performance status, stage, histology, and residual disease in an adjusted multivariable analysis.[42] Use of granulocyte colony-stimulating factors, with or without associated dose modification, did not have a discernable impact on PFS or OS. When considered together with a large body of negative data from prospective randomized trials evaluating platinum dose-intensity, it is likely that patients with dose modifications also had other prognostic factors contributing to increased risk, rather than there being a direct

relationship between minor variations in carboplatin AUC and survival.

- Within established ranges (AUC, 5 or 6), carboplatin dosing can be individualized depending on vital organ function, comorbidities, and tolerance. Similarly, paclitaxel can be administered in the range of 135 to 175 mg/m^2 as a 3-hour infusion, based largely on assessment of risk factors for peripheral neuropathy.
- Aberrant low creatinine levels and IDMS reporting should be considered when estimating GFR. In the absence of a measured GFR or a validated estimated GFR that is accurate at low creatinine levels, physiologic limits should be applied for patient safety (minimum creatinine, 0.70 mg/dL; estimated GFR not higher than 125 mL per minute).

IP CHEMOTHERAPY

Given that ovarian cancer is largely a locoregional disease with peritoneal dissemination predominating over visceral metastases, the idea of delivering a high local dose of cytotoxic therapy is appealing. However, peritoneal tumors are characterized by high interstitial pressures attributable to VEGF-mediated capillary leak and the absence of draining lymphatics, limiting the penetration of diffusion-limited drugs, such as cisplatin. The initial proof of principle for IP chemotherapy was provided by GOG 104, comparing intravenous (IV) cyclophosphamide plus either IV or IP cisplatin 100 mg/m^2.[43] This straight comparison favored IP cisplatin in terms of OS, but at the expense of increased cisplatin-mediated toxicity in both arms. Of note, a subset analysis suggested that the benefit was confined to patients with macroscopic small-volume residual disease, without benefit in patients with microscopic residual disease, challenging a number of assumptions. By the time of publication, the standard of care for first-line therapy had evolved to cisplatin and paclitaxel, followed by a rapid transition to carboplatin and paclitaxel, raising questions of relevance and prompting other trials.

GOG 114 compared IV paclitaxel (135 mg/m^2 over 24 hours) and IV cisplatin (75 mg/m^2) for six cycles with IV carboplatin (AUC, 9) for two cycles followed by IV paclitaxel (135 mg/m^2 over 24 hours) and IP cisplatin (100 mg/m^2) for six cycles (total of eight cycles).[44] Although there was improved efficacy in the IP arm, the study compared different doses and durations of platinum, associated with increased hematologic toxicity, and was not endorsed by the authors as practice changing.

GOG 172 then compared IV paclitaxel (135 mg/m^2 over 24 hours) with either IV cisplatin (75 mg/m^2) or IP cisplatin (100 mg/m^2) followed by IP paclitaxel (60 mg/m^2 day 8) in patients with postoperative residual disease less than 1 cm.[45] A significant survival benefit was demonstrated in favor of the IP arm (median, 66 *v* 50 months), and this triggered a National Cancer Institute alert recommending consideration of IP cisplatin in appropriate patients. However, the study was challenged on the basis of nonequivalent platinum dosing and the additional IP paclitaxel on day 8 (adding a once-per-week paclitaxel component in the IP arm), limiting conclusions about IV versus IP cisplatin. However, the median OS in the IP arm was exceptional, particularly in patients with no visible residual disease at the end of primary surgery (127 months).[46]

The most recently reported phase III GOG study (GOG 252) compared three arms, IV paclitaxel (80 mg/m^2 once per week) plus IV carboplatin (AUC 6, once every 3 weeks) with IV paclitaxel (80 mg/m^2 once per week) plus IP carboplatin (AUC 6, once every 3 weeks) with IV paclitaxel (135 mg/m^2 on day1), IP cisplatin (75mg/m^2 on day 2), and IP paclitaxel (60 mg/m^2 on day 8).[47] The third arm was a modification of the IP regimen from GOG 172. In this study, all patients received concomitant and maintenance bevacizumab (15 mg/kg once every 3 weeks) for a total of 22 cycles. There was no difference in either PFS or OS among the arms. Unlike prior studies, GOG 252 permitted limited enrollment of patients with suboptimal residual disease (as an exploratory end point), and a subset analysis excluding patients with suboptimal residual disease also showed no difference in PFS. This was a large study that accrued rapidly and included a contemporary chemotherapy foundation. Although concerns have been expressed regarding the modest reduction in IP cisplatin (compared with GOG 172), this improved tolerability and increased the number of IP cisplatin cycles per patient. Even with this change, the IP cisplatin arm was associated with increased toxicity compared with both carboplatin arms.

Concerns have also been raised regarding the inclusion of bevacizumab. However, in the setting of small-volume residual disease, bevacizumab would (at most) be associated with a modest improvement in PFS, without impact on OS. In addition, on the basis of data from GOG 262, there is no net gain in PFS anticipated from bevacizumab in combination with once-per-week scheduling of paclitaxel, as used in GOG 252. On a positive note, the median OS for all three arms in GOG 252 exceeded the median OS demonstrated in the IP arm in GOG 172 (and prior IP studies), consistent with improvements in surgery, chemotherapy, diagnostic imaging, and supportive care. Data from a Japanese trial of IP carboplatin without bevacizumab (iPocc) will further address these concerns.

- The optimal role of IP cisplatin–based chemotherapy (without hyperthermia) remains to be established, but it is an effective regimen that can be considered for individual patients, after a clear discussion of potential risks and benefits.
- Median and 5-year OS associated with contemporary IV chemotherapy have improved, compared with regimens used in earlier clinical trials, without a demonstrated advantage associated with IP chemotherapy.

DOSE-DENSE PACLITAXEL WITH CARBOPLATIN

As a single agent in the setting of recurrent disease, paclitaxel administered once per week seems superior to paclitaxel administered once every 3 weeks.[48] Although this has been loosely attributed to dose density, there are no prospective data to validate the importance of paclitaxel dose-intensity within a clinically tolerable range. Modifications of paclitaxel infusion duration (1 to 96 hours) and/or schedule have a clear impact on the spectrum and severity of host toxicity. In addition, sustained low-level exposure from once-per-week scheduling (independent of dose) can have an impact on tumor-associated angiogenesis.[49] In this regard, early trials documented tumor response at levels of 40 mg/m^2 per week, compared with a maximally tolerated single-agent dose of 80 mg/m^2 per week.[50]

In JGOG (Japanese Gynecologic Oncology Group) 3016, carboplatin in combination with dose-dense once-per-week paclitaxel (at 80 mg/m^2 per week) demonstrated improved PFS and OS compared with a standard regimen of once every 3 weeks. Not surprisingly, there was substantial hematologic toxicity, with frequent dose reductions and delays, and approximately 40% of patients received fewer than six cycles.[51] These intriguing data were further evaluated in multiple phase III trials, but with somewhat discordant results.

MITO-7 (Multicenter Italian Trials in Ovarian Cancer) compared once-per-week dosing of carboplatin (AUC, 2) and paclitaxel (60 mg/m^2) with a regimen of once every 3 weeks using equivalent cumulative dosing, without any advantage in PFS or OS. However, the once-per-week regimen was favored based on a reduction in neuropathy and hematologic toxicity.[52] The contrasting lack of improvement with once-per-week dosing raised questions about potential differences between Asian versus white populations, as well as the potential negative impact of fractionating carboplatin, which could be associated with lower peak drug concentrations and impaired tumor penetration.

ICON8 was a large (N = 1,565) three-arm trial that compared standard dosing of once every 3 weeks versus once-per-week scheduling of both drugs (similar to MITO-7) versus once-per-week paclitaxel (80 mg/m^2) with carboplatin once every 3 weeks (similar to JGOG 3016).[53] As anticipated, increased hematologic toxicity was observed in both once-per-week paclitaxel regimens. The primary analysis showed no significant difference in PFS for once-per-week paclitaxel (hazard ratio [HR], 0.92; 95% CI, 0.77 to 1.09) or once-per-week carboplatin and paclitaxel (HR, 0.94; 95% CI, 0.79 to 1.12). A subset analysis demonstrated an overall reduction in median PFS among patients with delayed cytoreductive surgery compared with immediate surgery, but drug scheduling had no impact in either cohort. Mature OS data are pending.

GOG 0262 compared standard dosing of once every 3 weeks versus once-per-week paclitaxel (80 mg/m^2) with carboplatin once every 3 weeks (similar to JGOG 3016), but with the addition of bevacizumab in both arms.[54] Patients could elect whether to receive bevacizumab, and 19% (n = 112) chose not to receive it. Among the entire intent-to-treat population and within the subset receiving bevacizumab, there was no difference in PFS. However, in the cohort that did not receive bevacizumab, paclitaxel once every 3 weeks was inferior to all other cohorts, and paclitaxel once per week without bevacizumab was similar to both arms that included bevacizumab (Fig 2). This interesting observation suggests that once-per-week paclitaxel had clinical antiangiogenic properties, as hypothesized from earlier single-agent studies. In addition, when blood volume indices were analyzed using perfusion-weighted computed tomography imaging within an exploratory companion study, ACRIN (American College of Radiology Imaging Network) 6695, there was an association between decreased tumor blood flow and improved PFS, providing additional support regarding the antiangiogenic impact of once-per-week dosing.[55]

It is challenging to reconcile these discordant observations across multiple randomized trials. However, there are some key points to consider:

- Among Asian patients not receiving bevacizumab, use of once-per-week dose-dense paclitaxel is preferred, and we await pharmacogenomic or other data to explain potential regional differences.[56]
- If primary chemotherapy is administered in conjunction with bevacizumab, standard therapy of once every 3 weeks is preferred.
- In patients with high-risk disease receiving NACT, use of once-per-week paclitaxel is preferred by the authors to avoid potential toxicity and perioperative complications associated with bevacizumab. In this setting, it would be reasonable to consider a lower once-per-week dose of paclitaxel (60 to 70 mg/m^2) to minimize cumulative hematologic toxicity and peripheral neuropathy while maintaining antiangiogenic potential. Alternatively, conventional paclitaxel and carboplatin dosing of once every 3 weeks with bevacizumab can be considered, omitting bevacizumab in the cycle before and the cycle after interval debulking surgery.

OPTIMAL USE OF BEVACIZUMAB

Hypoxia-driven proangiogenic pathways are activated in HGSC, with production of VEGF and other molecules that promote tumor neovascularization. Tumor capillary beds are characterized by abnormal branching, incomplete podocyte coverage, and leaky endothelial junctions, which contribute to poor tumor perfusion, production of ascites, and elevated tumor interstitial pressure, effectively limiting diffusion-based drug penetration. Targeting VEGF can rapidly reverse these findings, resulting in increased tumor drug penetration, including platinum agents.[57] However, macromolecules (including monoclonal antibodies) can exhibit decreased tumor penetration.[58,59] There is also

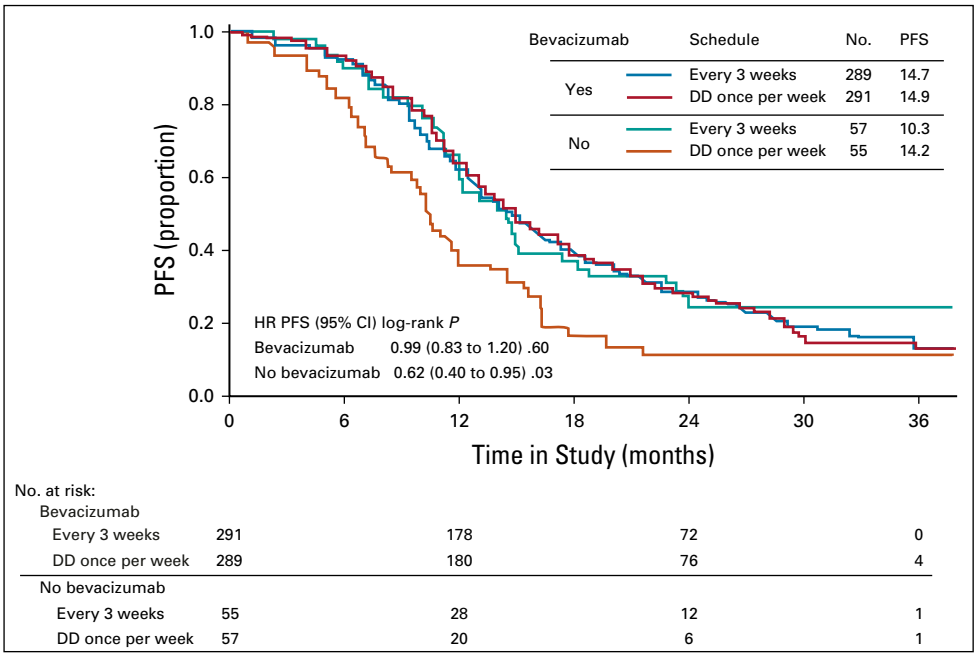

FIG 2. Association of improved progression-free survival (PFS) with use of dose-dense (DD) paclitaxel in the absence of bevacizumab. GOG (Gynecologic Oncology Group) 0262 compared conventional carboplatin (area under the curve, 6) once every 3 weeks and paclitaxel 175 mg/m^2 with a DD regimen of carboplatin (day 1) and paclitaxel 80 mg/m^2 (days 1, 8, and 15). Use of bevacizumab (concurrent and maintenance) was elected before random assignment, with 580 patients receiving bevacizumab and 112 patients not receiving bevacizumab. Among patients who did not receive bevacizumab, there was a significant improvement in the hazard ratio (HR) for PFS associated with once-per-week DD paclitaxel, similar to the impact of concurrent and maintenance bevacizumab in other front-line trials (GOG 0218 and ICON7).

heterogeneity in the tumor response to bevacizumab-induced hypoxia, which has been associated with bevacizumab resistance.[60] Resistance could also be associated with persistence of small-volume residual disease through simple diffusion, independent of tumor angiogenesis.[61] Questions regarding the dose-response and dose-toxicity relationships with bevacizumab have not been adequately explored, with some clinical data suggesting that excessive vascular remodeling could encourage resistance by reducing overall tumor perfusion and drug exposure.[62]

Front-line phase III trials (ICON7 and GOG 0218) have demonstrated improved PFS with incorporation of concurrent and maintenance bevacizumab, particularly in patients with bulky high-risk disease.[63,64] A subset analysis of ICON7 also suggested a modest improvement in OS within a predefined high-risk population.[65] However, an advantage in OS was not observed in GOG 0218, even though most patients enrolled with high-risk disease. This seeming discordance has been attributed to different international practice patterns, as well as crossover to commercial bevacizumab postprogression, which was estimated at 30% in GOG 0218, compared with essentially no crossover in ICON7.

Randomized phase III trials in recurrent disease (platinum sensitive and resistant) have also documented improvements in PFS with bevacizumab, achieving lower HRs, compared with front-line clinical trials.[66-68] As noted, microscopic residual disease (below the diffusion threshold) would be less affected by targeting VEGF, compared with established macroscopic disease, and this could limit the clinical effectiveness of front-line interventions. In addition, the combination of PCS and initial platinum-based chemotherapy frequently achieves greater than a 90% reduction in tumor burden, which also eliminates tumor-associated VEGF production, independent of targeted interventions.

Although bevacizumab is well tolerated by most patients, and common toxicities, such as hypertension, can be medically managed, it clearly contributes to treatment-related toxicity, financial costs, and complexity of care in this high-risk population. US Food and Drug Administration and European Medicines Agency regulatory approvals have been obtained in both front-line and recurrent disease settings, but industry-driven regulatory approvals do not have the same implications as consensus-based treatment guidelines or expert recommendations. The following points merit consideration:

- Among newly diagnosed patients who are candidates for platinum-based chemotherapy and cytoreductive surgery, the prolongation of PFS is modest,

approximately 4 months, in exchange for 6 months of concurrent therapy and single-agent maintenance extending beyond a year, without objective evidence of clinical benefit in terms of quality of life, time without symptoms or toxicity, or increased OS.

- Although data have validated the clinical role of VEGF and targeted interventions, it would be reasonable to plan primary therapy without bevacizumab, reserving bevacizumab for management of recurrent disease, when the benefit-risk ratio is maximized. Conversely, the use of bevacizumab in the first-line setting is also reasonable, especially if chemotherapy dosing of once every 3 weeks is used, after consideration of the risks and benefits of this strategy in the individual patient.
- Among patients with bulky disease, large-volume ascites, and/or pleural effusions, bevacizumab could be integrated with primary chemotherapy to accelerate clinical response, but the potential role of extended maintenance therapy would be subject to the same limitations noted.
- Focused postmarketing (phase IV) studies could address questions regarding dose, schedule, duration of maintenance, and predictive markers.
- Ongoing phase III trials are addressing combinations of bevacizumab with immune checkpoint inhibitors to enhance the host antitumor immune response.

TKIs THAT TARGET THE VEGFR PATHWAY

A majority of trials targeting VEGF-mediated angiogenesis in ovarian cancer have used bevacizumab, although two international trials led by the Arbeitsgemeinschaft Gynäkologische Onkologie have investigated multikinase inhibitors in the first-line setting. Pazopanib (an inhibitor of VEGFR, platelet-derived growth factor receptor, and c-kit) was evaluated as maintenance in patients with remission after first-line chemotherapy and resulted in a 5.6-month PFS advantage without improvement in OS.[69] Nintedanib (an inhibitor of VEGFR, platelet-derived growth factor receptor, and fibroblast growth factor receptor) was evaluated as concomitant and maintenance first-line therapy, resulting in a 0.6-month improvement in PFS.[70] In contrast to bevacizumab, an exploratory subset analysis with nintedanib indicated that prolongation of PFS was primarily associated with small-volume residual disease rather than large-volume disease. These results further validate the importance of angiogenic signaling and highlight potential differences between ligand binding (bevacizumab) and multikinase receptor inhibition, including organ-specific toxicity, but they have not had a broad impact on clinical practice.

ROLE OF PARP INHIBITION

After previous demonstrations of PARP inhibitor efficacy in both the single-agent monotherapy and maintenance relapsed disease settings, the SOLO1 study reported a striking impact of first-line maintenance olaparib among women with high-grade serous or endometrioid ovarian cancer associated with a *BRCA1* or *BRCA2* germline (or somatic) mutation, in remission after primary surgery and chemotherapy.[71] The HR for PFS was 0.30 (95% CI, 0.23 to 0.41), together with a 3-year advantage in median PFS, achieving US Food and Drug Administration approval for *BRCA*-mutated advanced ovarian cancer in December 2018, although mature OS data are pending. It remains unclear whether the impact of first-line maintenance would extend to unselected patients with *BRCA* wild-type (WT) tumors or whether there is a role for molecular selection on the basis of HRD or other factors. PRIMA (ClinicalTrials.gov identifier: NCT02655016) is a phase III trial evaluating first-line maintenance with niraparib within a more diverse patient population, including tumors with and without *BRCA* mutations. PAOLA-1 (Platine, Avastin and Olaparib in 1st Line; ClinicalTrials.gov identifier: NCT02477644) randomly assigns patients to olaparib or placebo maintenance in combination with bevacizumab maintenance after first-line platinum-based chemotherapy plus bevacizumab. These studies, which are expected to report within the next 12 months, should help to clarify the extent of benefit within the *BRCA* WT population and also shed some light on the utility of the PARP inhibitor bevacizumab combination in the first-line setting.

Combinations of PARP inhibitors with platinum-based chemotherapy have been difficult to develop because of increased hematologic toxicity, but a phase III trial of concurrent and maintenance veliparib (GOG 3005; ClinicalTrials.gov identifier: NCT02470585) has been completed, and primary end points are anticipated in 2019. Current considerations include the following:

- Women with germline or somatic *BRCA* mutations should consider first-line maintenance with olaparib while in remission after primary surgery and chemotherapy.
- Assessment of the relative risks and benefits associated with maintenance PARP inhibition in women without germline or somatic *BRCA* mutations awaits data from ongoing phase III trials.

ONGOING FIRST-LINE STUDIES

Benchmark phase III trials have highlighted the limitations of conventional cytotoxic chemotherapy, drug resistance, and addition of single-agent biologics. Key paradigms with the potential to transform first-line treatment emphasize the integration of antiangiogenics, PARP inhibitors, and immune checkpoint inhibitors, exploiting shared pathway interactions.

Preclinical evidence of synergy between antiangiogenic agents and PARP inhibitors derives from cancer cell lines that demonstrate hypoxia-induced downregulation of HRD genes (and the potential for this to result in increased PARP

inhibitor sensitivity).[72,73] In vivo models have also demonstrated that *PARP-1* gene knockout or PARP inhibition results in reduced angiogenesis.[74] In patients with relapsed platinum-sensitive high-grade serous or endometrioid ovarian cancer, administration of cediranib (a multi-VEGFR TKI) in combination with olaparib was associated with a prolongation in PFS, compared with olaparib alone, with a particularly marked effect in *BRCA* WT patients.[75] This observation led to randomized trials such as PAOLA-1 combining antiangiogenic agents with PARP inhibitors as first-line maintenance, with an emphasis on patients without germline or somatic *BRCA* mutations.

The efficacy of single-agent immune checkpoint inhibitors in relapsed ovarian cancer has been disappointing to date. The possibility that efficacy may be superior in the first-line setting has been explored in the JAVELIN Ovarian 100 trial of avelumab in combination with and/or as a maintenance treatment after carboplatin plus paclitaxel chemotherapy in previously untreated patients with stage III or IV ovarian cancer. Although results have not been formally reported, an interim analysis suggests that the study will not achieve superiority in the prespecified primary end point of PFS. There does remain interest in antiangiogenic-immunotherapy combinatorial strategies to block tumor-associated VEGF, which can interfere with normal dendritic cell maturation, largely mediated through VEGFR1.[76] Bevacizumab has also been shown to enhance CD8 lymphocyte localization within tumors and alter expression of major histocompatibility complex and chemokines associated with the antitumor immune response, particularly when administered in combination with anti–programmed death ligand 1 (PD-L1) antibodies.[77] Phase III trials are currently evaluating combinations of bevacizumab with immune checkpoint inhibitors during front-line therapy and maintenance postchemotherapy, with data anticipated to emerge over the next 3 years. IMagyn050 (GOG 2015/ENGOT [European Network of Gynaecological Oncological Trial Groups] OV39; ClinicalTrials.gov identifier: NCT03038100) is one such trial; it randomly assigns patients to carboplatin, paclitaxel, bevacizumab, and either atezolizumab or placebo (with both bevacizumab and atezolizumab or placebo being administered concomitantly with chemotherapy and as a maintenance).

The PARP inhibitor–immunotherapy combination has perhaps generated the most interest of late. Germline *BRCA1*- or *BRCA2*-mutated HGSC has increased neoantigen load, PD-1/PD-L1 expression, and lymphocyte infiltration compared with *BRCA* WT cancers.[78] These features, along with the suggestion that PARP inhibitors upregulate PD-L1 expression and enhance tumor-associated immunosuppression in breast cancer, provide some rationale for combining PARP inhibitors and immune checkpoint inhibitors.[79] A small phase I/II trial (MEDIOLA [MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors]; ClinicalTrials.gov identifier: NCT02734004) combining olaparib and durvalumab demonstrated a 70% response rate in patients with relapsed, platinum-sensitive, *BRCA*-mutated ovarian cancer.[80] Currently, at least five large randomized phase III studies of PARP inhibitors plus immune checkpoint inhibitors are now under way: ATHENA (rucaparib and nivolumab; ClinicalTrials.gov identifier: NCT03522246), DUO-O (Durvalumab-Olaparib in Ovarian Cancer; olaparib and durvalumab; ClinicalTrials.gov identifier: NCT03737643), FIRST (First-Line Ovarian Cancer Treatment With Niraparib Plus TSR-042; niraparib and TSR042; ClinicalTrials.gov identifier: NCT03602859), JAVELIN Ovarian PARP 100 (talazoparib and avelumab; ClinicalTrials.gov identifier: NCT03642132), and MK-7339-001/ENGOT-OV43 (olaparib and pembrolizumab; ClinicalTrials.gov identifier: NCT03740165).

Key considerations related to ongoing research:

- Maximal benefit has been achieved with cytoreductive surgery and conventional platinum-based chemotherapy, limited by the emergence of drug resistance.
- Addition of single agents targeting angiogenesis has extended PFS without a clinically significant improvement in OS.
- The activity of single-agent PARP inhibitors seems most significant in tumors with *BRCA* mutations or HRD. In addition, improvements in PFS have not yet translated to OS, and long-term outcomes are limited by emergence of PARP resistance.
- Preclinical studies and early-phase clinical trials have highlighted potential interactions between antiangiogenics, PARP inhibitors, and immune checkpoint inhibitors, providing a basis for ongoing phase III trials of targeted combinations together with primary chemotherapy and/or first-line maintenance.

LIMITATIONS OF CURRENT EVIDENCE

Despite the progress in first-line treatment of ovarian cancer, there remain a number of significant uncertainties. It is now clear that ovarian cancer histologic subtypes differ in terms of their cells of origin, molecular biology, chemotherapy sensitivity, and clinical behavior. Many of the pivotal trials discussed here are numerically dominated by HGSC. As such, consideration must be given to the extent to which the findings can be extrapolated to rarer subtypes, which may have had low representation within the key phase III trials.

Examples of this concept include the uncertainty surrounding the use of postoperative chemotherapy in low-grade serous ovarian cancer, a disease in which response rate to classic platinum-based chemotherapy may be as low as 5%.[81] Instead, consideration could be given to the use of aromatase inhibitors[82] or bevacizumab[83,84] based upon historic disease-specific data, without prospective randomized trials.. Another example of histology-related

uncertainty surrounds the use of adjuvant chemotherapy in early-stage CCC. The risk of relapse in patients with International Federation of Gynecology and Obstetrics stage IA or IB disease, as well as those with stage IC disease resulting from capsular rupture, seems to be low, and the benefit of adjuvant treatment in these patients may be small.[85] The extent of chemotherapy benefit in patients with other stage IC disease and beyond is unclear, particularly given that CCC is relatively chemotherapy resistant compared with HGSC in the advanced-disease setting (where disease is evaluable for response).

FUTURE DIRECTIONS

Immediate priorities for clinical research in the setting of primary therapy include combination strategies with antiangiogenic agents, PARP inhibitors, and immune checkpoint inhibitors. For example, it is important to build upon the success of SOLO1 front-line maintenance by determining whether adjuvant PARP inhibition also has significant efficacy in *BRCA* WT HGSC, whether molecular selection is required (eg, determination of HRD), or whether PARP inhibitor effectiveness can be enhanced through combinations with antiangiogenic agents or immune checkpoint inhibitors.

Current clinical trial paradigms generally rely on a reference arm with one novel drug and then add additional novel drugs in the primary treatment or maintenance setting, limiting the discovery of novel markers of sensitivity to individual agents; instead, the outcome data are a measure of the efficacy of the combination. However, the interrogation of longitudinal patient samples, whether tumor specimens or plasma cell-free DNA, may help identify inherent resistance mechanisms, such as secondary mutations in *BRCA1/2* or *RAD51C/D* genes for patients treated with PARP inhibitors, and facilitate individualization of care in this way.[86,87] Finally, greater understanding of the molecular landscape of rare chemotherapy-resistant histologic subtypes such as CCC and low-grade serous carcinoma is required to improve first-line therapeutic options for these patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Evolving Concepts in the Management of Newly Diagnosed Epithelial Ovarian Cancer

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