Management of Newly Diagnosed or Recurrent Ovarian Cancer

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Abstract: The treatment of newly diagnosed or recurrent ovarian cancer has changed significantly in recent years, with an increased number of treatment options available. Surgery and combination treatment with carboplatin and paclitaxel are the standard of care for patients with newly diagnosed disease, although the use of neoadjuvant chemotherapy is increasing. Clinical strategies have also evolved along with the understanding that ovarian cancer is not one disease but rather comprises several with different histologic and underlying genetic characteristics. The most common histologic type is high-grade serous carcinoma, which is associated with underlying DNA repair deficiencies and copy number alterations. Other, less common histologic types include endometrioid (both low- and high-grade) as well as low-grade serous, mucinous, and clear cell carcinomas. Antivascular agents (specifically bevacizumab) and poly(ADP-ribose) polymerase (PARP) inhibitors have received regulatory approval for many aspects of treatment. PARP inhibitors, which inhibit DNA repair, have shown the greatest activity in those ovarian cancers that harbor deleterious *BRCA* mutations, and they have also demonstrated activity in the maintenance setting after a response to and completion of platinum-based chemotherapy in patients with sensitive recurrent ovarian cancer regardless of *BRCA* status. Newer or experimental strategies to improve both up-front and second-line or later treatment include the addition of biologic agents to chemotherapy; the use of newer combination strategies that employ antivascular agents, PARP inhibitors, and immuno-oncology drugs; and the use of new agents such as antibody-drug conjugates.

Keywords
Antivascular agents, ovarian cancer, PARP inhibitors

Introduction

Ovarian cancer is diagnosed in approximately 22,440 women per year in the United States, most often at an advanced stage, and causes 14,080 deaths each year.[1] To date, no effective screening test exists that enables the early detection of ovarian cancer and leads to a reduction in mortality.[2]

Histologic Subtypes

Although once thought of as a single entity, ovarian cancer is currently divided into several histologic subtypes that differ in genetic composition and clinical characteristics, for which increasingly tailored treatments are now used.[2] Epithelial ovarian cancer comprises serous (high- and low-grade), endometrioid (high- and low-grade), clear cell, and mucinous histologic subtypes. High-grade serous carcinoma (HGSC) is the most commonly diagnosed subtype of ovarian cancer and frequently exhibits *TP53* gene, copy number, and DNA repair gene alterations. Approximately 50% of HGSCs have homologous repair deficiency (HRD), which increases sensitivity to platinum and poly(ADP-ribose) polymerase (PARP) inhibitors.[3,4] Low-grade endometrioid and low-grade serous carcinomas typically are biologically indolent and respond to hormonal therapies.[5,6] Mucinous cancers frequently have *KRAS* mutations, and these cancers are less sensitive to chemotherapy.[7,8] Clear cell cancers are associated with endometriosis, are less sensitive to platinum and chemotherapy, and have phosphoinositide 3-kinase pathway aberrations.[9,10] Specific guidelines outlining clinical and research challenges have been published for rare subtypes.[7,9]

Ovarian Cancer Genetics

The inheritance of high-risk genes is responsible for approximately 20% of all HGSCs, with *BRCA1* and *BRCA2* the ones most commonly inherited. As a result, methods to detect these high-risk mutations in women make up a sound preventive strategy.[3,4,11,12] Moreover, mutations in *BRCA* increase the risk for other cancers. People with the *BRCA1* mutation are at increased risk for breast cancer, and people with the *BRCA2* mutation are at increased risk for pancreatic cancer, prostate cancer, and melanoma.[3] An additional 9 genes besides *BRCA1* and *BRCA2* are known to increase ovarian cancer risk: *RAD51C*, *RAD51D*, *BRIP1*, *BARD1*, *PALB2*, *MLH1*, *PMS2*, *MSH2,* and *MSH6. RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, and *BARD1* are part of the Fanconi anemia pathway, whereas *MSH2*, *MLH1*, *PMS2*, and *MSH6* are involved in DNA mismatch repair.[12] The international standard of care is to offer genetic testing to all women in whom ovarian, peritoneal, or fallopian tube cancer is diagnosed (all of which are Müllerian derived and are grouped together), regardless of age, family history, or ovarian cancer histology.[13]

Treatment of Newly Diagnosed Ovarian Cancer

Surgery

The foundation of the treatment of newly diagnosed ovarian cancer traditionally has been up-front surgery (known as cytoreductive or debulking surgery), followed by platinum and taxane chemotherapy for 6 cycles. Surgery performed by a trained gynecologic oncologist improves survival and allows pathologic evaluation and staging with the International Federation of Gynecology and Obstetrics (FIGO) staging system.[14,15] The goal is to achieve the macroscopically complete resection of disseminated ovarian cancer. The results of surgical debulking are typically referred to as suboptimal (≥1 cm of residual cancer), optimal (<1 cm of residual cancer), or R0 (no visible residual disease), with newer studies defining optimal as the achievement of macroscopically complete resection. The level of cytoreduction predicts outcome; patients with R0 resections have the best outcomes.[16,17] Additionally, it is critical for the gynecologic oncology surgeon to determine the appropriateness of up-front surgery vs neoadjuvant chemotherapy (NACT), discussed below.

Neoadjuvant Chemotherapy

The treatment paradigm of debulking surgery followed by chemotherapy for patients with newly diagnosed advanced ovarian cancer has been challenged by the recognition that patients with R0 resections have the best outcomes, so those patients in whom cytoreduction to R0 is not possible may not benefit from up-front debulking surgery. Additionally, 2 studies have demonstrated equivalence in progression-free survival (PFS) and overall survival (OS) for debulking surgery followed by chemotherapy vs NACT, interval debulking surgery, and completion of chemotherapy.[18,19] The European Organisation for Research and Treatment of Cancer (EORTC) study that compared these 2 treatment paradigms demonstrated no significant differences between PFS (12 months for both groups) and OS (29 months for primary surgery and 30 months for NACT) in the 2 groups.[18] The CHORUS study, which was similarly designed, also showed no differences between the outcomes of debulking surgery followed by chemotherapy and those of the NACT approach (Table 1).[19] Additionally, in both studies, fewer postoperative deaths occurred in the NACT group. Controversy exists over the equivalency of the 2 approaches in those patients who are deemed operative candidates up front, for whom surgery is still considered the standard of care. In addition, techniques to assess surgical debulking have been studied,[20] and the Society of Gynecologic Oncology and the American Society of Clinical Oncology have jointly released guidelines on NACT.[21]

Chemotherapy

Chemotherapy for advanced ovarian cancer has evolved from the combination of cisplatin or carboplatin with cyclophosphamide, which was used in the 1980s and 1990s, to the current international standard of care,

which is intravenous (IV) carboplatin and paclitaxel given every 3 weeks (Table 1).[22-26] Some trials have challenged the platinum/taxane backbone standard, including the Gynecologic Oncology Group (GOG)-182 study, which tested newer sequential platinum doublets and triplets and found that none of the experimental arms was superior to carboplatin/paclitaxel.[27] Additionally, the outcomes with docetaxel/carboplatin were similar to those with paclitaxel/carboplatin, with less neuropathy observed in the docetaxel arm.[28] Nontaxane agents have been substituted for paclitaxel, specifically pegylated liposomal doxorubicin (PLD). Carboplatin/PLD achieved PFS and OS comparable to those with carboplatin/paclitaxel (Table 1),[29] thus offering an option for patients unable to receive paclitaxel. Other important studies include GOG-172, which tested intraperitoneal (IP) cisplatin and IV/IP paclitaxel vs IV cisplatin and paclitaxel in patients with optimally cytoreduced (defined as <2 cm of residual cancer at the completion of surgery) newly diagnosed ovarian cancer.[30] Although the IP regimen improved OS by 16 months, it also caused a higher rate of toxicities, especially long-term neuropathy. Because of the higher toxicity rates observed with the cisplatin dose of 100 mg/m^2, a lower dose of cisplatin was used in GOG-252, which tested IP cisplatin at a dose of 75 mg/m^2 and IV/IP paclitaxel vs IP carboplatin/IV weekly paclitaxel and IV carboplatin/weekly paclitaxel[31]; all regimens contained bevacizumab (Avastin, Genentech). No differences in PFS (the primary endpoint) were demonstrated among the 3 arms.[31] The results of GOG-252 and the toxicities of the IP regimen in GOG-172 have dampened the enthusiasm for IP chemotherapy. At some centers, however, including our own, IP chemotherapy is still reserved as an option for patients who have had optimal cytoreduction, are healthy and sufficiently motivated to receive IP cisplatin at a dose of 100 mg/m^2 per GOG-172, and have cancers with platinum-sensitive histology, such as HGSC. A study that tested heated cisplatin during interval debulking surgery recently showed an OS and PFS benefit for hyperthermic IP cisplatin.[32] Hyperthermic IP cisplatin at a dose of 100 mg/m^2 administered following 3 cycles of neoadjuvant carboplatin/paclitaxel and immediately after interval debulking surgery, followed by an additional 3 cycles of carboplatin/paclitaxel after surgery, resulted in an approximately 6-month improvement in OS and improved PFS compared with chemotherapy, interval surgery, and completion chemotherapy without hyperthermic IP cisplatin.[32]

Other efforts to improve the results of first-line treatment have included testing weekly paclitaxel vs paclitaxel every 3 weeks. The Japanese GOG-3016 study showed an improvement in PFS and OS when weekly paclitaxel was compared with paclitaxel every 3 weeks (Table 1).[33] GOG-262 compared carboplatin/paclitaxel every 3 weeks vs carboplatin every 3 weeks/paclitaxel weekly at 80 mg/m^2; the use of bevacizumab was optional.[34] Among the patients who did not receive bevacizumab, PFS was longer in those who received weekly paclitaxel than in those who received paclitaxel every 3 weeks,[34] but among those who received bevacizumab, PFS did not differ between those who received paclitaxel every 3 weeks and those who received it weekly (Table 1). ICON8 tested IV carboplatin/paclitaxel every 3 weeks, carboplatin every 3 weeks/weekly paclitaxel, and a third arm of weekly carboplatin/weekly paclitaxel.[35] No differences were found among the 3 arms in either OS or PFS; PFS was 17.9 months for carboplatin/paclitaxel every 3 weeks, 20.6 months for carboplatin every 3 weeks/weekly paclitaxel, and 21.1 months for weekly carboplatin/weekly paclitaxel (Table 1).[35] Therefore, physicians and patients with newly diagnosed advanced ovarian cancer have choices about the schedule and route of administration of the up-front regimen.

Chemotherapy Combined With Biologic Agents

Biologic agents have been combined with carboplatin/paclitaxel in patients with newly diagnosed ovarian cancer. Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody targeting vascular endothelial growth factor (VEGF). GOG-218 and ICON7 tested the addition of bevacizumab to carboplatin/paclitaxel and bevacizumab as maintenance.[36,37] In GOG-218, patients were randomly assigned to carboplatin/paclitaxel every 3 weeks, carboplatin/paclitaxel/bevacizumab, or carboplatin/paclitaxel/bevacizumab and bevacizumab maintenance (cycles 7 through 22). The median PFS was 10.3 months with chemotherapy alone, 11.2 months with chemotherapy/bevacizumab, and 14.1 months with chemotherapy/bevacizumab and bevacizumab maintenance (Table 1).[36] In ICON7, patients were randomly assigned to either carboplatin/paclitaxel every 3 weeks or carboplatin/paclitaxel/bevacizumab and bevacizumab maintenance.[37] Median PFS was 17.3 months in the chemotherapy-alone arm and 19.0 months in the bevacizumab-containing arm; further follow-up revealed that PFS was no longer statistically significantly different for both groups.[37,38] OS was not improved in the intent-to-treat population with the addition of bevacizumab in either study.[36,38] Trial design differed between GOG-218 and ICON7 as follows: (1) a lower dose of bevacizumab was used in ICON7, (2) GOG-218 was blinded and placebo-controlled whereas ICON7 was not, and (3) the duration of bevacizumab maintenance differed between the studies.[36,37] Bevacizumab in combination with carboplatin/paclitaxel has been approved by the European Medicines Agency (EMA) for patients with newly diagnosed advanced, high-risk ovarian cancer, defined as

Table 1. Selected Key Trials in Newly Diagnosed Advanced Ovarian Cancer

Study	Study Population	Arms	PFS, mo	OS, mo
GOG-111[23]	Stage III, suboptimally cytoreduced, and stage IV	IV Cis, Cyclo	13.0	24.0
		IV Cis, Pac	18.0	38.0
AGO OVAR 3[26]	Stages IIB-VI, optimally and suboptimally debulked	IV Cis, Pac	19.1	44.1
		IV Carbo, Pac	17.2	43.3
GOG-158[27]	Stage III, optimally cytoreduced	IV Cis, Pac	19.4	48.7
		IV Carbo, Pac	20.7	57.4
GOG-172[30]	Stage III, optimally cytoreduced	IV Cis, Pac	18.3	49.7
		IP Cis, IV/IP Pac	23.8	65.6
GOG-252[31] (NCT00951496)	Stages II-IV, optimally and suboptimally debulked	IP Cis, IV/IP Pac, Bev	27.8	NR
		IP Carbo, IV weekly Pac, Bev	28.7	NR
		IV Carbo, IV weekly Pac, Bev	26.8	NR
JGOG-3016[33]	Stages II-IV, optimally and suboptimally debulked	IV Carbo, Pac every 3 weeks	17.5	62.2
		IV Carbo every 3 weeks, Pac weekly (dose-dense regimen)	28.2	100.5
ICON8[35] (NCT01654146)	Stage IC/IIa (high-grade histology) or stages IIb-IV (all histologic subtypes), optimally and suboptimally debulked, or planned for interval debulking surgery	Carbo, Pac every 3 weeks	17.9	46.5
		Carbo every 3 weeks, weekly Pac	20.6	48.1
		Weekly Carbo, weekly Pac	21.1	54
MITO-2[29] (NCT00326456)	Stages IC-IV	Carbo, Pac	16.8	53.2
		Carbo, PLD	19	61.6
EORTC NACT[18]	Stage IIIC or IV	Upfront surgery followed by chemotherapy	12	29
		NACT, interval debulking surgery followed by completion of chemotherapy	12	30
CHORUS[19]	Stage IIIC or IV	Upfront surgery followed by chemotherapy	12	22.6
		NACT, interval debulking surgery followed by completion	10.7	24.1
GOG-218[36]	Stage III or IV	Carbo, Pac, Bev + Bev maintenance	14.1	39.7
		Carbo, Pac, Bev + placebo maintenance	11.2	38.7
		Carbo, Pac, placebo + placebo maintenance	10.3	39.3
ICON7[37,38]	Stage I or IIA clear cell or grade 3 cancers or stages IIB-IV cancers, all histologic subtypes	Carbo, Pac, Bev + Bev maintenance	19.8	45.5
		Carbo, Pac	17.4	44.6
GOG-262[34]	Stage II (optimally cytoreduced) or any stage III or IV	IV Carbo, Pac every 3 weeks +/- Bev	14.0	39.0
		IV Carbo every 3 weeks, IV Pac weekly +/- dose-dense Bev	14.7	40.2
PAOLA-1 (NCT02477644)	Stages IIIB-IV, CR or PR to Pac and Carbo and at ≥3 cycles of Bev	Bev maintenance	NR	
		Bev/Ola maintenance		
SOLO1 (NCT01844986)	Stage III or IV, responded to first-line platinum and *BRCA*m cancer	Ola	NR	
		No maintenance treatment		

(Table continued on next page)

Table 1. *(Continued)* Selected Key Trials in Newly Diagnosed Advanced Ovarian Cancer

Study	Study Population	Arms	PFS, mo	OS, mo
GOG-3005 (NCT02470585)	Stage III or IV high-grade serous ovarian cancer	Carbo, Pac	NR	
		Carbo, Pac, Vel		
		Carbo, Pac, Vel + Vel maintenance		
JAVELIN OVARIAN 100 (NCT02718417)	Stage III or IV with a high-grade serous component	Carbo, Pac	NR	
		Carbo, Pac, Avel		
		Carbo, Pac, Avel + Avel maintenance		
IMagyn050 (NCT03038100)	Stage III or IV	Carbo, Pac, Bev + Bev maintenance	NR	
		Carbo, Pac, Bev, Atez + Bev, Atez maintenance		

Atez, atezolizumab; Avel, avelumab; Bev, bevacizumab; *BRCA*m, *BRCA*-mutated; Carbo, carboplatin; Cis, cisplatin; CR, complete response; Cyclo, cyclophosphamide; IP, intraperitoneal; IV, intravenous; mo, months; NACT, neoadjuvant chemotherapy; NR, not reported; Ola, olaparib; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; PR, partial response; Vel, veliparib.

suboptimally debulked stage III or any stage IV cancer. The use of bevacizumab in patients with newly diagnosed advanced ovarian cancer is currently under review by the US Food and Drug Administration (FDA).

Other antivascular agents have been tested with carboplatin/paclitaxel. These include nintedanib, an oral inhibitor of VEGF receptors 1-3, which did not improve OS or PFS significantly,[39] and AMG386, which inhibits angiopoietin 1 (Ang1) and Ang2 interaction with Tie2 and is being tested in the TRINOVA-3 trial (NCT01493505); results are pending. Additional ongoing trials are testing the addition of other biologic agents, including PARP inhibitors and immuno-oncology agents (Table 1).

Maintenance Strategies

Single-agent chemotherapy, such as with paclitaxel or topotecan, has been unsuccessful as maintenance therapy because of a lack of benefit and/or excessive toxicities; Markman has written a review of maintenance chemotherapy.[40] In addition to bevacizumab, other anti-VEGF agents have been tested as maintenance strategies. Pazopanib (Votrient, Novartis), a multitargeted tyrosine kinase agent, increased PFS compared with no maintenance. However, pazopanib did not improve OS and was associated with significant toxicities.[41]

PARP inhibitors are currently being tested as maintenance therapy following the completion of platinum and taxane chemotherapy, and these ongoing studies are listed in Table 1. They are focused on both HGSC and non-HGSC *BRCA*-mutated (*BRCA*m) ovarian cancers, thus optimizing the chances of PARP inhibitor response. GOG-3005 is testing the PARP inhibitor veliparib in combination with up-front chemotherapy and as maintenance. The SOLO1 trial is testing maintenance with the PARP inhibitor olaparib (Lynparza, AstraZeneca) vs no maintenance after the completion of platinum/taxane chemotherapy in patients with *BRCA*m cancers. The PRIMA trial is testing the PARP inhibitor niraparib (Zejula, Tesaro) as maintenance following platinum/taxane chemotherapy in HGSC. The PAOLA-1 trial is testing olaparib/bevacizumab vs bevacizumab alone after response to platinum/taxane chemotherapy; eligibility includes having HGSC or another histologic type with a documented *BRCA* mutation.

Like strategies for subtypes of HGSC, up-front treatment for cancers with low-grade serous histology is also evolving. Evidence exists of PFS benefit when hormonal therapy is used as maintenance in patients with low-grade serous ovarian cancer after the completion of platinum-based chemotherapy; in a retrospective analysis, PFS was 64.9 months in patients who received hormonal maintenance therapy vs 26.4 months in those who did not receive it. Although no OS benefit was found for the population as a whole, subgroup analysis based on whether or not cancer was clinically present at the completion of chemotherapy did reveal an OS benefit for hormonal therapy.[42] Most of the women in this analysis received an aromatase inhibitor. Although this was not a prospective randomized trial, the use of a low-toxicity aromatase inhibitor as maintenance should be considered for all patients with low-grade serous ovarian cancer.

Treatment of Early-Stage Ovarian Cancer

The previous discussion has focused on treatment for patients with advanced ovarian cancer, although many studies have included patients with higher-risk stage I or II cancers. For patients with stage I or II cancers, decisions regarding treatment should be based on FIGO stage and histology, with careful discussions of risk and

benefit. Bell and colleagues randomly assigned patients with stage I or II ovarian cancers to either 3 or 6 cycles of chemotherapy, showing that treatment for 6 cycles was not superior to 3 cycles with respect to risk for recurrence.[43] However, in a subset analysis of this study, the risk for recurrence in patients with serous cancers was lower with 6 cycles of chemotherapy than with 3 cycles.[44] In patients with nonserous cancers, recurrence-free survival was not improved with 6 rather than 3 cycles.[44] Additionally, the National Comprehensive Cancer Network guidelines outline recommendations for newly diagnosed early-stage ovarian cancer.[13]

Follow-up in Newly Diagnosed Ovarian Cancer

After the completion of platinum/taxane chemotherapy, patients are followed to detect recurrence.[45] In more than three-quarters of patients with advanced ovarian cancer, the disease eventually recurs. The usual PFS is approximately 12 to 18 months, depending on the debulking status and response to up-front chemotherapy. Because early detection of recurrence on the basis of CA-125 elevation does not appear to affect OS, at least as determined in one study,[46] some guidelines have recommended follow-up every 3 months including a review of clinical symptoms, a physical examination, and optional CA-125 testing as well as radiographic testing in patients who may have recurrent disease.[45] However, the National Comprehensive Cancer Network guidelines recommend follow-up visits every 2 to 4 months for 2 years after treatment, to include measurement of CA-125 levels and radiographic imaging if indicated.[13]

Treatment of Recurrent Ovarian Cancer

The treatment plan for recurrent ovarian cancer, as soon as a definitive diagnosis has been made via radiographic imaging, biopsy, and/or physical examination, should include and consider the following: the magnitude of the recurrence and whether symptoms are present or are imminent, the platinum sensitivity status, the *BRCA* mutation status of the cancer, residual toxicities from prior therapies, the availability and appropriateness of clinical trials, the goals of care, and the patient's desire to avoid certain toxicities. Recurrences detected solely by a rising CA-125 level should be confirmed by radiographic testing, and causes of CA-125 elevation other than ovarian cancer should be ruled out before the patient is subjected to active treatment. Platinum-sensitive recurrent ovarian cancer is defined as cancer that recurs after a platinum-free interval (time elapsed between the last dose of platinum-based chemotherapy and evidence of cancer progression) of at least 6 months; cancers that recur after a platinum-free interval of less than 6 months are platinum-resistant. Platinum-refractory cancers grow during platinum chemotherapy or within approximately 4 weeks of the last platinum dose. Because of the heterogeneity and subjectivity of these definitions, they have been challenged.[47,48] Nonetheless, with earlier lines of therapy for recurrent cancer, these definitions continue to be used to plan treatment and design clinical studies. Additionally, platinum-sensitive recurrent cancer will eventually become platinum-resistant as the duration of response shortens with each subsequent administration of a platinum agent.[49]

Platinum-Sensitive Recurrent Ovarian Cancer

In addition to clinical trials, patients with platinum-sensitive recurrent ovarian cancer have options that include systemic chemotherapy (with or without the addition of biologic agents) and, in certain clinical situations, secondary surgical cytoreduction.

Surgery. The DESKTOP III trial from the Gynecologic Oncology Working Group is a randomized trial of chemotherapy alone vs debulking surgery followed by chemotherapy in patients with platinum-sensitive recurrent ovarian cancer.[50] The primary endpoint of the study is OS and the secondary endpoint was PFS; OS results are not yet available. PFS was longer in the surgery arm than in the nonsurgery arm (19.6 vs 14 months; hazard ratio [HR], 0.66; 95% CI, 0.52-0.83).[50] The original retrospective DESKTOP study, which examined the effect of surgery for recurrent ovarian cancer, showed that complete resection was associated with significantly longer OS compared with surgery that left postoperative residual cancer. Factors predicting a complete resection for recurrent ovarian cancer included a good performance status, early stage at initial diagnosis, little or no residual cancer after primary surgery, and the presence of ascites at the current surgery.[51] Another trial, GOG-213 (NCT00565851),[52] is also investigating the efficacy of secondary surgical cytoreduction for recurrent platinum-sensitive ovarian cancer; results of the surgical intervention are pending.

Platinum doublets. For patients with platinum-sensitive cancer in whom chemotherapy is indicated, multiple options now exist, and the patient and her oncologist should discuss the various treatment options (see the eTable at www.hematologyandoncology.net). The reuse of a platinum doublet, specifically carboplatin and paclitaxel, extends survival compared with platinum alone[53]; other platinum doublets that have been studied include carboplatin/gemcitabine[54] and carboplatin/PLD.[55] Carboplatin has been compared with carboplatin/gemcitabine[54]; median PFS was 8.6 months (95% CI, 7.9-9.7 months) for carboplatin/gemcitabine and 5.8 months (95% CI, 5.2-7.1 months) for carboplatin alone (HR

for PFS, 0.72; 95% CI, 0.58-0.90; *P*=.0031).[54] Because of the PFS benefit, the carboplatin/gemcitabine doublet received FDA approval in July 2006. In the noninferiority CALYPSO study, patients with platinum-sensitive recurrent ovarian cancer were randomly assigned either to carboplatin at an area under the curve (AUC) of 5 plus PLD at 30 mg/m^2 every 4 weeks or to carboplatin at an AUC of 5 plus paclitaxel at 175 mg/m^2 every 3 weeks for at least 6 cycles.[55] Median PFS was 11.3 months for the PLD arm vs 9.4 months for the paclitaxel arm, with PFS in the PLD arm statistically superior to that in the paclitaxel arm (HR, 0.821; 95% CI, 0.72-0.94; *P*=.005).[55] All 3 of these carboplatin doublets are appropriate for use in the platinum-sensitive setting and differ in regard to toxicities. The MITO-8 study examined whether platinum-based treatment or a nonplatinum therapy should be used first for the treatment of platinum-sensitive recurrent ovarian cancer (platinum-free interval of 6-12 months).[56] Although the study never completed accrual and closed early, the PFS was longer in the group receiving platinum first than in the group of patients initially receiving nonplatinum therapy.[56]

Toxicities observed with the reuse of platinum include additional bone marrow suppression and neuropathy, as well as the development of allergic reactions that are potentially life-threatening.[57] Toxicities will additionally depend on which agent is combined with platinum: paclitaxel, PLD, or gemcitabine. For those patients experiencing a chemotherapy drug allergy, desensitization protocols have been developed for the safe administration of platinum as well as other agents following an allergic reaction.[57,58]

Antivascular agents. Bevacizumab has been added to carboplatin/gemcitabine as well as to carboplatin/paclitaxel and has also been used as maintenance.[52,59,60] In the OCEANS trial, carboplatin/gemcitabine was compared with carboplatin/gemcitabine/bevacizumab and bevacizumab maintenance; median PFS (the primary endpoint) was 12.4 months with the bevacizumab-containing regimen and 8.4 months with carboplatin/gemcitabine alone (HR, 0.48; 95% CI, 0.39-0.61).[59] OS, which was a secondary endpoint and was not powered for in the study, did not differ significantly between the 2 groups.[60] GOG-213 tested carboplatin/paclitaxel vs carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance; the primary endpoint was OS.[52] For the intent-to-treat population, median OS was 42.2 months (95% CI, 37.7-46.2) in the chemotherapy/bevacizumab group vs 37.3 months (95% CI, 32.6-39.7; HR, 0.829; 95% CI, 0.683-1.005; *P*=.056) in the chemotherapy-alone group.[52] Incorrect treatment-free interval stratification was identified for 7% of the patients, and reanalysis showed an OS benefit for the bevacizumab arm (HR now 0.823; 95% CI, 0.680-0.996; *P*=.0447).[52] PFS in GOG-213 was longer for the bevacizumab-containing arm (eTable).[52] The FDA approved the addition of bevacizumab to either carboplatin/gemcitabine or carboplatin/paclitaxel and bevacizumab maintenance in December 2016 for platinum-sensitive recurrent ovarian cancer.

A discussion of bevacizumab toxicities is beyond the scope of this review. Other publications have addressed them,[61,62] including the FDA package insert for bevacizumab. Toxicities should be monitored throughout and beyond the course of treatment, given the bevacizumab half-life of 20 days; important toxicities of bevacizumab include hypertension, proteinuria, and gastrointestinal perforation.[61,62]

Other antivascular agents that have been tested in the platinum-sensitive setting include cediranib[63]; when combined with platinum doublets and used as maintenance,[64] it showed a PFS benefit in ICON6 (eTable). These results led to a phase 3 randomized study called ICON9 (NCT03278717). Additionally, a randomized phase 2 study compared olaparib with combination cediranib/olaparib as treatment for platinum-sensitive recurrent HGSC[65]; median PFS was 17.7 months (95% CI, 14.7 to not reached) for patients receiving cediranib/olaparib compared with 9.0 months (95% CI, 5.7-16.5) for those treated with olaparib alone (HR, 0.42; 95% CI, 0.23-0.76; *P*=.005; eTable).[65] These promising results have led to the phase 3 study NRG GY004 (NCT02446600), which is comparing platinum doublets vs olaparib vs olaparib/cediranib.

PARP inhibitors. PARP inhibitors are approved by both the FDA and EMA for the treatment of recurrent ovarian cancer. The eTable lists key randomized PARP inhibitor trials in the recurrent setting, and Table 2 lists current regulatory approvals of PARP inhibitors.

Olaparib. The first PARP inhibitor to receive regulatory approval was olaparib. In 2014, the EMA approved maintenance olaparib for recurrent platinum-sensitive *BRCA*m HGSC following response to platinum. Also in 2014, the FDA approved the original capsule formulation of olaparib for the treatment of patients with germline *BRCA*m ovarian cancer who have received 3 or more lines of chemotherapy. These approvals were based on the following: (1) Study 19 (Assessment of Efficacy of AZD2281 in Platinum Sensitive Relapsed Serous Ovarian Cancer), which demonstrated a significant PFS benefit of maintenance olaparib vs placebo after platinum in platinum-sensitive recurrent cancer[66,67] and (2) a 33% response rate and a response duration of approximately 8 months with olaparib in recurrent germline *BRCA*m ovarian cancer after the administration of 3 or more lines of chemotherapy.[68]

In Study 19, patients with platinum-sensitive recurrent HGSC and in response to platinum were randomly assigned in a 1:1 ratio to either olaparib capsules (400 mg twice daily) or placebo.[66] In the overall study population, PFS was 8.4 months for olaparib vs 4.8 months for placebo (HR, 0.35; 95% CI, 0.25-0.49; *P*<.001).[66] Retrospective analysis based on *BRCA* status showed prolonged PFS for olaparib vs placebo in patients whose cancers harbored *BRCA* mutations—11.2 vs 4.3 months (95% CI, 3.0-5.4; HR, 0.18; 95% CI, 0.10-0.31; *P*<.0001).[67] In patients with cancers that were *BRCA*–wild type (*BRCA*wt), median PFS was 7.4 months for olaparib (95% CI, 5.5-10.3) vs 5.5 months for placebo (95% CI, 3.7-5.6; HR, 0.54; 95% CI, 0.34-0.85; *P*=.0075)[67]; these results served as the basis for the EMA and FDA approvals of olaparib maintenance. OS has not been significantly prolonged with olaparib.[69] The phase 3 SOLO2 trial (Olaparib Treatment in BRCA Mutated Ovarian Cancer Patients After Complete or Partial Response to Platinum Chemotherapy) confirmed the results of Study 19 and incorporated olaparib tablets; median PFS was 19.1 months (95% CI, 16.3-25.7) for olaparib maintenance vs 5.5 months for placebo maintenance (95% CI, 5.2-5.8; HR, 0.30; 95% CI, 0.22-0.41; *P*<.0001; eTable).[70] In August 2017, the FDA approved maintenance olaparib tablets for patients with recurrent ovarian cancer in complete or partial response to platinum-based chemotherapy, regardless of tumor *BRCA* mutation status.

Niraparib. Niraparib was tested as maintenance therapy following a platinum response in the NOVA trial. A total of 553 patients were randomly assigned in a ratio of 2:1 to receive niraparib or placebo; the niraparib dosage was 300 mg by mouth daily.[71] The patients were enrolled in 2 independent cohorts on the basis of the presence or absence of a deleterious *BRCA* mutation, and results were analyzed simultaneously.[71] The PFS for niraparib was significantly longer than the PFS for placebo in all 3 primary efficacy groups: (1) germline *BRCA*m group: 21 months for niraparib vs 5.5 months for placebo (HR, 0.27; 95% CI, 0.17-0.41); (2) HRD-positive, germline *BRCA*wt group: 12.9 months for niraparib vs 3.8 months for placebo (HR, 0.38; 95% CI, 0.24-0.59), and (3) non–germline *BRCA*m group: 9.3 months for niraparib and 3.9 months for placebo (HR, 0.45; 95% CI, 0.34-0.61).[71] Both the FDA and EMA in 2017 approved niraparib as maintenance for patients with recurrent ovarian cancer who are in a complete or partial response to platinum-based chemotherapy regardless of tumor *BRCA* status; the EMA approval was restricted to HGSC histology, and the FDA approval was irrespective of histology.

Additional exploratory analyses of the NOVA data have been done to identify risk factors predictive of increased hematologic toxicities.[72] A baseline platelet count of less than 150 K/μL at the start of niraparib treatment and a baseline body weight of less than 77 kg were identified as predictors of increased risk for grade 3 or higher thrombocytopenia eventually requiring dose reduction. On the basis of these findings, it is recommended that patients with either risk factor start niraparib at a dosage of 200 mg orally daily.[72] If no significant hematologic events occur within the first 3 months of dosing, dose escalation may be considered with close monitoring of blood counts.

Rucaparib. Rucaparib (Rubraca, Clovis Oncology) has also been tested as a single agent in *BRCA*m cancers as well as for maintenance treatment in recurrent platinum-sensitive ovarian cancer.[73,74] In these studies, rucaparib demonstrated activity in *BRCA*m ovarian cancer (see Table 2 for FDA approvals) and as maintenance after a platinum response in platinum-sensitive patients, as did niraparib and olaparib. In ARIEL3, median PFS in patients with *BRCA*m ovarian cancer was 16.6 months (95% CI, 13.4-22.9) for rucaparib vs 5.4 months (95% CI, 3.4-6.7) for placebo (HR, 0.23; 95% CI, 0.16-0.34; *P*<.0001; eTable).[74] In patients with HRD-positive ovarian cancer, median PFS was 13.6 (95% CI, 10.9-16.2) for rucaparib vs 5.4 months (95% CI, 5.1-5.6) for placebo (HR, 0.32; 95% CI, 0.24-0.42; *P*<.0001; eTable). In the intent-to-treat population, median PFS was 10.8 months for rucaparib (95% CI, 8.3-11.4) vs 5.4 months (95% CI, 5.1-5.6) for placebo (HR, 0.36; 95% CI; 0.30-0.45; *P*<.0001).[74] In April 2018, rucaparib received approval for maintenance treatment of patients with recurrent ovarian cancer who are in a complete or partial response to platinum-based chemotherapy, regardless of BRCA status or histology.

Other PARP inhibitors. The response rate of veliparib as a single agent is lower than those of the other PARP inhibitors.[75] Veliparib has been shown to have DNA trapping capabilities[76] lower than those of the other PARP inhibitors. One of the best PARP trappers, talazoparib,[76] is currently in combination testing for ovarian cancer (NCT03330405).

PARP inhibitor toxicities. Clinicians should be familiar with the toxicities of the various PARP inhibitors before prescribing them. These include bone marrow suppression with neutropenia, anemia, and thrombocytopenia; fatigue; and gastrointestinal side effects such as nausea and vomiting. Blood counts should be followed cautiously, and the frequency of testing should be based on clinical assessment as well as on the package insert of the specific PARP inhibitor. For example, weekly blood cell counts are recommended for the first month after the start of niraparib treatment, followed by monthly checks. The rucaparib and olaparib package inserts recommend

Table 2. Current Regulatory Approvals of PARP Inhibitors

PARP Inhibitor	Dose	FDA Approvals	EMA Approvals
Olaparib	300 mg twice daily (tablet formation)	1. Treatment of germline *BRCA*m ovarian cancer in patients who have received ≥3 lines of treatment (Dec 2014) 2. Maintenance in patients with recurrent ovarian cancer[a] who are in CR or PR to platinum-based chemotherapy, regardless of tumor *BRCA* status or histology (Aug 2017)	First therapy for the maintenance treatment of patients with platinum-sensitive relapsed *BRCA*m (germline and/or somatic) HGSC ovarian cancer[a] who are in CR or PR to platinum-based chemotherapy (Dec 2014)
Rucaparib	600 mg twice daily	1. Treatment of *BRCA*m (either germline or somatic) ovarian cancer in patients who have received ≥2 lines of treatment (Dec 2016) 2. Maintenance in patients with recurrent ovarian cancer[a] who are in CR or PR to platinum-based chemotherapy, regardless of tumor *BRCA* status or histology (Apr 2018)	None
Niraparib	300 mg once daily[b]	Maintenance in patients with recurrent ovarian cancer[a] who are in CR or PR to platinum-based chemotherapy, regardless of tumor *BRCA* status or histology (Mar 2017)	Maintenance in patients with recurrent HGSC ovarian cancer[a] who are in CR or PR to platinum-based chemotherapy, regardless of tumor *BRCA* status (Sep 2017)

[a] This approval includes fallopian tube and primary peritoneal cancer in addition to ovarian cancer.

[b] For patients who weigh less than 77 kg and/or are starting with a platelet count of less than 150 K/μL, a 200-mg starting dose should be considered.[72]

*BRCA*m, *BRCA*-mutated; CR, complete response; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HGSC, high-grade serous ovarian cancer; PR, partial response.

monthly complete blood cell counts; nonetheless, treating oncologists should monitor complete blood cell counts on the basis of the patient's baseline counts, level of prior hematologic toxicities, and observed bone marrow effects of the specific PARP inhibitor. Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) are rare but important risks of PARP inhibitors, with an overall risk of less than 2%. Randomized studies of PARP inhibitors vs placebo show comparable risks for AML and MDS in both groups[66,67,71]; nonetheless, patients need to be counseled about the risks for AML and MDS with PARP inhibitors.

Platinum-Resistant Recurrent Ovarian Cancer

For patients with platinum-resistant cancer, treatment consists of chemotherapy, chemotherapy/bevacizumab, or a clinical trial. For patients with a low-grade cancer, such as a low-grade serous or endometrioid cancer, a hormonal therapy can be considered.[77]

Single-agent nonplatinum agents with and without bevacizumab. In addition to PLD, topotecan, or weekly paclitaxel, other agents can be used for recurrent platinum-resistant ovarian cancer, such as gemcitabine, vinorelbine, and etoposide.[3] The response rates are low, however (typically <10%-15%), with short PFS times of approximately 3 months.[3,13] The AURELIA trial led to FDA and EMA approval of bevacizumab combined with weekly paclitaxel, PLD, or topotecan for platinum-resistant treatment; patients were allowed to have had up to 2 prior chemotherapy regimens for ovarian cancer.[78] Median PFS was 3.4 months for chemotherapy alone vs 6.7 months for chemotherapy and bevacizumab (95% CI, 0.38-0.60; $P<.001$).[78] The paclitaxel/bevacizumab regimen was particularly striking in regard to response rate and median PFS, which were 53.3% and 10.4 months, respectively.[79] Topotecan as a single agent had a 0% response rate, and combined topotecan/bevacizumab had a response rate of 15%,[74] which is approximately the response rate of bevacizumab as a single agent.[80,81]

Other agents for the treatment of platinum-resistant cancer. Other agents for the treatment of platinum-resistant cancer include PARP inhibitors, antibody-drug conjugates, and immunotherapy.

PARP inhibitors. As in the platinum-sensitive setting, previously discussed, patients with a documented deleterious *BRCA* mutation are eligible to receive either olaparib or rucaparib per their respective FDA approvals. The

response rates of PARP inhibitors decrease as the number of prior treatment lines increases and as platinum resistance increases.[82] Additionally, the response rates of PARP inhibitors are lower in patients with *BRCA*wt cancers than in patients with *BRCA*m cancers,[83] and the response rates are negligible in patients with platinum-refractory *BRCA*m ovarian cancer.[82]

Antibody-drug conjugates. New agents for platinum-resistant ovarian cancer include mirvetuximab soravtansine, an antibody-drug conjugate targeting folate receptor alfa (which is overexpressed in approximately 75% of HGSCs).[84] Promising results of this agent used alone in platinum-resistant ovarian cancer[84] has led to phase 3 testing of mirvetuximab soravtansine vs standard-of-care chemotherapy (NCT02631876).

Immunotherapy. Programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) monoclonal antibodies have been tested for use in recurrent ovarian cancer, with an overall response rate of 10% to 15%. To date, no convincing biomarkers have been identified to help predict response.[85,86] Nivolumab (Opdivo, Bristol-Myers Squibb) has a demonstrated response rate of 15% in PD-L1–positive platinum-resistant ovarian cancer.[85] Several trials are combining chemotherapy with checkpoint blockade to increase the activity of immuno-oncology agents; examples are the JAVELIN OVARIAN 100 trial (NCT02718417; Table 1) in patients with newly diagnosed disease and the JAVELIN Ovarian 200 trial (NCT02580058), in which PLD is being compared with PLD/avelumab (Bavencio, EMD Serono/Pfizer) for patients with recurrent platinum-resistant ovarian cancer. PARP inhibitors are also being combined with immuno-oncology agents, with some promising and intriguing results.[87,88]

Pembrolizumab (Keytruda, Merck) at a dosage of 200 mg given intravenously every 3 weeks has received approval as a single agent for those cancers with microsatellite instability (MSI), regardless of site of origin. This approval was based on the finding that mismatch repair deficiency is predictive of response to PD-1 blockade[89,90] The FDA package insert for pembrolizumab included data on 149 patients with MSI-high cancers, identified through either polymerase chain reaction for MSI-high status or immunohistochemical testing for mismatch repair deficiency.[88] There were 59 patients with non-colorectal cancer, none of whom had ovarian cancer. However, fewer than 2% of all epithelial ovarian cancers are MSI-high.[89]

Conclusions

This is a very exciting time in the development of treatments and drugs for ovarian cancer. Many options are available for patients with newly diagnosed or recurrent ovarian cancer. Antivascular agents and PARP inhibitors have received regulatory approval in both the United States and Europe and are being used as part of up-front and later treatment. New directions for treatment include combination approaches, novel agents such as antibody-drug conjugates, and immunotherapy strategies, all of which are currently undergoing testing in clinical trials.

Disclosures

Dr Matulonis has served on paid scientific advisory boards for Myriad Genetics, Fujifilm, 2X Oncology, Geneos, Clearity Foundation, and Merck Oncology and has served on the unpaid scientific advisory board for AstraZeneca. Her work is supported by the Ovarian Cancer Research Fund Alliance and the Breast Cancer Research Foundation.

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Supporting Online Material for "Management of Newly Diagnosed or Recurrent Ovarian Cancer"

This eTable accompanies a review article by Ursula A. Matulonis, MD, in the May 2018 issue of *Clinical Advances in Hematology & Oncology.*

eTable. Randomized Trials Testing Biologic Agents for Platinum-Sensitive Recurrence

	ITT *BRCA*m		*BRCA*m		HRD-Positive		*BRCA*wt and HRD-Negative	
	PFS, mo	OS, mo	PFS, mo	OS, mo	PFS, mo	OS, mo	PFS, mo	OS, mo
PARP inhibitor maintenance studies								
Study 19[66,67,69]								
Olaparib	8.4	29.8	11.2[c]	34.9[c]	NR		7.4[a,c]	24.5[a,c]
Placebo	4.8	27.8	4.3[c]	30.2[c]			5.5[a,c]	26.6[a,c]
HR	0.35	0.73	0.18	0.62			0.54	0.83
NOVA[71]								
Niraparib	Patients separated into g*BRCA* and non-*BRCA* groups		21	NR	12.9	NR	6.9	NR
Placebo			5.5	NR	3.8	NR	3.8	NR
HR			0.27		0.38		0.58	
SOLO2[70]								
Olaparib	Only patients with *BRCA*m cancers eligible		19.1	NR	NA		NA	
Placebo			5.5	NR				
HR			0.30					
ARIEL3[74]								
Rucaparib	10.8	NR	16.6	NR	13.6	NR	6.7	NR
Placebo	5.4	NR	5.4	NR	5.4	NR	5.4	NR
HR	0.36		0.23		0.32		0.58	
Platinum doublet +/- bevacizumab								
OCEANS[59,60]								
Carbo/Gem	8.4	32.9	NR		NR		NR	
Carbo/Gem/Bev + Bev maintenance	12.4	33.6						
HR	0.484	0.95						
GOG-213[52]								
Carbo/Pac	10.4	37.3	NR		NR		NR	
Carbo/Pac/Bev + Bev maintenance	13.8	42.2						
HR	0.63	0.83						
Studies involving cedirinab								
ICON6[64]								
Plat doublet (A)	8.7	21[d]	NR		NR		NR	
Plat doublet + Ced (B)	9.9	NR	NR		NR		NR	
Plat doublet/Ced + Ced maintenance (C)	11.0	26.3	NR		NR		NR	
HR for arm A vs arm C[b]	0.56		NR		NR		NR	

(Table continued on next page)

eTable. *(Continued)* Randomized Trials Testing Biologic Agents for Platinum-Sensitive Recurrence

	ITT *BRCA*m		***BRCA*m**		**HRD-Positive**		***BRCA*wt and HRD-Negative**	
	PFS, mo	**OS, mo**	**PFS, mo**	**OS, mo**	**PFS, mo**	**OS, mo**	**PFS, mo**	**OS, mo**
***Olaparib vs olaparib/cedirinab*[65]**								
Olaparib	9.0	NR	16.5[c]		NR		5.7[a,c]	
Ola/Ced	17.7	NR	19.4[c]		NR		16.5[a,c]	
HR	0.42		0.55[c]		NR		0.32[a,c]	

[a] Data did not report out HRD results.

[b] The primary efficacy endpoint was PFS difference between arms A and C.

[c] Retrospective analysis.

[d] OS results are immature per manuscript.

Bev, bevacizumab; *BRCA*m, *BRCA*-mutated; *BRCA*wt, *BRCA*–wild type; Carbo, carboplatin; Ced, cediranib; g*BRCA*, germline *BRCA*; Gem, gemcitabine; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; mo, months; NA, not applicable; Nira, niraparib; NR, not reported; Ola, olaparib; OS, overall survival; Pac, paclitaxel; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; Plat, platinum; Ruca, rucaparib.