OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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Update on Drugs in Advanced Ovarian Cancer

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H&O What is the prognosis for patients with ovarian cancer, and how has it changed in recent years?

DO Ovarian cancer is usually diagnosed at an advanced stage, when the prognosis is poor, because no reliable screening test exists. Despite all of our advances in treatment, the recurrence rate in these patients is approximately 80% to 85%. Although the recurrence rates have been fairly flat over the past 1 or 2 decades, we have seen median overall survival improve from 2 to 3 years to approximately 5 years over that time. This represents a near-doubling of the time patients are alive after diagnosis.

We have seen a slight decrease in the incidence of ovarian cancer, most likely because we have been removing fallopian tubes more often at the time of hysterectomy. Advances in and emphasis on genetic testing mean that we perform cascade testing of family members of patients with ovarian cancer and do prophylactic surgery if warranted. Ironically, the number of people in the United States who are living with ovarian cancer has markedly increased, but this is a good thing because it means that patients are living much longer.

H&O What new drugs have been approved for ovarian cancer in the past few years?

DO We have had more new drug indications in gynecologic cancers, and specifically ovarian cancers, in the last 5 years than in the prior 50 years. Bevacizumab was approved in platinum-resistant ovarian cancer in 2014, in platinum-sensitive disease in 2016, and for first-line use in patients with advanced disease in 2018.

We have also seen the approval of 3 different poly(ADP-ribose) polymerase (PARP) inhibitors—olaparib (Lynparza, AstraZeneca), rucaparib (Rubraca, Clovis Oncology), and niraparib (Zejula, GSK)—for multiple indications. The first indications were in the treatment setting. In 2014, olaparib was approved for use in ovarian cancer patients with germline *BRCA* mutations who had received 3 or more prior therapies. In 2016, rucaparib was approved for use in advanced ovarian cancer patients with somatic or germline *BRCA* mutations who had received 2 or more chemotherapy regimens. Niraparib received approval in 2019 for heavily pretreated patients with recurrent ovarian cancer that is associated with homologous recombination deficiency (HRD). Most importantly, all 3 drugs have been approved for use in the maintenance setting for platinum-sensitive disease.

In addition, olaparib was approved last year in the first-line maintenance setting in *BRCA*-mutated patients. In May, the olaparib indication was expanded so it can be used in combination with bevacizumab in first-line maintenance setting in patients whose cancer is associated with HRD, as defined by a deleterious *BRCA* mutation and/or genomic instability. Immediately prior to the expanded olaparib/bevacizumab approval, niraparib was approved for first-line maintenance therapy in all patients who have responded to platinum-based therapy. In April, niraparib was approved for first-line maintenance therapy in patients who have responded to platinum-based therapy.

H&O Could you go into more detail about the role of PARP inhibitors in ovarian cancer?

DO Not only are the PARP inhibitors gaining multiple indications, their use is moving to earlier lines of therapy. The results of 3 recent trials of first-line use are likely to expand our utilization of these agents.

Olaparib was the first agent approved in the first-line maintenance setting for patients with *BRCA* mutations. The trial that served as the basis for that approval, SOLO-1 (Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy), found that more than half of patients were still alive without evidence of recurrence at 3 to 4 years of follow-up.

The 3 most recent trials are PRIMA, PAOLA-1, and VELIA, all of which were presented at the 2019 annual meeting of the European Society for Medical Oncology (ESMO; PRIMA and VELIA were also published in the *New England Journal of Medicine*). PRIMA (A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on First-Line Platinum-Based Chemotherapy) compared niraparib vs placebo in all-comers in the maintenance setting, with positive results. Although the benefit in this trial was largely driven by patients with HRD-positive disease, niraparib is now approved by the US Food and Drug Administration for all-comers in the up-front setting.

PAOLA-1 (Olaparib Plus Bevacizumab as Maintenance Therapy in Patients With Newly Diagnosed, Advanced Ovarian Cancer Treated With Platinum-Based Chemotherapy) looked at the use of olaparib combined with bevacizumab as first-line maintenance treatment in all-comers. An important difference between these 2 trials is that PAOLA-1 was the first trial in the maintenance setting to have an active comparator arm—it compared bevacizumab plus olaparib vs bevacizumab alone in the maintenance setting in patients who had responded to first-line treatment. As with PRIMA, PAOLA-1 met its primary outcome in the entire population of patients, but an exploratory subgroup analysis found that the group that seemed to benefit the most was the HRD population.

VELIA (Veliparib With Carboplatin and Paclitaxel and as Continuation Maintenance Therapy in Subjects With Newly Diagnosed Stage III or IV, High-Grade Serous, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer), a 3-arm trial that examined the use of veliparib in addition to induction chemotherapy and as maintenance therapy, also met its primary outcome and was shown to improve median PFS in all groups of patients who received the agent with chemotherapy. An important difference between VELIA and the other 2 trials is that VELIA is the only one to combine PARP inhibitors with chemotherapy and then look at the PARP inhibitor in the maintenance setting. The combination of PARP inhibitors and chemotherapy was previously found to be too toxic, but veliparib at lower doses was able to be combined with standard chemotherapy.

H&O Do the 3 PARP inhibitors have any notable differences?

DO These agents are more similar than different, although some dosing considerations and toxicities separate them. For example, rucaparib and olaparib are taken twice a day, whereas niraparib provides the convenience of once-a-day dosing. Niraparib has higher hematologic toxicity, specifically thrombocytopenia. As a result, the dosage is now based on "weights and plates." That is, if someone weighs less than 77 kg or has a platelet level of less than 150,000 µL at the beginning of treatment, we start the dose at 200 mg rather than 300 mg. Although that approach has been successful in reducing reports of thrombocytopenia, niraparib still has notable hematologic toxicity.

Veliparib, which is not yet approved by the US Food and Drug Administration, may become another option in the future.

H&O Are any new antivascular agents being developed for use in ovarian cancer?

DO The experimental agent cediranib has been studied extensively, particularly in combination with olaparib. The excitement about cediranib is tempered by the potential toxicity profile of the drug. We currently have 2 ongoing phase 3 trials, GYN004 (NCT02446600) and GYN005 (NCT02502266), that were designed to address the question of whether cediranib with or without olaparib is a viable treatment strategy in ovarian cancer compared with standard chemotherapy. Although we have been informed that GYN004 did not meet its primary endpoint, additional data should be presented at a future meeting. The results of these trials will significantly influence our approach. Additionally, multiple other antivascular agents that have previously been studied in ovarian cancer (eg, nintedanib [Ofev, Boehringer Ingelheim], pazopanib [Votrient, Novartis], and trebananib), which have shown improvements in progression-free survival in different treatment settings, could be re-evaluated for development.

Some additional drugs that have an antivascular effect are being studied for use in ovarian cancer. These include ofranergene obadenovec, also known as VB-111, which also induces an immune response against the tumor. This agent is being studied in an ongoing prospective trial called OVAL (NCT03398655) that is comparing paclitaxel alone vs paclitaxel plus VB-111. Another potential agent is navicixizumab, which is a bispecific anti-DLL4/anti–vascular endothelial growth factor antibody. This

agent received fast-track designation from the US Food and Drug Administration in 2019.

H&O How about immune therapies?

DO The results with checkpoint inhibitors, alone or combined with a chemotherapy, have been disappointing so far. Two phase 3 JAVELIN trials with avelumab—JAVELIN Ovarian 100 and JAVELIN Ovarian 200—were both negative, although so far we have results only from a press release and the recent presentation of JAVELIN100 at the Society of Gynecologic Oncology (SGO) annual meeting.

Currently, the more exciting approach to using checkpoint inhibitors seems to be combining them with PARP inhibitors, antivascular therapy, or both. Multiple large, ongoing phase 3 trials in the first-line and recurrent settings are trying to answer these questions. We will start to see some of the results of these trials in the next 1 to 3 years.

One such trial is IMagyn050 (NCT03038100), which is looking at bevacizumab with or without a checkpoint inhibitor. Another is ATHENA (NCT03522246), which is looking at a PARP inhibitor with or without a checkpoint inhibitor. The 3-arm DUO-O trial (NCT03737643) is comparing different maintenance options: bevacizumab alone vs bevacizumab/olaparib vs bevacizumab/olaparib/durvalumab (Imfinzi, AstraZeneca). Another trial of note is the Gynecologic Oncology Group's GOG-3036 (NCT03740165), which is also known as MK-7339 or ENGOT-ov43. This ongoing trial is very similar to DUO-O in design. In addition, the MOONSTONE trial (NCT03955471) is looking at the PARP inhibitor niraparib plus the experimental checkpoint inhibitor TSR-042, also known as dostarlimab. MEDIOLA (NCT02734004) is evaluating olaparib in combination with durvalumab and bevacizumab.

H&O What is the status of T-cell therapy in ovarian cancer?

DO T-cell therapies—specifically chimeric antigen receptor (CAR) T-cell therapy, tumor-infiltrating lymphocyte (TIL) therapy, and vaccine therapy—all represent potential avenues for the treatment of ovarian cancer. The data are still evolving regarding these treatment strategies.

H&O What is the status of the antibody-drug conjugates?

DO Antibody-drug conjugates (ADCs) are an exciting class of agents in the treatment of ovarian cancer. These agents have the potential to maximize efficacy, minimize toxicity, and provide a more personalized approach to treatment. We would like to be able to identify the best ADC for each patient based on her unique tumor characteristics.

The negative results of the FORWARD I trial (NCT02631876), which compared the folate receptor alpha (FRα)-targeting ADC mirvetuximab soravtansine with standard-of-care chemotherapy, were surprising and disappointing. One important lesson we learned from that trial, however, was the importance of a high level of FRα expression in the tumors. A redesigned version of the trial called MIRASOL (NCT04209855) is already enrolling patients. This trial is specifically for patients whose tumors have a high expression of FRα.

Another ADC that is being studied is XMT-1536, which targets NaPi2b. A phase 1b trial in solid tumors—including ovarian tumors—was presented at the 2019 annual meeting of the American Society of Clinical Oncology (ASCO). Additional results were recently presented online by Dr Debra Richardson as part of the 2020 SGO annual meeting. The study is now enrolling patients in an expansion cohort focusing on platinum-resistant ovarian cancer (NCT03319628).

H&O Are new drugs being developed to target specific mutations in ovarian cancer?

DO Yes, numerous drugs are being developed that target specific mutations. One of the more advanced agents is afuresertib, an AKT inhibitor that has been studied in platinum-resistant ovarian cancer. ATM inhibitors are being developed in an effort to overcome resistance to PARP inhibitors in patients with ATM mutations. . Two recent trials that looked at MEK inhibitors vs physician choice therapies in patients with low-grade ovarian cancer, which is rarely studied, had very interesting results. MILO (NCT01849874) looked at binimetinib (Mektovi, Array BioPharma), whereas GOG-0281 (NCT02101788) looked at trametinib (Mekinist, Novartis). Although both agents showed activity, only GOG-0281 was a positive trial. Patients with mutations in the RAS/RAF pathway may be provided an improved benefit. Newer agents that target these pathways are now being studied. We are in an unprecedented era of drug development.

H&O What should the next steps in research be?

DO The greatest unmet need is to cure more patients. We need to continue to identify biomarkers that will provide us with smarter targets, and offer personalized therapy to minimize nonbeneficial exposure to drugs. In this way, we can limit toxicities while maximizing efficacy.

The next-greatest area of unmet need is to effectively treat those patients who do not have a defined biomarker.

We need to identify the best treatment strategies for patients without *BRCA* mutations or HRD. One of the greatest disappointments in our biomarker development strategy is the lack of a reliable biomarker to predict response to antivascular therapy. Going forward, we need to develop biomarkers in parallel with our targeted agents to make sure that we are maximizing this rational treatment strategy of personalized medicine.

Disclosure

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Suggested Readings

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