Management of Advanced Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

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ABSTRACT

Treatment approaches for advanced ovarian cancer should consider several factors. Among the most important are platinum sensitivity, the status of BRCA and homologous recombination deficiency (HRD), and the changing indications for PARP inhibitors in recurrent disease and maintenance. PARP inhibitors have demonstrated clear benefit in patients with BRCA mutated tumors, especially in the first-line setting, and HRD testing can guide their use for patients without BRCA mutations. A new antibody-drug conjugate, mirvetuximab soravtansine, has been approved for use in a subset of patients with platinum-resistant disease. Newly diagnosed patients with advanced-stage ovarian, fallopian tube, or primary peritoneal cancers should always be evaluated by a gynecologic oncologist if possible.

For ovarian cancer, the 5-year overall survival (OS) has improved modestly over time, and is now approximately 50%. Hereditary mutations, mostly BRCA1 and BRCA2, contribute to risk, and since up to 50% of patients with ovarian cancer may have a BRCA mutation, all patients should have genetic counseling regarding germline BRCA testing. However, classification of ovarian cancer is evolving beyond BRCA mutations to include molecular data. Ovarian cancer subtypes can now be identified with different clinical and genomic characteristics, which may influence response to treatments beyond the standard carboplatin/paclitaxel regimen. Genetic testing of newly diagnosed patients not only informs patient care but also prompts cascade testing of family members, and is therefore critically important in ovarian cancer, said Joyce F. Liu, MD, MPH, Associate Chief, and Director of Clinical Research, Division of Gynecologic Oncology, Dana-Farber Cancer Institute, and Associate Professor, Harvard Medical School, and member of the NCCN Guidelines Panel for Ovarian Cancer.

The approach to initial treatment should consider several factors: Is there a place for neoadjuvant chemotherapy or intraperitoneal chemotherapy? Could the patient benefit from bevacizumab? Is testing for homologous recombination deficiency (HRD)/genomic instability appropriate? What is the role of maintenance therapy with PARP inhibitors? Of note, because the treatment of advanced ovarian cancer is complex and nuanced, all newly diagnosed patients should be referred to a gynecologic oncologist, Dr. Liu emphasized.

Role of Neoadjuvant Therapy
In newly diagnosed patients with advanced disease, neoadjuvant chemotherapy can be considered if upfront surgery is felt not to be advisable. Data from the phase III EORTC 55971 trial and the CHORUS trial suggest that progression-free survival (PFS) and OS are equivalent between up-front chemotherapy and up-front surgery (Table 1). However, historically, the best outcomes have been reported when upfront surgery that leaves no residual disease can be achieved, and upfront surgery should be considered for patients in whom optimal cytoreduction can be safely achieved. For this reason, it is important that the question of upfront surgery versus neoadjuvant chemotherapy be discussed with the involvement of a gynecologic oncologist.

Role of Intraperitoneal Chemotherapy
The efficacy and safety of intraperitoneal chemotherapy has been considered the standard of care since 2006, when GOG-172 demonstrated that intraperitoneal chemotherapy was associated with a significant PFS (23.8 vs 18.3 months) and OS (65.6 vs 49.7 months) advantage over standard intravenous chemotherapy; the National Cancer Institute issued recommendations for its use as a preferred treatment regimen in 2006. However, the uptake of intraperitoneal chemotherapy has remained limited for various reasons. Data from the GOG-252 confirmatory trial later indicated that intraperitoneal chemotherapy may have no PFS or OS benefit over standard intravenous chemotherapy. Intraperitoneal chemotherapy can be considered for certain patients but is no longer the preferred adjuvant regimen for most. Hyperthermic (heated) intraperitoneal chemotherapy will be evaluated in GOG-3068 (HOTT) and currently remains an open question (ClinicalTrials.gov identifier: NCT05659381).
Maintenance Therapy

Bevacizumab in Newly Diagnosed Patients

The addition of bevacizumab to chemotherapy (with continuation of bevacizumab) extended PFS in newly diagnosed ovarian cancer in GOG-218 and ICON7,9,10 leading to its approval for use in the maintenance setting. However, the PFS benefit was approximately 2 to 4 months, and an OS benefit was lacking, begging the following question: “Are there subsets who benefit more [from this therapy]?” The decision to use this drug or not is often made by clinical presentation. It is possible that patients at high risk for disease progression and those warranting a prompt treatment response are the ones for whom there may be “more bang for your buck by adding bevacizumab,” noted Dr. Liu.

PARP Inhibitors in Newly Diagnosed Patients

Maintenance therapy with PARP inhibitors has improved PFS rates in a number of large trials. In studies of patients with BRCA-mutated disease with newly diagnosed disease following platinum therapy, hazard ratios (HRs) were 0.30 (95% CI, 0.23–0.41) in SOLO1,11 0.40 (95% CI, 0.27–0.62) in PRIMA,12 and 0.40 (95% CI, 0.21–0.75) in ATHENA-MONO.13 In the 7-year follow-up of SOLO1, median OS was not reached with maintenance olaparib and was 75.2 months with observation (HR, 0.55; 95% CI, 0.40–0.76; P=.0004).14 Time to first subsequent therapy was also greatly extended (HR, 0.37; 95% CI, 0.28–0.48), with 45% of patients not requiring subsequent therapy at 7 years compared with 21% of the placebo arm.

“This is impressive … It suggests we may actually be changing the natural history of ovarian cancer by giving PARP inhibitors to women with BRCA-mutated ovarian cancer,” Dr. Liu remarked.

For patients without BRCA mutations, HRD status may help to predict response to PARP inhibition. Tumors that test positive on HRD testing (ie, HR-deficient tumors) do not have the ability to repair double-strand breaks in DNA, and they tend to respond better to PARP inhibition than tumors that test negative on HRD testing (ie, HR-proficient tumors). HRD test status has, therefore, become part of the evaluation of benefit with PARP inhibitors. In the PAOLA-1 study, newly diagnosed patients with HRD test positive BRCA wild-type tumors and those with BRCA-mutated disease derived benefit from treatment with both bevacizumab and a PARP inhibitor.15

In summary, Dr. Liu discussed recommendations for prescribing first-line PARP inhibitor maintenance therapy for newly diagnosed patients with advanced disease, which include the recommendation of PARP inhibitor maintenance for patients with BRCA-mutated (germline or somatic) tumors based on a significant PFS benefit and improved OS when given with or without bevacizumab.11–15 Next, HRD testing should be considered for patients with BRCA-nonmutated tumors because it provides information for shared decision-making regarding PARP-inhibitor maintenance. Additionally, patients with HRD-proficient tumors should not receive PARP inhibitors as maintenance if they are receiving bevacizumab. Lastly, the duration of PARP inhibitor maintenance is 2 years for olaparib and rucaparib and 3 years for niraparib.

Recurrent Advanced Ovarian Cancer in 2023

Unfortunately, most patients with advanced stage ovarian cancer will experience disease recurrence. Considerations regarding preferred treatment include whether the patient has platinum-resistant disease (recurrence ≤6 months after last platinum-based therapy) or platinum-sensitive disease (recurrence >6 months) (Figure 1).

Dr. Liu suggested that clinicians ask some questions when selecting treatment for recurrent disease, which include: What is the degree of platinum resistance? Is the patient symptomatic and in need of aggressive treatment?
What are the toxicities from prior therapies? Are there any clinical trials available? What is more convenient and preferred by the patient? Does the patient have allergies to certain drugs? Does the tumor express FOLR1, for which mirvetuximab soravtansine is now approved?

In this patient population, bevacizumab added to platinum-based chemotherapy, followed by bevacizumab maintenance, appeared to improve PFS in platinum-sensitive recurrent disease in the OCEANS, GOG-0213, AGO-OVAR 2.21/ENGOT-ov18, and MITO16b/MANGO-OV2/ENGOT-ov17 trials, and in platinum-resistant disease in the AURELIA study, where outcomes were particularly good with the weekly paclitaxel regimen.

The use of PARP inhibitors for maintenance in platinum-sensitive recurrent disease, on the other hand, has been “very fluid in the past few months,” explained Dr. Liu. Several early trials were positive, leading to the approval of niraparib, olaparib, and rucaparib as maintenance therapy following platinum response in platinum-sensitive disease. Although patients with BRCA-mutated and PARP inhibitor–naïve tumors may achieve significant benefit from maintenance PARP inhibition, these patients are now largely treated with PARP inhibitors in the frontline setting, where they will derive the most benefit.

“For our patients with BRCA wild-type tumors, things have gotten more complex,” added Dr. Liu. Despite initial positivity, OS analyses in key trials showed no benefit and, in fact, HRs exceeded 1.0. This prompted the manufacturers to announce the withdrawal of the indications for maintenance niraparib after ≥2 lines of therapy in patients with BRCA wild-type tumors, with the same expected soon for rucaparib.

PARP Inhibitors for Primary Recurrence

PARP inhibitors for primary recurrence demonstrated a PFS benefit in SOLO3 and ARIEL4 but also a possible OS detriment compared with chemotherapy. In 2022, the following indications were withdrawn: olaparib in the fourth line and beyond for BRCA–mutated disease, rucaparib in the third line and beyond for BRCA–mutated ovarian cancer, and niraparib for the treatment of recurrent HRD-deficient ovarian tumors. “This was in the recurrent setting, which is different from the frontline setting,” Dr. Liu emphasized.

Novel Therapy for Recurrent Platinum-Resistant Ovarian Cancer: Mirvetuximab Soravtansine

The antibody-drug conjugate mirvetuximab soravtansine, which targets FOLR1, was recently approved for recurrent platinum-resistant ovarian cancer in patients with high FRα expression. Although the FORWARD I trial was not positive, a retrospective evaluation showed that patients with high expression of FRα had a 45% reduction in the risk for disease progression (P = .015).

The SORAYA trial of patients with FRα–high, platinum-resistant recurrent disease who were previously treated with 1 to 3 lines of mirvetuximab soravtansine (and agnostic as to previous exposure to PARP inhibition) met its primary end point (objective response rate), leading to accelerated approval of the agent in November 2022. Objective response rates ranged from 32% to 38%, depending on prior treatments, with prior exposure to PARP inhibition not detrimental to response.

Mirvetuximab soravtansine is not without toxicities, however, including peripheral neuropathy, blurred vision, keratopathy, and dry eye. There is a black box warning for ocular toxicities; clinicians should follow instructions for monitoring and supportive care, Dr. Liu emphasized.
References


