New Therapies for Ovarian Cancer

Presented by David M. O'Malley, MD

ABSTRACT

After 3 to 4 decades of stagnation, several new options are available for the treatment of ovarian cancer, some of which produce longer survival compared with historical controls. Additionally, 3 new PARP inhibitors (olaparib, rucaparib, niraparib) have been approved for use in ovarian cancer, with different indications as maintenance therapy or treatment of recurrence. Indications for bevacizumab have been extended, and there are now multiple combination chemotherapy regimens that include bevacizumab as part of initial treatment and as an option for maintenance therapy in select patients, both for first-line primary/adjuvant chemotherapy and for treatment of recurrent or refractory disease.

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"Over the past 10 years, there have been many innovations in the treatment of ovarian cancer; it has been an unprecedented time in development. More indications have been approved in the past 10 years than in the prior 50 years," stated David M. O'Malley, MD, Professor, Director of Gynecologic Cancer Clinical Research, and Co-Director of the Gynecology Oncology Phase I program, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute. "PARP inhibitors and bevacizumab have made a profound difference in progression-free survival (PFS) for patients with ovarian cancer. All patients should have genetic testing and be treated accordingly. The potential for cure is on the horizon," he added.

Dr. O'Malley pointed out that the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Epithelial Ovarian Cancer have expanded significantly since 2007. In fact, the list of acceptable therapies for primary treatment and recurrence is now quite long.

"We have now started to look at individual histologies in newly diagnosed and advanced disease, including endometrioid and serous high-grade carcinoma," Dr. O'Malley told the audience. One of the most important advances in the treatment of stage II–IV ovarian cancer is the use of maintenance therapy after first-line primary/adjuvant chemotherapy. For patients who achieve a response after platinum-based first-line chemotherapy (± bevacizumab) for advanced disease, olaparib maintenance is a category 1 recommendation for those with germline *BRCA* mutations and a category 2A recommendation for those with somatic *BRCA* mutations. For patients with stable disease or partial or complete remission after one of the recommended first-line bevacizumab-containing chemotherapy regimens, single-agent maintenance therapy with bevacizumab is a category 2A recommended option.

"Among gynecologic cancers, ovarian cancer is the number 1 cancer killer. The median survival has improved from 2 to 5 years with newer approaches. Now, with maintenance therapy, we can even discuss the possibility of a cure," Dr. O'Malley said. "As high as 50% of patients can live for 10 years. This is in the context of higher prevalence and more patients living with cancer."

"We must keep in mind the need for supportive care for toxicities associated with the newer therapies," he noted.

Upfront Use of Bevacizumab

Two randomized, phase III trials led to the incorporation of upfront bevacizumab in the NCCN Guidelines for Ovarian Cancer: GOG-0218 and ICON7.[1,2]

A 3-arm trial that enrolled 1,873 patients with newly diagnosed stage III–IV ovarian cancer, GOG-0218 randomly assigned patients 1:1 to carboplatin/paclitaxel followed by placebo maintenance therapy; carboplatin/paclitaxel/bevacizumab followed by placebo maintenance; or carboplatin/paclitaxel/bevacizumab followed by single-agent bevacizumab maintenance.[1] All patients underwent debulking surgery before randomization.

ICON7 was a 2-arm trial of 1,528 patients with stage I–IV disease randomized to carboplatin/paclitaxel (control arm) for 6 cycles versus the same chemotherapy plus bevacizumab, 7.5 mg/kg every 3 weeks (half the dose used in GOG-0218) for 5 to 6 cycles, followed by up to 12 cycles of single-agent bevacizumab maintenance.[2] Patients in the experimental arm received bevacizumab treatment and maintenance therapy for a total of 12 months.

"ICON7 did not hit the primary outcome," Dr. O'Malley stated. In GOG-0218, median PFS was 10.3, 11.2, and 14.1 months for the (chemotherapy) control, chemotherapy plus bevacizumab initiation only (no maintenance), and chemotherapy plus bevacizumab throughout arms, respectively.[1] In ICON7, median PFS was 17.3 months in the control arm versus 19.0 in the bevacizumab-containing arm.[2] When results of both trials were analyzed in greater detail, there appeared to be a greater benefit for bevacizumab in high-risk patients. A profound difference in overall survival (OS) was observed in an exploratory analysis of GOG-0218 in patients with stage IV disease treated with bevacizumab throughout the trial: median OS was 32.6 months with carboplatin/paclitaxel versus 42.8 months when bevacizumab was used for treatment and maintenance.[3]

In an analysis of survival in 502 patients with high-risk disease enrolled in ICON7, median OS was improved from 30.2 months in the control to 39.7 months in the bevacizumab-containing arm (P=.03).[4]

Platinum-Sensitive Disease

"The NCCN Guidelines recommendations for treatment of platinum-sensitive disease are fairly complex," Dr. O'Malley acknowledged. Platinum-sensitive disease refers to patients who achieve complete remission and experience relapse ≥6 months after completing prior chemotherapy. Options for patients with radiographic or clinical relapse include secondary cytoreductive surgery, followed by either a clinical trial, platinum-based chemotherapy (preferred for first recurrence; category 1), recurrence therapy (multiple options), or best supportive care. For patients who experience a biochemical relapse and have no radiographic evidence of disease, recommendations include enrollment in a clinical trial, delaying treatment until clinical relapse, immediate platinum-based recurrence therapy (category 2B), or best supportive care.

For patients with platinum-sensitive disease that relapses and is treated with platinum-based recurrence therapy, postrecurrence therapy options include observation, enrollment in a clinical trial, or, if in a complete or partial remission, maintenance therapy. If the recurrence chemotherapy regimen contained bevacizumab, then single-agent bevacizumab maintenance can be continued. Patients who have completed ≥2 lines of platinum-based chemotherapy can consider maintenance therapy with 1 of 3 PARP inhibitors (niraparib, olaparib, or rucaparib).

The list of preferred recurrence therapies for platinum-sensitive disease is quite long (available online, in these guidelines, at NCCN.org [OV-C 6 of 9]). Several combination therapies can be used with bevacizumab for recurrence in platinum-sensitive disease. The addition of bevacizumab to carboplatin/gemcitabine was based on the OCEANS trial, which showed significantly improved PFS with carboplatin/gemcitabine/bevacizumab followed by bevacizumab indefinitely versus carboplatin/gemcitabine alone (median PFS, 12.4 vs 8.4 months; P<.0001).[5] OS was not significantly different between the treatment arms.

Results from GOG-0213 showed significantly improved PFS with carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance versus carboplatin/paclitaxel in patients with recurrent platinum-sensitive ovarian cancer.[6] Median PFS was 13.8 months in the bevacizumab-containing arm versus 10.4 months in the control arm (P<.0001). Median OS was not significantly different according to an intention-to-treat analysis of GOG-0213, but a sensitivity analysis of OS adjusted for incorrect data on treatment-free interval for 45 patients (6.7%) suggested that survival was better in the group treated with bevacizumab (P=.0447).[6]

Platinum-Resistant Ovarian Cancer

Patients with platinum-resistant disease are defined as those who experience recurrence within 6 months of their most recent platinum treatment. However, Dr. O'Malley noted that, "This definition is in flux. Because of maintenance therapy, we are not sure what platinum resistance means."

The current NCCN Guidelines recommended the following bevacizumab-containing regimens for platinum-resistant disease: cyclophosphamide (oral)/bevacizumab, liposomal doxorubicin/bevacizumab, weekly paclitaxel/bevacizumab, topotecan/bevacizumab, and (single-agent) bevacizumab.

PARP Inhibitors

"First-line PARP inhibitor [maintenance] therapy is the most significant finding in ovarian cancer, ever. PARP inhibitors are recommended as first-line [maintenance] therapy in patients with *BRCA1/2* mutations and advanced disease who have achieved a complete or partial response," Dr. O'Malley told listeners.

The SOLO-1 trial enrolled 391 patients with newly diagnosed stage III–IV high-grade serous or endometrioid ovarian cancer with germline or somatic *BRCA* mutations and who had experienced complete or partial response to first-line platinum-based chemotherapy. Patients were randomized 2:1 to olaparib versus placebo and stratified according to response to platinum-based chemotherapy.[7] Treatment was continued for 2 years if there was no evidence of disease. According to investigator assessment, after a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo. The rate of freedom

from disease progression or death at 3 years was 60% versus 27%, respectively ($P<.001$). Median PFS was not reached in the treatment arm.

"The benefit of a 2-year treatment continues to persist. Are we seeing a 50% cure rate? Time will tell," he said.

PARP Inhibitor Maintenance Therapy for Platinum-Sensitive Disease

Currently, bevacizumab and 3 PARP inhibitors (olaparib, niraparib, rucaparib) are all FDA-approved as maintenance therapy following recurrence therapy for select patients with platinum-sensitive disease, based on evidence from phase III trials.[8–10]

PARP Inhibitor Therapy for Recurrent Disease

Olaparib is FDA-approved for use in patients with recurrent germline *BRCA*-mutated ovarian cancer and who have received ≥3 prior lines of therapy. Rucaparib is FDA-approved for use in patients with recurrent somatic or germline *BRCA*-mutated ovarian cancer and who have received ≥2 prior lines of therapy.

Germline and Somatic Testing

The NCCN Guidelines recommend that all patients with newly diagnosed (pathologically confirmed) ovarian cancer undergo germline and/or somatic *BRCA1/2* testing, because it may help inform the best choice for maintenance therapy following first-line chemotherapy. Primary treatment should not be delayed for genetic counseling. For patients with recurrent or refractory disease, validated molecular testing should be performed in a CLIA-approved facility using the most recently obtained tissue. Testing for patients with recurrent or refractory disease should include at least *BRCA1/2*, microsatellite instability (MSI), or DNA mismatch repair, if not previously done. Testing for homologous repair deficiency can be considered. "Many will argue that MSI is rare in ovarian cancer. Approximately 1% of all patients with serous platinum-sensitive ovarian cancer have MSI. In clear cell and mucinous ovarian cancer, the percentage approaches 20%, and pembrolizumab is indicated for tumors with MSI," Dr. O'Malley stated.

"My plea is to test all patients with ovarian cancer for germline and somatic mutations. We have genetic counselors who consult with the patient after diagnosis. We send tumor tissue for testing after biopsy, but for next-generation sequencing we need more tissue so we usually wait until we have a surgical specimen," Dr. O'Malley continued. "Commercially available tests don't satisfy the need for an extended somatic panel. The hope is to develop a single test to obtain all the necessary information at one time."

Disclosures: Dr. O'Malley has disclosed that he is a consultant for AbbVie, Inc., Ambry Genetics, and AstraZeneca Pharmaceuticals LP; that he has received honoraria from Clovis Oncology, Genentech, Inc., and TESARO, Inc.; and that he is a scientific advisor for Agenus Inc.; AstraZeneca Pharmaceuticals LP; Clovis Oncology; Genentech, Inc.; ImmunoGen, Inc.; Janssen Pharmaceutica Products, LP; Marker Therapeutics, Inc. (previously TapImmune Inc.); Myriad Genetic Laboratories, Inc.; Novocure; OncoQuest Inc.; and Regeneron Pharmaceuticals, Inc. He has also received grant/research support from AbbVie, Inc.; Agenus Inc.; Ajinomoto Co, Inc; Array BioPharma Inc.; AstraZeneca Pharmaceuticals LP; Clovis Oncology; ERGOMED Clinical Research Ltd; Exelixis Inc.; Genentech, Inc.; GlaxoSmithKline; ImmunoGen, Inc.; INC Research, Inc; Janssen Pharmaceutica Products, LP; Novartis Pharmaceuticals Corporation; Novocure; Regeneron Pharmaceuticals, Inc.; TESARO, Inc.; and TRACON Pharmaceuticals, Inc.

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