OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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Optimal Treatment for Platinum-Sensitive Recurrent Ovarian Cancer

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H&O How common is ovarian cancer?

BJM The American Cancer Society estimates that ovarian cancer will be diagnosed in 22,440 women and that 14,080 women will die of the disease in 2017 in the United States. The term *ovarian cancer* generally refers to epithelial ovarian cancer and includes fallopian tube cancer and primary peritoneal cancer as well as ovarian cancer.

H&O What is the standard frontline treatment of ovarian cancer?

BJM The frontline treatment is surgery plus platinum-based chemotherapy, generally with carboplatin and paclitaxel.

H&O How common is recurrence after the initial treatment of ovarian cancer?

BJM We do not have good screening tools for epithelial ovarian cancer, and in three-quarters of cases it is diagnosed in stage III or IV. Because the disease is diagnosed in these advanced stages, the chance of recurrence after treatment is high—approximately 75%. The average time to recurrence after primary surgery and platinum-based chemotherapy is 1 to 2 years.

H&O What is the definition of a platinum-sensitive relapse?

BJM A platinum-sensitive relapse is one that recurs at least 6 months after the patient's final dose of platinum-based chemotherapy. Most patients—at least three-quarters—whose disease recurs have a platinum-sensitive relapse.

H&O How are platinum-sensitive relapses treated?

BJM The treatment of a platinum-sensitive relapse is another platinum doublet. This generally consists of carboplatin plus 1 of 3 additional chemotherapy agents: gemcitabine, liposomal doxorubicin, or a second course of paclitaxel. US Food and Drug Administration (FDA) labeling allows the addition of the anti-angiogenesis agent bevacizumab (Avastin, Genentech) to 2 of these doublets—carboplatin/gemcitabine and carboplatin/paclitaxel.

The approval of bevacizumab in December 2016 for use with carboplatin/gemcitabine was based on the results of OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease), conducted by Aghajanian and colleagues, which showed that bevacizumab improved progression-free survival (PFS)—although later follow-up revealed no improvement in overall survival (OS; Table 1).

The approval of bevacizumab for use with carboplatin/paclitaxel was based on the results of GOG-0213 (Carboplatin, Paclitaxel and Gemcitabine Hydrochloride With or Without Bevacizumab After Surgery in Treating Patients With Recurrent Ovarian, Epithelial, Primary Peritoneal, or Fallopian Tube Cancer), conducted by Coleman and colleagues, which found that bevacizumab improved OS.

Bevacizumab also can be used off label in combination with carboplatin/liposomal doxorubicin. A randomized phase 3 trial by the Gynecologic Oncology Working Group is comparing carboplatin/gemcitabine/bevacizumab vs carboplatin/liposomal doxorubicin/bevacizumab (NCT01837251).

Table 1. Trials Leading to FDA Approval of Use of Bevacizumab in Ovarian Cancer

Study	Population	Groups	Results	Conclusion
OCEANS	Platinum-sensitive recurrent ovarian cancer	Gemcitabine/carboplatin + bevacizumab (n=242) OR Gemcitabine/carboplatin + placebo (n=242)	PFS: 12.4 vs 8.4 mo (HR, 0.48; *P*<.0001) OS: 33.6 vs 32.9 mo (HR, 0.95; *P*=0.65)	Bevacizumab improved PFS, although there was no significant difference between OS in the 2 groups.
GOG-0213	Platinum-sensitive recurrent ovarian cancer	Paclitaxel/carboplatin + bevacizumab (n=377) OR Paclitaxel/carboplatin (n=337)	OS: 42.2 vs 37.3 months (HR, 0.83; *P*=.056; adjusted HR, 0.82; *P*=.0447)	Addition of bevacizumab did not improve OS overall, but it did improve OS in analysis based on corrected treatment-free interval stratification.

FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Sources: Aghajanian C et al. *J Clin Oncol*. 2012;30(17):2039-2045; Aghajanian C et al. *Gynecol Oncol*. 2015;139(1):10-16; Coleman RL et al. *Lancet Oncol*. 2017;18(6):779-791.

H&O How effective is the treatment of platinum-sensitive relapses?

BJM The response rate is approximately 55% with chemotherapy alone and 75% when bevacizumab is added. When bevacizumab is added to chemotherapy, maintenance therapy usually consists of bevacizumab alone.

An alternative to maintenance therapy with bevacizumab is maintenance with the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor niraparib (Zejula, Tesaro). The FDA approved niraparib in March 2017 for use as maintenance therapy in patients with platinum-sensitive ovarian cancer on the basis of the results of NOVA (A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer), conducted by Mirza and colleagues and published in the *New England Journal of Medicine* in 2016. This study found that niraparib as maintenance therapy improved PFS compared with placebo in patients with a germline *BRCA* mutation (21.0 vs 5.5 months) and in those without a germline *BRCA* mutation (9.3 vs 3.9 months). The most common grade 3 or 4 adverse events were thrombocytopenia, anemia, and neutropenia (Table 2).

The PARP inhibitor olaparib (Lynparza, AstraZeneca) is under FDA review for use as maintenance therapy in patients with platinum-sensitive ovarian cancer who have a germline *BRCA* mutation. The SOLO2 study (Olaparib Treatment in BRCA Mutated Ovarian Cancer Patients After Complete or Partial Response to Platinum Chemotherapy), which was published by Pujade-Lauraine and colleagues in *Lancet Oncology*, found that olaparib improved PFS vs placebo in patients with a germline *BRCA* mutation (19.1 vs 5.5 months).

Another PARP inhibitor that is being studied as maintenance therapy in patients with platinum-sensitive ovarian cancer is rucaparib (Rubraca, Clovis Oncology). The results of ARIEL3 (A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer) have not been presented, but Clovis announced early results in a press release. Dr Jonathan Ledermann of University College London in London, the United Kingdom, will be presenting the complete data at the European Society for Medical Oncology (ESMO) annual meeting in September.

Additional PARP inhibitors in development for ovarian cancer are talazoparib and veliparib.

H&O How are treatment decisions made?

BJM The factors we consider in making decisions about treatment are the following: (1) the number of lines of therapy; (2) platinum sensitivity; (3) histology (high-grade serous tumors account for 85% of ovarian cancers, but low-grade serous, clear cell, and mucinous ovarian cancers also occur); and (4) the molecular signature—whether a *BRCA* mutation is present.

The response to PARP inhibition depends on 3 factors. Patients are more likely to respond if they are in an earlier line of treatment, if the duration of their response to platinum is longer, and if they have a *BRCA* mutation. Olaparib and rucaparib are approved for treatment with germline BRCA and somatic BRCA, respectively, and may be given before consideration of maintenance in the appropriate setting.

H&O What are the potential side effects of the various agents used in ovarian cancer?

BJM Cytotoxic chemotherapy can cause fatigue, bone marrow suppression, alopecia, and neuropathy. PARP

Table 2. Phase 3 Trials of PARP Inhibition in Patients With Platinum-Sensitive Ovarian Cancer

Study	Population	Groups	Results	Conclusion
NOVA	Platinum-sensitive recurrent ovarian cancer, with or without germline *BRCA* mutation	Niraparib (n=138 in g*BRCA* cohort and n=234 in non-g*BRCA* cohort) OR Placebo (n=65 in g*BRCA* cohort and n=116 in non-g*BRCA* cohort)	PFS in g*BRCA* cohort: 21.0 vs 5.5 mo (HR, 0.27; *P*<.001) PFS in non-g*BRCA* cohort: 9.3 vs 3.9 mo overall (HR, 0.45; *P*<.001) and 12.9 vs 3.8 mo for patients with HRD (HR, 0.38; *P*<.001)	Median duration of PFS was significantly longer in the niraparib group than in the placebo group, regardless of g*BRCA* mutation status or HRD status; result led to FDA approval.
SOLO2	Platinum-sensitive recurrent ovarian cancer with germline *BRCA* mutation	Olaparib (n=196) vs placebo (n=99)	Investigator-assessed PFS: 19.1 vs 5.5 mo (HR, 0.30; *P* <.0001) PFS on independent central review: 30.2 vs 5.5 mo (HR, 0.25; *P* <.0001).	Olaparib improved PFS as assessed by investigators and by independent central review.
ARIEL3	Platinum-sensitive, high-grade ovarian cancer	Rucaparib vs placebo, 2:1 (n=564)	Investigator-assessed PFS: 16.6 vs 5.4 mo (HR, 0.20; *P*<.0001) in *BRCA*-mutant population; 13.6 vs 5.4 (HR, 0.34; *P*<.0001) in HRD-positive population; 10.8 vs 5.4 (HR, 0.35; *P*<.0001) in intent-to-treat population	Rucaparib improved PFS as assessed by investigator review in *BRCA*-mutant, HRD-positive, and overall intent-to-treat populations.

FDA, US Food and Drug Administration; HR, hazard ratio; HRD, homologous recombination deficiency; PARP, poly(adenosine diphosphate-ribose) polymerase; PFS, progression-free survival.

Sources: http://www.businesswire.com/news/home/20170619005376/en/Clovis-Oncology%e2%80%99s-Rucaparib-Significantly-Improved-Progression-Free-Survival; Mirza MR et al. *N Engl J Med.* 2016;375(22):2154-2164; Pujade-Lauraine E et al. *Lancet Oncol.* doi:10.1016/S1470-2045(17)30469-2.

inhibitors cause fatigue and bone marrow suppression, along with gastrointestinal disturbances such as nausea, diarrhea, and dyspepsia. Bevacizumab can cause hypertension and proteinuria, and there is a risk for bleeding that on rare occasions will lead to problems such as thrombosis and gastrointestinal perforation.

The good news is that many of these drugs are very well tolerated. By optimizing the dose and schedule, we can personalize the treatment regimen to maximize efficacy and avoid compromising quality of life.

H&O What other agents are being examined for use in recurrent ovarian cancer?

BJM There is a fascination with using immunotherapy to treat ovarian cancer, as there is with other solid tumors. Checkpoint inhibitors such as atezolizumab (Tecentriq, Genentech) and avelumab (Bavencio, EMD Serono/Pfizer) are being aggressively studied. Antibody-drug conjugates (ADCs) also are being developed for use in ovarian cancer. ImmunoGen is testing the ADC mirvetuximab soravtansine in FORWARD I (NCT02631876), and Bayer is developing an ADC, called anetumab ravtansine, that targets the folate receptor mesothelin.

Suggested Readings

Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30(17):2039-2045.

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Pujade-Lauraine E, Ledermann JA, Selle F, et al; SOLO2/ENGOT-Ov21 Investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial [published online July 25, 2017]. *Lancet Oncol.* doi:10.1016/S1470-2045(17)30469-2.