

OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

Section Editor: Robert L. Coleman, MD

The Role of Maintenance Therapy in Ovarian Cancer



Amit M. Oza, MD, MBBS, FRCPC
Professor of Medicine
University of Toronto
Toronto, Ontario, Canada

H&O What is the rationale behind maintenance therapy in ovarian cancer?

AO The general idea behind maintenance therapy is to keep the cancer under control for as long as possible after initial treatment. Although maintenance therapy in oncologic malignancies is not a new concept, it is relatively new in ovarian cancer and other solid tumors. The first agent to receive approval from the US Food and Drug Administration (FDA) as maintenance therapy in ovarian cancer was bevacizumab, in 2016 (Table). Since then, several poly(ADP-ribose) polymerase (PARP) inhibitors have received FDA approval for maintenance in ovarian cancer: niraparib (Zejula, Tesaro), olaparib (Lynparza, AstraZeneca), and rucaparib (Rubraca, Clovis Oncology). Maintenance therapy has changed the way we approach and treat ovarian cancer.

H&O When is maintenance therapy considered in ovarian cancer?

AO Maintenance therapy in ovarian cancer has been shown to be effective in both the first-line and the recurrent settings. Bevacizumab can be given concurrently with platinum-based chemotherapy, then continued on its own as maintenance therapy. PARP inhibitors can be used as maintenance therapy following the completion of primary chemotherapy, or following the completion of chemotherapy in a platinum-sensitive recurrent setting.

H&O When was maintenance therapy first used in ovarian cancer?

AO The first clinical trials of maintenance therapy in ovarian cancer started in the early 2000s, with bevacizumab, paclitaxel, and tyrosine kinase inhibitors such as erlotinib (Tarceva, Genentech/Astellas) and nintedanib (Ofev, Boehringer Ingelheim). In 2008, Study 19 (Assessment of Efficacy of AZD2281 in Platinum Sensitive Relapsed Serous Ovarian Cancer) began to look at the use of the PARP inhibitor olaparib in patients with platinum-sensitive relapsed ovarian cancer. So we have seen the evidence mounting for maintenance treatment over the last decade and have been able to look at the practical implications of long-term treatment, including how we manage its side effects and how patient quality of life is affected.

Even though the FDA did not approve treatment with bevacizumab in the frontline setting until 2016, it was widely used off label for this indication before then. It had been approved in Europe, Canada, Australia, and other countries about half a dozen years earlier, on the basis of results from ICON7 (International Collaboration on Ovarian Neoplasms) and GOG-0218 (Carboplatin and Paclitaxel With or Without Bevacizumab in Treating Patients With Stage III or Stage IV Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube Cancer). These were the 2 pivotal first-line studies that shaped our thinking regarding maintenance treatment.

H&O Could you discuss the results of the bevacizumab studies?

AO ICON7, a phase 3 trial of 1528 patients, examined the addition of bevacizumab to chemotherapy as primary treatment and maintenance in stages I through IV ovarian

Table. Agents Approved for Use in Maintenance Therapy for Ovarian Cancer

Year of FDA Approval	Agent	Drug Class	Indication
2016	Bevacizumab	Antiangiogenic	Platinum-sensitive disease
2017	Niraparib	PARP inhibitor	Platinum-sensitive disease
2017	Olaparib	PARP inhibitor	Platinum-sensitive disease
2018	Rucaparib	PARP inhibitor	Platinum-sensitive disease
2018	Olaparib	PARP inhibitor	Frontline germline disease and somatic <i>BRCA</i> -mutated disease
2018	Bevacizumab	Antiangiogenic	In combination with carboplatin and paclitaxel, followed by bevacizumab alone

PARP, poly(ADP-ribose) polymerase.

cancer. Although this trial demonstrated no improvement in overall survival (OS) with bevacizumab in the group as a whole, bevacizumab did improve restricted mean survival time from 34.5 months to 39.3 months among 502 patients who had been defined as being at particularly high risk for progression when they entered the trial. Additional studies have since tried to clarify how to use antiangiogenics, such as whether longer treatment is better. We have some evidence that longer treatment is better than treatment for 12 or 15 months, which is what the initial studies suggested.

GOG-0218 initially found a progression-free survival (PFS) advantage with bevacizumab as first-line treatment and maintenance in 1873 patients who had stage III or IV ovarian cancer. In an updated analysis of GOG-0218 that was presented at the 2018 annual meeting of the American Society of Clinical Oncology (ASCO), bevacizumab produced an OS advantage only in patients with high-risk stage IV disease, not in those with stage III disease.

Bevacizumab is quite effective, but one caveat is that it needs to be started concurrently with chemotherapy and then continued to maintenance. Patients are especially likely to benefit from bevacizumab in the setting of first-line residual disease, if their disease has been suboptimally debulked, or if they have stage IV disease.

H&O How effective are PARP inhibitors as maintenance treatment in ovarian cancer?

AO Like bevacizumab, PARP inhibitors are very effective. The patient's genomic profile affects how well PARP inhibitors work; evidence suggests that patients with *BRCA* mutations are very sensitive to PARP inhibition and are the ones most likely to benefit from maintenance with PARP inhibitors. Patients who have homologous recombination deficiency (HRD) also benefit significantly from PARP inhibitors. Patients who are HRD-negative

also seem to benefit from PARP inhibitors as long as they have platinum-sensitive disease, but the magnitude of the benefit is lower. Although we are now using a clinical algorithm to determine which patients are candidates for PARP inhibitors, molecular predictive factors are becoming increasingly useful.

H&O What are the most common adverse events with bevacizumab?

AO Bevacizumab is generally well tolerated, but it does have potential side effects. The most common side effect is hypertension, which occurs in approximately 30% to 40% of patients. The hypertension is usually relatively mild and can be managed fairly easily. Some patients will need to start taking antihypertensive medication while they are on bevacizumab.

Antiangiogenics also increase the likelihood of bleeding and blood clots. Another important side effect is the development of a bowel complication, such as a bowel perforation or fistulation. This is a fairly major concern in patients who have bulky disease, particularly disease that is invading the bowel, but it is less likely to apply in the maintenance setting.

Another drawback of bevacizumab is that patients need to go to an infusion center or hospital every 2 to 3 weeks for intravenous administration.

H&O What are the most common side effects with the PARP inhibitors?

AO The side effects tend to be milder with PARP inhibitors. The most common side effect is nausea. Usually the nausea is mild, but it can be persistent, particularly among patients who are taking PARP inhibitors long term. As a result, some patients require anti-nausea medication. They may also experience fatigue and tiredness. Physicians

need to monitor patients on PARP inhibitors, especially niraparib, with regular complete blood cell counts.

Rucaparib can cause liver function abnormalities, and PARP inhibitors can cause a slight elevation of serum creatinine. These are not likely to cause any functional or clinical impairment, but they may cause biochemical abnormalities that will be noted as long as patients are being followed regularly.

We are concerned that these agents may increase the risk for a myelodysplastic syndrome or another type of myeloproliferative disorder. This is a toxicity of special interest given the ongoing long-term effects on the bone marrow of PARP inhibitors, but the exact risk still needs to be defined. Prior chemotherapy and *BRCA* mutations may also make patients more susceptible to myeloproliferative disorders.

H&O If a patient needs first-line maintenance treatment and is eligible for both an antiangiogenic agent and a PARP inhibitor, which one should you use?

AO That is the million dollar question. Right now, we are trying to see how we can be more selective in terms of which one to use. Results from an interesting study, PAOLA-1 (Platine, Avastin and Olaparib in 1st Line), were presented at the 2019 European Society for Medical Oncology (ESMO) meeting a few months ago by Dr Isabelle Ray-Coquard. In this study, patients with advanced ovarian cancer received maintenance treatment with bevacizumab alone or bevacizumab plus olaparib. The study showed that adding the PARP inhibitor improved median PFS from 16.6 months to 22.1 months (hazard ratio, 0.59; 95% CI, 0.49-0.72; $P < .0001$).

So there is an advantage to giving both a PARP inhibitor and an antiangiogenic over bevacizumab alone in the maintenance setting in most cases, particularly if the patient has HRD. We do not necessarily need to decide between the 2 agents; the answer for at least some patients is to give both.

H&O Is it appropriate for studies of maintenance therapy to use a placebo or observation as the control arm, given that most of the studies include patients without a complete response to treatment?

AO Control arms that use placebo or observation are essential in assessing PFS because patient bias and bias from the physician or other observers can affect how soon the patient is assessed. The placebo arm is not as relevant if the primary endpoint is OS. However, OS studies are very difficult to do in ovarian cancer because patients receive subsequent lines of treatment after disease progression. So

I think PFS is still a very important endpoint for ovarian cancer, and that does require a placebo type of control arm.

Now that the evidence for PARP inhibitors is so strong, future studies need to build on that knowledge.

There is an advantage to giving both a PARP inhibitor and an antiangiogenic in a maintenance setting in most cases, particularly if the patient has HRD.

As a result, patients in groups that have level 1 evidence of benefit from PARP inhibitors—those with *BRCA* mutations or HRD who have either recurrent ovarian cancer or first-line ovarian cancer—should always receive them. Any additional maintenance treatments would need to be on top of the PARP inhibitor.

H&O Is there a role for immunotherapy in maintenance treatment?

AO The jury is still out regarding the possibility of benefit from the addition of immunotherapy to maintenance treatment in ovarian cancer. Some ongoing large randomized studies are addressing this question, and a couple of studies have been completed. We should know more in the next 18 months.

H&O Are enough patients with ovarian cancer receiving maintenance therapy?

AO It's hard to know for sure. The evidence is now well understood and is being disseminated widely, but maintenance therapy carries a significant financial burden that needs to be factored in. Side effects are another consideration; these need to be managed effectively in their early stages to ensure that patients do not discontinue treatment too soon.

H&O What are the challenges in counseling women regarding maintenance therapy?

AO We need to clarify for patients the risk/benefit profile of long-term maintenance therapy, which includes

providing accurate information on both the short-term and long-term side effects. It is important to refer patients to genetic counseling if they have germline *BRCA* mutations, given that we are now evaluating patients for *BRCA* mutation status and, increasingly, HRD status.

H&O Can maintenance therapy be given more than once?

AO We have evidence from MITO 16B (Bevacizumab Beyond Progression in Platinum Sensitive Ovarian Cancer), a randomized clinical trial that was presented at the 2018 ASCO annual meeting, that bevacizumab is effective after prior bevacizumab. The equivalent evidence still needs to be gathered regarding PARP inhibitors. The findings likely will depend on numerous factors, including the evolution of genomic resistance. The reasons why patients come off treatment with PARP inhibitors are different from the reasons why they come off bevacizumab. For example, they may discontinue treatment because of progression or resistance. As a result, the ability to rechallenge effectively will vary.

H&O What questions remain when it comes to maintenance therapy?

AO Multiple questions remain, including the optimal duration of therapy, reasons for failure, ways to overcome failure and resistance, ways to predict who will benefit (particularly in a recurrent setting), and ways to overcome cross-resistance based on prior chemotherapy

H&O What is the best way or best endpoint to measure the benefit of maintenance therapy?

AO Ultimately, OS is the most important endpoint, although determining this is challenging and takes a long time. PFS and PFS2 (the time to second subsequent therapy) are also important measurable endpoints.

Disclosure

Dr Oza has been a primary investigator and has served on steering and advisory committees for trials from AstraZeneca, Tesaro, and Clovis Oncology.

Suggested Readings

Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473-2483.

Burger RA, Enserro D, Tewari KS, et al. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: a NRG Oncology/Gynecologic Oncology Group (GOG) study [ASCO abstract 5517]. *J Clin Oncol.* 2018;36(15)(suppl).

Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol.* 2016;17(11):1579-1589.

Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 2015;16(8):928-936.

Pignata S, Lorusso D, Joly F, et al. Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: the randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17 [ASCO abstract 5506]. *J Clin Oncol.* 2018;36(15).

Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med.* 2019;381(25):2416-2428.