OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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When in the Treatment Continuum to Use PARP Inhibition in Ovarian Cancer

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H&O What are the phases of the treatment of ovarian cancer in which poly(ADP-ribose) polymerase (PARP) inhibitors can be considered?

MRM PARP inhibitors can be considered for use in the first-line treatment of advanced ovarian cancer or in the treatment of relapsed disease. In the first line, PARP inhibitors are used as maintenance therapy after primary treatment, which typically consists of surgery plus chemotherapy. Patients with ovarian cancer are eligible for first-line treatment with PARP inhibitors regardless of the histologic classification of their disease, *BRCA* mutation status, or homologous recombination (HR) deficiency status. Patients with relapsed disease are eligible for PARP inhibitor treatment if relapse has occurred after a platinum-free interval of more than 6 months.

H&O What are the indications for the specific agents?

MRM Both olaparib (Lynparza, AstraZeneca) and niraparib (Zejula, GSK/Tesaro) are approved for use as single agents in the first-line maintenance therapy of patients with *BRCA*-mutated disease. Also in the first-line maintenance setting, olaparib in combination with bevacizumab can be used in patients with HR-deficient disease, whereas niraparib can be used as monotherapy in all patients, regardless of HR deficiency status. Olaparib, niraparib, and rucaparib (Rubraca, Clovis Oncology) can all be used as maintenance therapy in platinum-sensitive relapsed disease.

H&O What are the reasons for using PARP inhibitors earlier rather than later?

MRM I would much rather use PARP inhibitors up front than to treat relapsed disease. We do not have any randomized trials comparing earlier vs later administration, but existing trials provide some hints. For example, in SOLO2, which examined the use of olaparib in patients with *BRCA*-mutated, platinum-sensitive ovarian cancer, a response was more likely to occur in those who received olaparib earlier in the course of their disease than in those who received it after multiple relapses.

Another advantage of using PARP inhibitors earlier is the shorter duration of treatment. When we use PARP inhibitors in first-line treatment, patients receive them for 2 to 3 years, and a response is highly likely to occur during this time. When we use PARP inhibitors for relapsed disease, the agents are given until the next progression of disease.

The only reason not to use PARP inhibition up front is its cost, given that the toxicity profile is highly favorable.

H&O In which cases are physicians using PARP inhibition for relapsed disease?

MRM European physicians are still using PARP inhibition for relapsed disease because first-line use was approved only a few months ago in Europe. However, now that first-line use has been approved, going forward, patients will receive PARP inhibitors in first-line treatment.

H&O Do physicians ever use PARP inhibitors in relapsed disease after using them in first-line treatment?

MRM We do not give PARP inhibitors after PARP inhibitors because no evidence exists to support this approach. The ongoing OReO (NCT03106987) and DUETTE (NCT04239014) clinical trials are addressing this question. We will have data from the OReO trial later this year.

H&O How should oncologists go about deciding when to use PARP inhibition in individual patients?

MRM PARP inhibitors should definitely be the first choice in the treatment of patients who have mutated *BRCA* or who have wild-type *BRCA* but HR deficiency. If a patient is HR-proficient, niraparib can be considered; the other option is to treat with bevacizumab and reserve PARP inhibitors for the time of relapse.

H&O What are the specific studies that support the recommendations for when to use PARP inhibition?

MRM Three phase 3 trials support the use of PARP inhibitors in first-line therapy. SOLO1, which was published by Moore and colleagues in the *New England Journal of Medicine* in 2018, showed a clear benefit for 2 years of olaparib vs placebo maintenance in patients with *BRCA*-mutated ovarian cancer. The PRIMA trial, published by González-Martín and colleagues in the *New England Journal of Medicine* in 2019, established that niraparib is effective maintenance treatment in all patients, regardless of *BRCA* or HR status. The PAOLA-1 trial, published by Ray-Coquard and colleagues in the *New England Journal of Medicine* in 2019, showed that the combination of olaparib plus bevacizumab is effective in patients with *BRCA*-mutated tumors, as well as in those with HR-deficient, *BRCA*–wild-type tumors.

H&O Which ongoing studies are examining the question of when to use PARP inhibition?

MRM One approach that is being studied is the combination of PARP inhibition and immunotherapy, to see if immunotherapy can further improve response. Four major trials are looking at this approach. The ATHENA trial, which has already completed recruitment, is looking at the addition of nivolumab (Opdivo, Bristol-Myers Squibb) to rucaparib (NCT03522246). We expect to see data from this trial later in 2021. The FIRST trial, which is examining the addition of the experimental immunotherapy agent dostarlimab to niraparib, should have data available in 2022 (NCT03602859). The DUO-O trial, which is still recruiting patients, is looking at the addition of durvalumab (Imfinzi, AstraZeneca) to olaparib (NCT03737643). Finally, the ENGOT-OV43 trial is looking at the addition of pembrolizumab (Keytruda, Merck) to olaparib (NCT03740165).

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H&O What further research needs to be done?

MRM Two major areas require study. First, we need to identify a negative predictive biomarker so we can determine which patients are unlikely to respond to PARP inhibition. The best test that we have is for HR deficiency, which does not tell us enough.

Second, we need to learn whether giving PARP inhibition after PARP inhibition is beneficial. If a patient has already responded to a PARP inhibitor, is it possible to achieve a later response? We know that the use of PARP inhibitors creates at least some PARP inhibitor resistance. Perhaps we can overcome that resistance by adding an additional agent, but which one? This area of research will be extremely important.

H&O What has been the effect of PARP inhibitors in ovarian cancer?

MRM We have changed the landscape dramatically in ovarian cancer, with amazing success. According to the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, the prevalence of ovarian cancer has increased by 33% in the last 5 years. This means that more women are living with the disease rather than dying, which is something that never happened before. The introduction of PARP inhibitors to the treatment of ovarian cancer is the major reason for that improvement. We should be proud that we have been able to make such a big difference for our patients.

Disclosure

Dr Mirza has personal financial interests in AstraZeneca, BIOCAD, Clovis Oncology, Eisai, Geneos Therapeutics, Genmab, Karyopharm Therapeutics, Merck, Mersana Therapeutics, MSD, Oncology Venture, Pfizer, Roche, Seagen, Sera Prognostics, SOTIO, Takeda, Tesaro-GSK, and Zai Lab. His institution has received study grants from AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Pfizer, Tesaro-GSK, and Ultimovacs.

Suggested Readings

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