

Current and Future Directions for PARP Inhibition

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Megan Grudem, APRN, CNP, and Andrea Wahner Hendrickson, MD, reviewed the potential role of PARP inhibition in various malignancies, how to select patients who are appropriate candidates, and guidance on devising treatment plans that include PARP inhibitors for patients with ovarian or breast cancer based on genetic profiles, tolerability, dosing schedules, and other key factors.

Although immunotherapy has dramatically altered the treatment paradigm for numerous types of cancer, the results have not been nearly as positive for ovarian cancer. Fortunately, a new class of agents that target the enzyme poly(ADP-ribose) polymerase (PARP) have had a major impact, especially against tumors that have dysfunctional DNA repair. What's more, the potential role of PARP inhibitors is not limited to gynecologic cancers but includes prostate, pancreatic, and breast malignancies as well. At JADPRO Live 2019, Megan Grudem, APRN, CNP, and Andrea Wahner Hendrickson, MD, of Mayo Clinic in Rochester, Minnesota, discussed the identification of appropriate candidates for PARP inhibitor therapy based on genetics, disease biology, and other key factors.

“We're very excited about this new class of drugs that appears to

work best in tumors with dysfunctional DNA repair,” said Dr. Wahner Hendrickson. “Patients who are suspected to have an inherited mutation based on personal or family history of breast or ovarian cancer should be tested for *BRCA* mutations.”

As Dr. Wahner Hendrickson reported, these mutations lead to difficulty in repairing DNA damage, and PARP inhibitors enhance that difficulty. These mutations can be a germline (inherited) mutation or a somatic (tumor only) mutation, but the largest impact is seen in patients with *BRCA1* or *BRCA2* mutation, which are important proteins in the homologous recombination pathway. Dr. Wahner Hendrickson also noted that PARP inhibitors can benefit patients with homologous recombination deficiency (HRD). Dr. Wahner Hendrickson and Ms. Grudem outlined the four PARP inhibitors currently approved by the U.S. Food & Drug Administration (FDA).

OLAPARIB

Olaparib is FDA approved in breast and ovarian cancers. The indication for breast cancer was released in January 2018 for the treatment of patients with deleterious or suspected deleterious germline *BRCA* mutation, HER2-negative metastatic breast cancer who have been treated with chemotherapy, either in the neoadjuvant, adjuvant, or metastatic setting. The approval was based on data from the randomized, phase III OlympiAD trial, which showed a progression-free survival of 7.0 months in patients receiving olaparib vs. 4.2 months with chemotherapy and a response rate of 60% and 29%, respectively (Robson et al., 2017). In addition, only 5% of patients discontinued due to toxicity.

“That’s a low number when we think about treatment options for our patients,” said Dr. Wahner Hendrickson, who noted that the most common side effects observed were fatigue, nausea, vomiting, and anemia.

The indication for ovarian cancer was released in December 2018 for the maintenance treatment of adult patients with germline *BRCA*-mutated or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Data from the clinical trial showed a progression-free survival of at least 32 months on olaparib vs. 13.8 months without maintenance therapy (Moore et al., 2018). As Dr. Wahner Hendrickson explained, however, most patients with *BRCA*-mutated cancer will probably receive PARP inhibitors in the first-line setting in the future.

Ms. Grudem noted that toxicities associated with olaparib were by and large treatable, but dose reduction is also an option, as PARP inhibitors have been shown to be effective at multiple dose levels (Table 1).

“Nausea tends to improve with time, and diarrhea can usually be treated,” said Ms. Grudem. “We do struggle to help patients through fatigue, however. It’s hard to come up with a good prescription for that symptom.”

RUCAPARIB

In 2016, rucaparib was approved by the FDA for patients with germline *BRCA*-mutated or somatic *BRCA*-mutated ovarian cancer and two or more prior therapies. Treatment requires a FoundationFocus CDxBRCA test. More recently, rucaparib was approved as maintenance therapy for patients with recurrent ovarian cancer who are in complete or partial remission to platinum-based therapy, regardless of mutation status. The latter approval was based on data from ARIEL1 and ARIEL2, which showed an 80% response rate to the PARP inhibitor among patients with a germline or somatic *BRCA* mutation (Swisher et al., 2017). Notably, said Ms. Grudem, patients with unmutated *BRCA* who were “HRD high” responded better to treatment compared to patients who were “HRD low” (29% vs. 10%, respectively).

Regarding toxicity, Ms. Grudem reported that nausea and vomiting were the most common side effects. Patients requiring nausea medication twice a day (before each rucaparib dosing) typically have their rucaparib dose reduced, she explained.

Table 1. Dosing for PARP Inhibitors

	Starting dose	First dose reduction	Second dose reduction	Third dose reduction
Niraparib (100-mg capsules)	300 mg daily	200 mg daily	100 mg daily	-
Olaparib ^a (100-mg and 150-mg tablets)	300 mg twice daily	250 mg twice daily	200 mg twice daily	-
Rucaparib (300-mg, 250-mg, and 200-mg tablets)	600 mg twice daily	500 mg twice daily	400 mg twice daily	300 mg twice daily
Talazoparib (0.25-mg and 1-mg capsules)	1 mg daily	0.75 mg daily	0.5 mg daily	0.25 mg daily

Note. ^aOlaparib capsules are available, but require 8 pills twice daily to reach dose.

“A majority of patients on rucaparib are also dealing with fatigue,” Ms. Grudem added. “However, most of them are willing to undergo some fatigue for the chance at a longer remission.”

NIRAPARIB

Niraparib is another PARP inhibitor that is approved by the FDA only in ovarian cancer. As Ms. Grudem reported, niraparib is used mostly in clinical trials for maintenance therapy, and two patients at Mayo Clinic, both of whom had two prior recurrences of ovarian cancer, have been on maintenance niraparib for more than 2 years and 4 years, respectively.

“That’s a pretty remarkable response,” said Ms. Grudem. “Both of these patients also ended up on the lowest dose level due to cytopenias and were still able to get a lasting response.”

“The convenient thing about niraparib,” Ms. Grudem added, “is that it’s the only PARP inhibitor that has once-a-day dosing.”

Niraparib is approved for maintenance therapy for recurrent disease (not after first chemotherapy; Mirza et al., 2016). As Ms. Grudem explained, the tumor must have partially or completely “responded” to the most recent platinum chemotherapy, and all women are eligible regardless of mutation status. More recently, niraparib was FDA approved for the treatment of ovarian cancer after three lines of therapy for patients who are still platinum sensitive.

“Patients don’t usually remain platinum sensitive for that many lines of therapy, and now, because most patients are going on maintenance earlier, this indication may not get a lot of use,” said Ms. Grudem.

Regarding toxicities, Ms. Grudem reported that niraparib is associated with nausea, and thrombocytopenia has been frequently observed along with fatigue and anemia. Nevertheless, said Ms. Grudem, niraparib still seems to be very effective.

TALAZOPARIB

Talazoparib, the fourth and final PARP inhibitor, was approved by the FDA in 2018 for germline *BRCA*-mutated, *HER2*-negative locally advanced or metastatic breast cancer. Like niraparib, talazoparib is once-daily dosing. Approval for talazoparib was based on data from the EMBRACA

trial that demonstrated progression-free survival of 8.6 months vs. 5.6 months in patients receiving talazoparib vs. standard of care, respectively (Litton et al., 2018). The response rate on talazoparib was also improved, from 27% in the control arm to 62% on the PARP inhibitor. In addition, said Dr. Wahner Hendrickson, patients who received talazoparib had a longer period of response, so they were able to stay on the medication longer.

Dr. Wahner Hendrickson also noted slight differences in side effects. However, the safety profile is mostly similar to the other PARP inhibitors, she said, with fatigue, cytopenias, and nausea being the major concerns. Although low risk, Dr. Wahner Hendrickson reported that myelodysplastic syndrome and acute myeloid leukemia may develop from PARP inhibitors, so patients who experience prolonged anemia, thrombocytopenia, or neutropenia should undergo a blood smear or a bone marrow biopsy.

PANCREATIC CANCER

Finally, as *BRCA1* and *BRCA2* are present in pancreatic cancer as well, PARP inhibitors are also being studied in metastatic pancreatic cancer, a disease that is desperately in need of better treatment, said Dr. Wahner Hendrickson. The POLO trial published in 2019 looked at patients with germline *BRCA* mutation who had received a platinum-based therapy (Golan et al., 2019). Patients who did not progress during initial chemotherapy were then randomized to olaparib vs. placebo. Patients randomized to olaparib had a progression-free survival of 7.9 months vs. 3.8 months on placebo. While much shorter than the 32 months of progression-free survival seen in ovarian cancer, said Dr. Wahner Hendrickson, these results are still encouraging.

“It would be preferable to have something better for our patients with pancreatic cancer, but this is still a move in the right direction,” Dr. Wahner Hendrickson concluded. “Olaparib is not FDA approved for pancreatic cancer yet, but it’s currently under review.” ●

Disclosure

Ms. Grudem and Dr. Wahner Hendrickson have no conflicts of interest to disclose.

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