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What to Know About PARP Inhibitors for Advanced Ovarian Cancer

Announcer Introduction
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by GSK. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss poly-ADP ribose polymerase, or PARP, inhibitors for advanced ovarian cancer is Dr. Joshua Kesterson, who's the Medical Director of the Gynecologic Oncology Program at UPMC in central Pennsylvania. Dr. Kesterson, welcome to the program.

Dr. Kesterson:
Thank you. Pleasure to be here, Charles.

Dr. Turck:
So to get us started, Dr. Kesterson, would you tell us about the mechanism of action of PARP inhibitors?

Dr. Kesterson:
The way I think about it and the way I explain to patients is the fact that a PARP is a means of repairing DNA. Now we'd all like a good PARP in our normal cells to repair DNA errors. We don't want a functional PARP in tumor cells. And so a PARP inhibitor is responsible for inhibiting that PARP that is responsible for repair of single-strand breaks along DNA. If there are enough single-strand breaks or those single-strand breaks lead to double-strand breaks, those can be associated with a lethal event, therefore killing off a cell. The reason that PARP inhibitors work better for some patients than others, or some tumor types than others, is because those tumors may have a mechanism of action of DNA repair that is also impaired. So what you have is a situation what we call synthetic lethality, where you have two mechanisms of action that inhibit DNA repair, thus leading to cell death.

Dr. Turck:
Now let's zero in on how PARP inhibitors fit into the overall treatment landscape for advanced ovarian cancer. First, which of our patients would be ideal candidates for this class of medication?

Dr. Kesterson:
That's a good question, Charles, because the landscape has changed recently. Initially, the indications for PARP inhibition were more broad for patients with high-grade advanced stage ovarian carcinoma. As we look at it now, when I think about patients who would be candidates for PARP inhibition, it would be those patients with high-grade advanced stage ovarian cancer who have responded to upfront chemotherapy, platinum-based chemotherapy in this situation. And then our goal would be then to maintain that disease status as long as possible, which PARP inhibition has proven to do. The indication for the treatment setting and for the recurrent setting has changed more recently secondary to some new data that has come out.

Dr. Turck:
So you're starting to get into this a little bit, but in what lines of therapy should PARP inhibitors be used?

Dr. Kesterson:
So when I think about the greatest impact of PARP inhibition, it would be for that patient in what we call the frontline setting. So this is a new diagnosis with initial treatment with a combination of surgery and platinum-based chemotherapy. After completion of that initial therapy, our goal would be to keep the disease, in this case, ovarian cancer, away as long as possible. And so with PARP inhibition, we're able to, in that setting, prolong their progression-free survival or time without disease compared to, as the trials have demonstrated, placebo or no further treatment.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Joshua Kesterson about PARP inhibitors for advanced ovarian cancer.

So Dr. Kesterson, let's switch gears a bit and turn our attention to these medications efficacy and safety. Starting with efficacy, would you highlight some key data points?

Dr. Kesterson:
Certainly. So when we think about the natural history of advanced stage high-grade ovarian cancer, what we know is that despite initial aggressive therapies with surgery and platinum-based chemotherapy, these processes are more likely to recur than not recur. And so what we want to do is change that natural history and delay the time of recurrence as long as possible. There have been multiple studies that have demonstrated that in the maintenance setting, continuing with PARP inhibition improves one's progression-free survival versus treatment with placebo, which was the prior standard of care, what we call “watchful waiting.”

Dr. Turck:
And how about safety? What common adverse effects should we be on the lookout for when using PARP inhibitors?

Dr. Kesterson:
So when we think about categories of side effects, one of the things that we think about initially with PARP inhibition is hematologic toxicity. So that's the effect that it can have on the patient's blood or bone marrow. And what we see in the initial cycles, if it were the first couple months, is anemia, thrombocytopenia, as well as neutropenia. Now thankfully, those issues will resolve with a dose interruption or a dose reduction, allowing the patient to continue on therapy.

Some of the symptoms that patients may have are gastrointestinal, and within that, we think about nausea being the most common, but also other issues like constipation and emesis; that's kind of our biggest category as far as the GI side effects go. Patients will also experience fatigue. One of the things that we counsel patients on is the risk of a secondary malignancy, such as myelodysplastic syndrome or leukemia. This is where, based on taking treatment that is damaging to DNA, you can induce a secondary malignancy that may be bone marrow or blood based. And so that is something in terms of the hematologic side effects and in terms of the risk of secondary malignancy that we follow with lab values. And the symptoms the patient may experience is where it becomes incredibly important to have an open line of communication with the patient so that we can mitigate any adverse side effects, including GI-based side effects, so that the patient can continue on therapy for a prolonged duration hopefully.

Dr. Turck:
Now we've certainly covered a lot of ground today, Dr. Kesterson. So bringing things together and taking a global view, how have PARP inhibitors impacted the treatment of advanced ovarian cancer?

Dr. Kesterson:
That's a great question, Charles. And I think one that allows us to appreciate how far we've come in a short period of time as far as options and outcomes for our patients. While I tell my patients it's never a good time to have ovarian cancer, it is certainly associated with a better outcome now than even 10 years ago. And one of the main influencers of that is our ability to have more options and keep the disease away longer with PARP inhibition.
In doing so, we're able to turn what is an acute disease with symptomatic presentation and aggressive interventions initially into a chronic disease where patients can take a pill and keep their ovarian cancer from recurring for a longer duration versus the prior standard, which was essentially nothing, and so what we have is more options. And those additional options have thankfully led to better outcomes for more patients.

Dr. Turck:
Well as those thoughts bring us to the end of today's program, I want to thank my guest, Dr. Joshua Kesterson, for joining me to discuss PARP inhibitors for advanced ovarian cancer. Dr. Kesterson, it was great having you on the program!

Dr. Kesterson:
Pleasure to be here, Charles. Thank you for those insightful questions and the opportunity to educate patients and providers alike in this setting.

Announcer Close
This episode of *Project Oncology* was sponsored by GSK. To access this and other episodes in this series, visit ReachMD.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for listening!