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Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer: PARP Inhibitor-Related Adverse Events and Team-Based Care

Announcer Open:
Welcome to CME on ReachMD. This activity, titled I*mproving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer: PARP Inhibitor-Related Adverse Events and Team-Based Care* is developed by AXIS Medical Education and is supported by educational grants from GSK, Merck Sharp & Dohme LLC, and AstraZeneca Pharmaceuticals. Before starting this activity, please be sure to review the disclosure statements as well as the Learning Objectives.

Chapter 1: How Do Team-Based Management Strategies Mitigate PARP Inhibitor–Related Adverse Events? PARP Inhibitor Adverse Event Profile and Tips and Tricks to Ensuring Adherence
Dr. Moore:
Hello and welcome to this educational activity titled *Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer: PARP Inhibitor-Related Adverse Events and Team-Based Care*.

I'm Dr. Kathleen Moore, and I'm the Virginia Kerley Cade Chair in Developmental Therapeutics and the Deputy Director of the Stephenson Cancer Center in Oklahoma City.

Today, I will be reviewing potential treatment-related complications that may occur with PARP inhibitor-based therapy, shared decision-making strategies, and case examples highlighting the integration and management of first-line maintenance treatment with PARP inhibitors in advanced ovarian cancer.

And I'll just remind you that there is a Part 1, where we discussed the efficacy around PARP inhibitors as first-line maintenance, and team-based management strategies around how you select PARP inhibitors.

Key considerations that came out of the Part 1, just as a review, is the unfortunate fact that we can't screen for ovarian cancer yet, and because of that, most patients present with advanced stage disease – stage 3, 4 disease. And despite initially exquisite responses to platinum-based chemotherapy in combination with surgery, we really do expect the vast majority of our patients will relapse, and once relapsed, we can no longer expect cure. Now, what we can expect is that we have and continue to develop many lines of active chemotherapy, and so we are prolonging, I believe, the overall time that patients with ovarian cancer live, but they are spending the majority of that time on some sort of therapy. And I think it goes without saying that multiple lines of chemotherapy, repeated lines, is associated with cumulative toxicity, less benefit. Every subsequent line of therapy the patient has more tumors and so there're more disease-related side effects as well and so just quality of life can decline up until the end where many of our patients will pass away from carcinomatous ileus. And so, our best intervention there to try and prevent that, or just prolong that away as long as possible, is a screening we can't do yet. But until then, cure more patients at the front-line, or really, really markedly improve progression-free survival at the front-line and really push off subsequent therapies to the future. And the best opportunity to do that is with the use of PARP inhibitors especially amongst biomarkers, like in populations.

PARP inhibitors, specifically with BRCA-associated cancers, really are the first intervention where we have an inkling that we are impacting survival and, more importantly, moving more patients into the cure fraction. So currently, PARP inhibitor approvals in frontline include olaparib monotherapy only for those patients with BRCA-associated cancers. Olaparib plus bevacizumab in patients whose tumors are homologous recombination deficiency test positive. So, that includes BRCA, but also those BRCA wildtype HRD test–positive. Niraparib is approved in all-comers; BRCA, BRCA wildtype, HRD test–positive, and HRD test–negative. Those are the 3 FDA

approved PARP inhibitors in the frontline. But I will mention that based on ATHENA-mono data, rucaparib is NCCN listed based on it's very consistent efficacy and safety profile, which we're not going to talk a lot about today, in all-comer populations as well, very similar to niraparib. But it is not, as of yet FDA approved.

So that's sort of where we are in terms of medications that are available for you to use, and again, if you want details of that, please refer to the Part 1 of this series.

What we're going to talk about today is how the team-based management strategies mitigate PARP inhibitor-related adverse events.

And so, we'll start with olaparib. And I'm showing you just a reminder of the schema for SOLO-1, which was the first study to bring PARP inhibitor maintenance into the frontline treatment of women with ovarian cancer here, and those with BRCA positive tumors. And patients in response to their frontline chemotherapy were randomized 2 to 1 to receive 2 years of olaparib or placebo.

This slide really takes you through kind of the high-level overview of treatment-emergent adverse events. And when I look at a new therapy, the last three rows from this table are kind of the first things I look at before I look at the individual adverse events. I really want to know how often does whatever drug I'm using need to be interrupted due to an adverse event, how often do I have to dose reduce it. And the most important thing to me is how often does a patient just say, I don't care if this is working but I am not taking this medication. So outside of progression, when does someone say I'm not taking it. Those are kind of the things I look at that are giving me a sense of how well-tolerated a drug might be for a patient.

And so, this is what you can see for olaparib, and then versus placebo. You have dose interruption in about 50% of patients on olaparib, and I actually tell patients that up front. Fifty percent of the time we're going to need to interrupt here and there because of an adverse event. And I think that's important to do, and that's why I like to know this information, because sometimes patients get nervous if they want to take a break. And sometimes they do, and then they feel guilty because they feel like they've harmed themselves. But on the SOLO-1 study, which had phenomenal outcomes, half the patients had to take at least one interruption, and they still did great. So, I like to know information. Fifty percent of the time patients have to interrupt. But interruption doesn't equate to reduction. So, only a little less than 29% needed a dose reduction. And then, importantly, only a little less than 12%, 11.5%, stopped olaparib because of treatment-emergent adverse events. So that is the kind of high-level safety profile for olaparib.

Now we can look at some of the more common class effects of all the PARP inhibitors, really, so this will be a theme you see as we talk about the PARP inhibitors, common but low-grade gastrointestinal toxicities, some heme toxicities, and fatigue. Those are the class effects, and then we'll talk about some of the outliers.

So here you see that in a table form: nausea, fatigue, and vomiting. So, let's look at nausea, which is incredibly common. Seventy-seven percent of patients report any grade nausea. It happens really fast. And I told patients this, too, when I counsel them. It's a few days in and they feel queasy. But 75% of them had a resolution date. So really, of 25% that have some ongoing nausea, but for most patients, it does resolve. But it takes a little bit of time, you're about 6 weeks in. And that's that accommodation period that, you know, over which time patients get used to the medication, we get used to the mitigation strategies that they need, and they kind of level out 6 to 8 weeks.

Fatigue, a little bit different. Really common. Sixty-three percent with any grade. It's about 3 weeks in that you start to see the fatigue. Only about 50% have resolution of this, which I think is important to tell patients about. Now, they do accommodate just like the GI toxicities over that first 6 to 8 weeks, but it's always there. It's this sort of low grade but pervasive tiredness that patients do learn to work around and work through. But setting that expectation that that's normal and expected is really important for your patient. And the median duration until it does really resolve if it's going to resolve is almost 4 months, so it takes a little bit of time for this to resolve.

Vomiting is not as common but does happen. It tends to be early in onset and then we get it mitigated. But 40% of patients on SOLO-1 reported some vomiting, as predominantly grade 1 or 2. This was a little later in onset, about 6 weeks in. About 40% had resolution and it resolves pretty quickly because, of course, we intervene with antiemetics, and so we can turn these around relatively quickly.

And the other common set of adverse events with PARP inhibitors are hematologic, and so we talk about anemia, neutropenia, and thrombocytopenia. Across the PARP inhibitors, the most common amongst the three is anemia, and that's certainly what you see here. So, 40% of patients on olaparib have some degree of anemia. You'll see it usually as they come in for that pre-chemo visit before their third cycle, so it's about 2 months in, most of them do come down a grade. And it may not ever completely resolve because you may kind of have someone that's running at grade 1 anemia for the rest of the time on the PARP inhibitor, or on olaparib. But it does tend to come down a bit with a higher grade through mitigation strategies, it comes down to a low grade. So, this is really your most common for olaparib – the most common hematologic side effects, and I'll show you some more granular data about that in a moment.

Neutropenia and thrombocytopenia are very much less common. So, 23% neutropenia, 11% thrombocytopenia any grade. These tend to be low grade, like high-grade neutropenia or thrombocytopenia is really, really uncommon with olaparib, and that's different than the

niraparib, which we'll talk about in a little bit.

The onset for neutropenia is about the same as anemia. You see it just under the 2-month mark. And you will see resolution over time and with dose modifications. For neutropenia and thrombocytopenia, you see a sort of a similar trend with not complete resolution, but resolution down to the lowest grade possible, and then it sort of just runs and is stable over the course of exposure to the olaparib. But again, these are usually grade 1 sorts of events.

This is work that my colleague Dr. Nicoletta Colombo presented. And it just sort of shows you graphically over time what to expect and sometimes I'll show these to patients just so they, sort of, can see graphically what we look at over time. This is over the 24 months of exposure to olaparib. This is nausea. Very common in those first 2 months where you're almost 70%, the vast majority are grade 1, though, and then a little bit of 2, and like a smidgen of 3. So, this is mainly a grade 1/2 toxicity and not a lot of grade 2, nausea is low grade by definition, but it's still very uncomfortable for patients. By that 4th dose, we're really eliminating a lot of those grade 2s. And so, most of our patients by about 4 to 5 months in are running along, 30-ish percent of patients with grade 1 nausea that they learn to accommodate around with diet interventions. Sometimes they need pharmacologic intervention that we'll talk about, but most patients don't need that ongoing and they just learn to modify diet and expectations for the length of time that they are on this medication.

And do the same thing with anemia, where you do see we bump into grade 3 and I'll show you this in a moment. But you see grade 3 in about 21% of patients on olaparib, and it happens relatively quickly. You see those kind of bigger green bars at month 3 and month 4 and then it starts to dissipate as we either dose modify or correct underlying nutritional deficiencies like iron deficiency or folate and then they reach the steady state that you can see kind of starting about 7 to 8 months. You know, it's about a 10 to 15% rate overall of anemia after that point, and predominantly grade 1, which is greater than 10. But you do see a kind of fairly constant band of grade 2, 8 to 10 hemoglobin across that second year of use of olaparib that kind of sits right at that maybe 5 to 8% of patients, sort of right in that band. And then just a few will pop up into the grade 3 zone in later lines of therapy. But we really see most of that early on. We mitigate and we don't see a lot of it as a kind of cumulative effect over time. But we do have to watch for it. So there is ongoing monitoring for anemia with monthly labs.

This is the management for some of these adverse events and again, I'm coming back to non-hematologic nausea and fatigue and vomiting. So, for nausea, as an example, we did supportive treatment in almost 60%. So, this is usually antiemetics. Seventeen percent of patients got a dose interruption for a few days, though. And a lot of times this is all patients need and you can start to make it a full dose and they just sort of feel better and then they restart, and they do OK. So that's a strategy. Only 5% needed a dose reduction for nausea, and of those well, of the total 3% of patients on SOLO-1 discontinued due to the nausea. Fatigue is harder to treat, as all of you recognize, there's no magic pill for it because it's so multifactorial in what's causing it. Certainly, the olaparib is causative. It does have a role, but it is synergistic in a negative way with other things that contribute to fatigue, and we'll talk about that when we get to some of the case examples. So, it is harder to treat because of that multifactorial etiology. But you give supportive treatment – we have about 7% with supportive treatment. The most common intervention was really giving patients a small break, an interruption, letting them feel a little bit better and then restarting., And then 9% got a dose reduction and 4% discontinued due to fatigue. Vomiting, 27% with supportive treatment, 24% got a dose interruption, primarily we were giving them antiemetics and then we restart. No dose reductions and 2 patients discontinued due to the vomiting.

Then you see the rates for resolution below, very high rates for resolution of nausea and vomiting and not insubstantial really for fatigue and asthenia, you're above 60% recovery on olaparib, so we are improving things with our mitigation strategies. But you do have roughly 40% of our patients on olaparib with some degree, likely low grade, but they are fatigued the duration of their experience on olaparib. And you can see at the very bottom row, the incidence of grade 3 or higher events that are non-hematologic is really, really low, like, really almost should be a never event. So, if it happens you should question sort of what else might be going on because it's so uncommon to have grade 3 or higher nausea and vomiting. We do see grade 3 fatigue in a few patients, 4%, but look at the placebo group, it's 2%. So, there are other things that can cause fatigue that we just need to pay attention to as well.

Now if we look at the same sort of data, though, with hematologic adverse events, it looks a little bit different. Top row is just the same rates of all grades of hematologic side effects, again anemia and neutropenia and thrombocytopenia. For anemia, supportive treatment is very common. Seventy-one percent of patients got some kind of supportive treatment, either a blood transfusion or addition of iron, either oral or injectafer, or replacement of folate. Those sorts of interventions, you know, depending on the etiologies of the anemia. But a high proportion of the patients who have anemia, which is 40% had anemia and 57% of that 40% got a dose interruption, which is per protocol. So, if you had anemia on this protocol, if you dropped less than 10, we had to dose interrupt until we had that recovered. Very common interruptions, very common reductions. Again, that was per protocol. Forty-four percent of those with anemia ended up with the dose reduction, only 6% discontinued. And this was usually due to kind of recurrent episodes of anemia.

Neutropenia – supportive treatment was given in about 18%, interruption in 50%. Again, that was per protocol, of patients with

neutropenia, which is only 23%. So, 50% of 23% had to interrupt, 17% of 23% had to dose reduce and then very few discontinuations. And then, you can see thrombocytopenia is similar because really there's not a lot of supportive treatment that you can do for thrombocytopenia other than a transfusion. Interruptions were your most common intervention.

You can see below the recovery and resolution for all of these is quite high, really because if you didn't recover at least to a grade 1, we couldn't restart you on therapy, so this is to be expected per protocol. And they you did have roughly 10-ish percent of our anemia and neutropenia that at the time of study closure had not resolved. Patients with grade 3 or greater events, which is really where you're like, hmm, what's going on with this medication from a hematologic standpoint, was 22% for anemia. So, this is the most common hematologic side effect, both for all grades, but also grade 3 and higher, is anemia. That is the hematologic side effect we see with olaparib. So, 22% grade 3 or higher, 9% grade 3 or higher neutropenia and 1% grade 3 or higher thrombocytopenia. So very, very uncommon to have high-grade neutropenia and thrombocytopenia on monotherapy olaparib. So, if you see this, and you see this repetitively, this is something that can happen, but it is unusual and so your antennas should go up maybe about the robustness of that patient's bone marrow to remain on study.

This is just another nice graphic showing the kind of tolerability of olaparib over time. The blue bars are patients that started on the full dose, which is 300 mg twice a day, and ended on that dose. You can see it's right about 65%. The orange bars are those that got one little dose reduction to 250 BID. So, if you look at 300 and 250, which is pretty close to full dose, you're at 80% dose compliance. And then you had about 20% of patients that needed to come down to 200 mg BID, which was the smallest dose per protocol. But I think the point here is just to say, the majority of patients who start on 300 twice a day finish on 300 twice a day, so this is a well-tolerated medication with appropriate mitigation strategies.

And I made a comment about bone marrow just because we are always worried and watchful for treatment-related myeloid neoplasms. And of course, we say MDS/AML, but there's a myriad of these treatment-related myeloid neoplasms that we watch for. We've watched for them long term and so we've seen them in the recurrent setting, sometimes at kind of surprisingly high frequencies, especially amongst our BRCA population, and so this is of great interest as we've moved PARP into the front line. And across the studies the rate has been very low. These are the 3 cases as of study completion for SOLO-1. It's a little less than 2% of patients that developed a treatment-related myeloid neoplasm. You can see the duration of olaparib therapy in days listed in that middle, and the time to AML onset after stopping the olaparib. There's not been a clear pattern in any of the studies of frontline PARP inhibitor, other than the rate is really low and there probably is some pre-existing vulnerability but we're not seeing a tremendous uptick when we use in the frontline as opposed to what we saw in the recurrent setting. And why is that? Well, at least with SOLO-1, and I think we're seeing the same thing in the other studies, is that there's a lot of patients on SOLO-1 that have not recurred yet, like 45%. So, they've not gotten any other therapy. And one of the major risk factors as we all know of treatment-related myeloid neoplasms is repeated exposure to DNA-damaging agents such as platinum, which is a key drug in ovary. Our patients may get this many, many times. But when you have such a high fraction of patients who haven't recurred, or they haven't gotten subsequent lines, that may explain the lower rate that we are seeing. Also, unlike recurrent setting where you treat to progression, the frontline, wherever we're using PARP inhibitors, we're using them for a set amount of time and then we stop. And that may also be important. Time will tell. But this is our current rate, it remains low, but it still has to be on our radar, always watchful for patients at risk. So that's SOLO-1.

What happens when you add bevacizumab to olaparib? And when you bring it into an all-comer population? Well, number one, I'll just tell you up front, we really haven't seen differences in side effects in BRCA versus non-BRCA, germline BRCA populations. So, I'm not going to kind of separate that other than just to make that statement, otherwise we're just looking at the addition of bevacizumab. So, this is the PAOLA study. Just to remind you, all-comers, stratified by BRCA, in response to frontline platinum-based chemotherapy with bevacizumab, randomized 2 to 1, bevacizumab for 15 cycles and olaparib for 2 years, or placebo for 2 years plus bevacizumab for 15 cycles. So basically, olaparib/bev versus bev.

So, let's look at the most common adverse events. This is a tornado plot, olaparib/bev versus bev, and this should look very similar other than the hypertension. You see very common, but low-grade GI and fatigue. So, fatigue is 53%, 5% grade 3. Nausea is 53%, actually lower than what we saw in SOLO, which is interesting but still pretty common, 2% grade 3 and up, and then vomiting 22%. And that's what you see roughly with olaparib, so that didn't change and didn't get worse with the addition of bevacizumab. What you do see is the hypertension here. Forty-six percent of patients with hypertension, 19% of which were grade 3 or higher. Interestingly, in the placebo plus bevacizumab group, both of those were higher, 60% and 30%, which none of us can really explain. To be honest, it just may be spurious. But I think we can certainly say that there's not synergistically more hypertension when you combine olaparib and bevacizumab. Those rates of bevacizumab-induced hypertension just look like what we see with monotherapy bevacizumab. And then you can see the rest of the adverse events here honestly look quite similar between the placebo and the olaparib group because a lot of this is just background symptoms that we see with ovarian cancer.

These are the adverse events of special interest for olaparib in general, and they were just highlighted in the PAOLA study. Treatment

related myeloid neoplasms, again, 1.1% versus 0.4% in the placebo arm. So again, we're still running less than 2% with these frontline studies. PAOLA and we looked at this in SOLO as well, looked at secondary malignancies that were not hematologic, like breast cancer and lung cancer and pancreas, other things associated with BRCA. And it's because there was sort of this theory that if you use PARP inhibitor on the frontline, then maybe patients with BRCA would be less likely to get other cancers. I don't think we've proven that yet. So, I wouldn't say that. It's certainly not more. So, you see very equal distribution of new primary malignancies in the two arms here and it's very low. And then we do, just like with every targeted drug, there's a risk of pneumonitis and interstitial lung disease. With PARP inhibitors it's there, it's about 1%. So low, but something we need to be mindful for if our patients have new ground-glass opacities or patchy infiltrates or fibrous linear changes. But if you see that, and/or your patient has symptoms of respiratory symptoms, so you should be thinking about pneumonitis because we do see it rarely, but something to watch.

Now back to those, sort of, high-level safety signals that I like to look at. Here's dose interruption reduction and discontinuation. Again, here comparing SOLO-1, which I've already shown you, so that's on the left-hand side, and now we're looking at PAOLA. When you use two drugs in the maintenance, how does this change? The median duration of exposure is a little bit lower in PAOLA, but remember, this had a lot of patients that didn't have BRCA and so their risk is higher, so they may have progressed sooner than those with BRCA mutation.

So, the median duration of exposure is a little bit different between the two studies, 25 versus 17 months. Dose interruptions are very similar, though. About 50% of patients need a dose interruption. Dose reductions 28%, in SOLO 41% – so it is a little higher in PAOLA. And then, treatment discontinuation was about double, 11.5% and then to 20% for PAOLA-1, which is a little bit surprising to me. But we did see higher rates, still not huge compared to other interventions. But I do think it's probably a variety of reasons why patients chose to discontinue for reasons other than progression so it's hard to say what drove this, but there is something with the doublet that's a little tougher and so we have to keep that in mind when we're sort of monitoring somebody who's on olaparib/bev versus just olaparib monotherapy.

Here's again, just a couple more comparison slides and remember, these are different populations. So just different studies, different time periods, but just to kind of give you some benchmarking. Dose reductions, again, 28% versus 41%. Dose interruptions, very similar, and dose discontinuations were higher, 12 versus 20%. Hematologic toxicity is really similar, so about 39% versus 41%. Anemia, grade 3 is 22 and 17%. And you can look at neutropenia and thrombocytopenia, very similar. And then of course, hypertension is unique to bevacizumab and you can see the rates there at 46 and 19%. And that's just nice for benchmarking for your patients. So, that's the olaparib story.

What about niraparib? So, let's talk about the PRIMA trial. PRIMA was another – just like PAOLA was an all-comer study. And patients had to be in very good response to their frontline platinum-based chemotherapy with or without surgery, and they were stratified by homologous recombination deficiency testing. So, it was 2 to 1 randomization to niraparib or placebo for 3 years, and the primary input was progression-free survival first in the HRD test–positive group, which includes BRCA, but also includes that 20% or BRCA wildtype HRD. And if that's positive, which it was, so we went through that in Part 1, then you hold alpha to the intention to treat arm, and look at that, which they did and of course that was positive as well.

These are the adverse events from PRIMA, and I'm showing you the same kind of slide that I did before. If you look at the bottom 4 rows you can see they're a little bit different order, but dose interruption was really common. About 80% of patients on PRIMA needed a dose interruption, 18% on placebo, which is interesting, but 80% on the drug. Reductions happened in almost that exact amount, mainly because this is related to platelets. So, this is a little bit of a different ratio than we saw with olaparib. Eighty percent dose interruption, 71% dose reduction, but only 12% of patients discontinued due to treatment-emergent adverse events. So, even though the interruptions and reductions were much, much higher, the mitigation strategies that were put in place kept patients on study at the same proportion as we saw in monotherapy olaparib, which is interesting. And so that's, sort of, just to give you a little bit of a head-to-head of what we saw on PRIMA as compared to the SOLO-1 study. And I think I have a slide to show you that a little bit more.

As we said, the rate of discontinuations was really relatively low, very similar to olaparib. But we did see a lot of interruptions and reductions. And why was that? Predominantly because of the platelets. And so, what happened during the course of PRIMA is that – and I'm going to show you this in a few slides, it's a little bit backwards – but, it was known that we were seeing a lot of high-grade thrombocytopenia and so there was a lot of interest in figuring out who was at risk and why, and an analysis was done of the NOVA study, which is the study that was done in platinum-sensitive recurrent disease, which is actually one of the first maintenance studies, actually the first maintenance study, Phase 3 to be presented in 2016, and led to the first approval of maintenance PARP shortly thereafter. But it had a high rate of thrombocytopenia, high rate of high-grade thrombocytopenia. And they discovered that this was related to the baseline patient platelet count and baseline patient weight. And so, they incorporated, after doing a lot of work, they incorporated that into the PRIMA study, which was two thirds of the way accrued when this amendment came in to change from fixed

starting dose, which is called FSD to individualized starting dose, which is called ISD. So, it is an unequal proportion of the study, but it was important to do, from a safety standpoint. So, in the top of the figure, the top figure on the left-hand side, you can see the overall population, all patients included any treatment adverse event 100%. We see that in everything. Dose interruptions, 80%, dose reduction, 71%, and then discontinuations, 14%. Once we started the individualized starting dose, so this is only 255 patients of that 728, you can see that there's a little bit nudge down in the dose interruptions that went from 80 to 72%, dose reductions went from 71 to 62%. The treatment discontinuations remained about the same, the mitigation strategies that were successful before continued to be.

So, a little bit of a signal that what they had done had worked. And I'm going to show you a little more granularly kind of what they did. So again, on the far left is the overall population, all patients included. So, most patients on the study were treated at a fixed starting dose with just 300 mg once a day. In the middle of your slide, you can see the carve out of the patients who started at an individualized starting dose. And what that meant is, for patients that had no risk factors, they started at 300. For patients that had either a weight less than 77 kg, or platelets less than 150,000 at baseline, either one, they started at 200 mg, and they didn't escalate. It was just 200 mg. So that's the individualized starting dose.

So, what you can see here is that the key adverse event for niraparib, which is high-grade thrombocytopenia, went from 62% all-grade fixed starting dose to 54%. And grade 3 or 4 went from 40% for the whole population down to 22% with individualized starting dose. So, cut in half. And then, you saw the same drops in high-grade anemia and neutropenia as well. The rest of the side effects stayed about the same. So, the impact of fixed versus individualized starting dose really seems to be a hematologic one.

So, where that came from, just to remind you, it came from the NOVA study, which was the second-line platinum-sensitive recurrent study that looked at niraparib versus placebo following response to platinum in the recurrent setting, either first recurrence or second recurrence.

Wildly positive and became standard of care, and they saw a lot of grade 3 or higher thrombocytopenia, 33.8% in grade 3 or higher thrombocytopenia.

And just like we saw early on in PRIMA, lots of dose interruptions, lots of dose reductions, but not a lot of discontinuations because even then, their mitigation strategies worked, but really patients' platelets were dropping, pretty quickly. And that's evidenced by this.

This is – remember I showed you this for olaparib frontline where most of the patients stayed on their starting dose. It's like the opposite here. This starting dose of niraparib was maintained in 23% of patients. That's that light green. And about 40% of patients ended up at 1 level dose reduction, 200 milligrams, and about a little less than 40% ended up at 2 dose reductions at 100. And this was before fixed versus individualized starting dose. Everyone started 300, so almost 40% had two dose reductions, anymore they'd have to come off. So, clearly the drug was not tolerated for all patients at 300 mg.

This was a lot of work that went into who was at risk and a lot of analyses. it would be super interesting to talk about, but a little beyond the scope of this talk. So, I'm just going to go to this slide, which really breaks down the incidence of grade 3-4 thrombocytopenia by the two things that were shown to be important, and that's called weights and plates, body weight and baseline platelet count. So, as you can see on the left-hand side is the grade 3/4 thrombocytopenia events by month 1, because this drop in platelets is a really early effect, you see it in month 1 by weight. And so, you can see for those patients that were greater than 77 kg per weight was 16%. Anybody less than 77 kg, the rate was close to double. It was 29%. And if they were really small individuals, like less than 58 kg, almost half of them had grade 3 or higher thrombocytopenia. So, they made the cut-point 77 kg.

Similarly, with thrombocytopenia from baseline platelet count for patients that had really robust platelets, like greater than 270, the risk of getting down to grade 3 or 4 was still 20%, which is a little surprising when you're starting that high. But for patients less than 180 platelets at baseline, the rate was 42%, just still, which is really high. So, they dropped it, actually, to 150,000 to try and be very cautious about, what your baseline platelets should be to get 300 mg.

And then they reapplied that analysis to the NOVA study. They said, OK, let's look at baseline and see everybody who's weight's greater than 77 kg and platelets are greater than 150,000. How did they do versus any of the patients who had either one of those. So, the patients that had neither risk factor had a 12% risk of high-grade thrombocytopenia. And patients that had either of those then the rate was 35%. So, that's really what was driving it and why that became part of the label. So, that's a very important thing just to have seared in your brain. If you're using the niraparib, which is a very safe PARP inhibitor to use, you really have to look at the day you're starting the patient, what's that baseline weight? If it's less than 77 kg, she gets started at 200. And you never try to escalate. And/or if baseline platelets are less than 150,000, she starts at 200 mg, and you never re-escalate. And then if they have problems, you drop them to 100, and then if they have problems again, then you have to consider whether they can remain on a PARP, and you maybe have to rotate to a different PARP.

Chapter 2: Shared Decision-Making and Practical Management of Adverse Events for Patients on PARP Inhibitors

So, let's move on to shared decision-making and management of adverse events for patients who are on PARP inhibitors.

This is the shared decision-making model, which I think we all do, you just didn't know there was a nice acronym for it. Seek your patient's participation in the process. Help your patient explore and compare the treatment options for her and maintenance. What are her values and preferences about oral versus infused medications? Once daily versus twice daily? Weekly labs versus every three-week labs? What's important to her and how do you align with that? And then you reach a decision and then continue to evaluate the decision you made ongoing. So, this is the SHARE decision-making model.

So, when we look at how you set someone up for success with a PARP inhibitor, it really comes down to just really selecting appropriate patients, those who've responded to frontline platinum, they understand how to take oral medications. And then you look at sort of the specific toxicity management.

And you really have to look for a couple of things up front. Can they tolerate pills? There're some patients that cannot tolerate oral medications and these cannot be crushed. And also, they can't have significant hepatic or renal dysfunction. There are modifications for olaparib at least, with moderate renal dysfunction, and so it's important to pay attention to that and dose modify from the beginning appropriately. But significant hepatic, like a bili greater than 1.5 times the upper limit of normal or significant renal dysfunction, PARP inhibitors have not been tested and should not be used.

We talked about the starting doses already, but just to remind you for olaparib, they come as 100 mg tablets or 150 mg tablets. The starting full dose is 300 mg twice a day, so 2 tablets twice a day. If they have moderate hepatic impairment, not significant, but moderate, you start at 200 twice a day. And then moderate renal similar, 200 twice a day. And niraparib comes only in 100 mg capsules. And so for patients who have neither low weight or low platelets, they take 3 capsules once a day. And, if they have either of those risk factors, they take 2 tablets once a day. So, it's 300, 200, 100 of the doses for niraparib.

You do have to be a little bit careful with olaparib because there is the potential for CYP3A4 interactions, so use of CYP3A4 inhibitors can increase your olaparib concentration, and so, just reminders of what some of our CYP3A4 inhibitors are, include the mycins, or diltiazem, or fluconazole, or ciprofloxacin, which are not uncommon, so if your patient's taking any of these, remember to drop their dose while they're taking them and then you can re-escalate.

I think when you're starting someone on PARP inhibitors, setting expectations is really key. You really want to set expectations and mitigation strategies for fatigue, GI toxicities, hematologic toxicities, and then we'll talk a little bit more about AML/MDS.

Fatigue is really common, and we should kind of evaluate it – it's like pain, like a vital sign. Patients often underreport it, or they don't want to complain. But it's important to know if your patient's so fatigued, they're like not leaving the house. So, it's important just to tell them that it's expected side effect of PARP inhibitors. It's the worst during the first 6 to 8 weeks and then it improves with time. And so, sometimes if we just get them through those first two cycles, they start to feel better. But we do have to evaluate it and make sure it is getting better over time. And so, we encourage self-reporting. And it's just really important to evaluate other causes that are contributing to the fatigue, and I'm not trying to create like that PARP is innocent, PARP causes this, but if there's others of these in play, it's going to be worse. For example, if there's baseline anemia, if the patient has poor sleep hygiene, if the patient has undiagnosed or untreated depression, undiagnosed or untreated pain, undiagnosed and untreated hypothyroidism, all of those contribute to fatigue, and so if we sort of address all of those and are working on treating those, we can mitigate the severity of the fatigue as well as those other symptoms. So, that's important.

Treatment of fatigue is hard, though, as I just said. All these things are contributing, so if you address some of these other features, that is, the treatment for the fatigue. Other things, non-pharmacologic interventions for patients depending on their resources can be massage therapy, cognitive behavioral therapy, early involvement of supportive care for those of you in bigger centers that have that nice resource. It's not available everywhere, I know. Probably the most data, though, exists really for just physical exercise, which is 30 minutes of walking 5 of 7 days. And it doesn't even have to be 30 minutes all at once, it can be broken up over the day for patients who are really tired. But if they can use and maintain their lean body mass in their lower extremity, that at least prevent some of the worsening of fatigue. There are pharmacologic interventions. But you can also just give a dose interruption for low-grade recurrent. Give them 3 or 4 days off, let them feel better, and then you restart at the same dose and if they're fine, they're fine. If it happens again, then you can consider a dose modification. But dose interruption sometimes can be incredibly useful over the 2 years of olaparib. Grade 3 fatigue should launch a workup for what else is going on, number one, and if it really is the PARP, you want to dose hold and then dose reduce.

Nausea and vomiting also incredibly common, and so patient counseling is key. Symptoms are fast in terms of onset and they're the worst that first 6 to 8 weeks. So again, if we can get them through that, they improve with time. Patients accommodate to it, and they actually can do quite well after. Some kind of tips and tricks. Niraparib, if you're using niraparib, it's once a day, so you can administer at

bedtime and even pre-dose with an antiemetic. They take it at bedtime, and they can sleep through the nausea. With the twice daily dosing, you can start patients off – I start my patients off with an antiemetic for the first 30 to 45 days-ish. And if they're doing great, I'll start taking them off of that because no one wants to be on that many pills for 2 years. But I just don't like to have that cycle set that they're going to be nauseated. Others of my colleagues will just have a script ready for their patient and if at the first signs, they don't even have to ask, they just have the script that they can fill. They can do it that way as well. All of those are fine. As long as you have a plan and your patient's comfortable with it so that they can rescue this symptom quickly, because as we all know, nausea is just so disturbing. We don't want them to come off when we can mitigate this really effectively. And so, you can see on the slide you want to rule out other causes. Now, this is usually the part when I'm going to say, but make sure they don't have gastritis or other sorts of things. This is an early thing, like an early symptom, so somebody that's been on a PARP for a good amount of time and then all of a sudden they come in with nausea and vomiting, there you really do want to be looking for another cause because it's probably not the PARP at this point so I'd be worried about something else going on. Dose interruptions are very helpful here as well. Few days off, let them feel better. You can start at the same dose and if you have recurrent problems, you certainly have dose reduction options.

Hematologic toxicities. So, monitoring of these vary based on the drug. So, for niraparib, when you start the medication, it has to be weekly CBCs at least, and you want to do monthly salts just to look at the CMP and make sure you're not having anything peak with the creatinine or anything else. But CBCs you need weekly to make sure that the platelets aren't dropping. If you see those platelets start to drop, that patient needs to be held and then you follow them a little more closely to make sure they're not still dropping and coming back up. So, if you have someone dropping below 100, you hold. So, this is one where, like, someone has to look at these labs. They cannot sit over the weekend if someone's platelets could be 4. Now if they get through that first 4 weeks fine and they're platelets are stone cold fine, then you can back off and just do every 21- to 28-day labs with careful counseling that if they start to notice petechiae or anything, they're going to call you. If someone's platelets drop and you have to hold and then restart, you restart the weekly labs until they're stable for at least four weeks in a row. I usually do 8 to be honest because I'm just nervous, but at least four weeks in a row. And then you can back off to monthly labs, you know, for the remainder of the time on niraparib. For olaparib, you start with just every cycle labs every 21 or 28 days, and once they're fine for like 6-month mark, I'll usually just check them every 3 months from there. And we keep an eye on them with just the ability to call us if they're feeling fatigued or anything else. And we'll do a set of labs unscheduled at that point. Just really because the anemia here is the main side effect that it doesn't appear to be cumulative. So, once you have someone stable for many months, you really don't have to go as crazy with the labs with olaparib.

With anemia, I do think it's important to rule out other causes at the beginning. Depending on the part of the country you live and your patient population. Here in Oklahoma, we have a lot of nutritional deficiencies, like almost everyone is vitamin D deficient, iron deficient, pretty high rate of folate deficiency. So, we do a panel upfront and really just start trying to replace our patients almost prophylactically when we start PARP inhibitors and we're even trying to get it before chemo, now. We're using injectafer instead of oral iron because of compliance issues and just trying to make sure that we have patients really teed up to be successful. It doesn't eliminate the nausea, because again, olaparib causes anemia. But it can mitigate the grade, so someone that might have gotten a grade 3 because they're also iron deficient, maybe only drops to a 1 or a 2. And then you can keep them dosing. So, do consider testing for those upfront and just make sure you have your patient really teed up to be successful.

Neutropenia and thrombocytopenia – we talked about thrombocytopenia at length already for the niraparib. Anything less than 100, you need to hold. And I would say the same thing is true, really, for olaparib. It's so uncommon that you see platelets start to drop, you should hold and investigate. Neutropenia, grade 1 doesn't require intervention. Grade 2, neutropenia requires interruption and consideration of what's going on, because that's not common. And if you're confident that the patient's bone marrow is doing ok, restarting at the same dose versus a dose modification really depends on the rapidity of the drop. Is it repetitive and then sometimes I'll involve my heme colleagues to help me make those decisions. Anything with significant heme toxicity, or recurrent heme toxicity, warrants a referral to our hematology colleagues for evaluation.

And that's really because we're worried about AML/MDS, and also patients who are at risk for it in the future and trying not to set them up for development of this. So, we do have to make patients aware of the risk. So again, patients with prolonged hematologic toxicity should be referred for heme consultation plus/minus a bone marrow biopsy. And at this point, other than just your gut, you don't have screening tests to identify patients at high risk, so we just have to kind of pay attention and have our antennas up as we watch the CBCs and diffs on our patients as they come in.

So, when we think about first-line therapy decisions for patients, we have to just consider multiple factors, like what are the clinical characteristics of the disease, did it respond to platinum, did it not. What are the molecular characteristics, does she have BRCA? Is that someone that 100% needs to be offered a PARP? Has she had HRD testing, what does that show? And then what's the best medication to really try and help our patients have a higher likelihood of cure and/or the longest progression-free survival possible? The drug properties, the safety and efficacy, patient preferences regarding administration, drug interactions, other medications they're on, all

these things have to be taken into consideration just along with the patient herself as kind of the center of how we make these decisions.

Chapter 3: Practical Application Case Illustrations

So, I wanted to take you through a couple of examples of how you think about things.

So, this is patient A. She has BRCA 1 mutation carrier. She has high-grade serous ovarian cancer, she's stage 3. She had primary surgery that was really good, got everything out. She's a small person, 78 kg, and she had some nausea with chemo but otherwise did fine. She had 6 cycles of chemo as per standard of care. She has no evidence of disease. CA-125 is normal. Baseline platelets are 240. And so, she's going to get a PARP inhibitor. She's already asking about it because her medical literacy is quite high. And you talked to her about it, and she does not think she can do twice daily dosing. So, she wants to do something once a day. She does not want to come in for other infusions because she wants to go back to work. So, we're deciding on, sort of, monotherapy PARP inhibitor options.

And I'm just putting this up here to remind you of the BRCA. In SOLO, it's the whole study. But in PAOLA and PRIMA, the BRCA cohorts which were 30% of each of the studies, so, substantial cohort. And what the magnitude of benefit is for progression-free survival, we're talking about 60 to 70% reductions in the hazard of progression or death with use of a PARP. Bevacizumab alone is not an equitable option unless you're giving it with a PARP. But it's not an option instead of a PARP.

So, with once daily dosing, you're leaning towards niraparib and you're thinking about dosing and you're just remembering that we're using individualized starting dose here, and again, that's ISD. FSD is the fixed starting dose, 300, and you're wondering well, gosh, is that as effective? If I have to use individualized starting dose, am I just short-changing her? And this analysis was done, it is very exploratory, but it has been done in a couple of different ways. And the hazard ratio point estimates do look a little different. It actually looks a little better for individualized starting dose, probably because they could stay on therapy for longer. But the confidence intervals really overlap. So, I think the take-home is that we certainly aren't losing efficacy by using individualized starting dose versus fixed starting dose. So, the safer dosing is not less effective, and you should feel confident in using the right dose based on weights and plates.

The safety profile, again, this is just a summary slide just to remind you of PRIMA, which is on the purple, and then SOLO is in red. Monotherapy is what she wants, she is now on combination therapy. These are not head-to-head studies. This is warning/warning and cross-trial comparison. But just so you can see common dose interruptions, dose reductions, but very few discontinuations due to adverse events. And with individualized starting doses, fewer interruptions and dose reductions still.

Again, this is just more on PRIMA, which is what you're leaning towards with your niraparib for this particular patient. With individualized starting dose, which is kind of on the middle of this slide, you can see the rate of thrombocytopenia grade 3 or higher is only 19%. So, it's still 19%. You still have to do the weekly labs, you still have to watch for it, but it's not 50%, which is what it was. This is just for BRCA with fixed starting dose. Anemia is about the same at 30 percent, 13% neutropenia. So, far safer but we still have to monitor.

As I mentioned early on, a lot of these studies have quality-of-life and patient-reported outcome components, which have been reported. I'm showing them to you here just in the BRCA population. For PRIMA this is the FOSI in the EQ-5D-5L with no detriment to quality-of-life measures in niraparib versus placebo.

And then just to be fair and balanced, this is SOLO-1 and PAOLA where they used different measures admittedly. But again, no statistical signal that there's any difference in these quality-of-life measures with use of PARP versus placebo.

For patient case study A, then, when you're thinking about her maintenance, and I kind of already gave this away, you would never use active surveillance unless the patient wanted that. But that would not be what you would suggest. You would not suggest VEGF inhibitor monotherapy. That is not equivalent. You could use VEGF inhibitor, like the bev plus a PARP, but she doesn't want to come in. So, your option really for her is, D: PARP inhibitor monotherapy and you can use olaparib or niraparib. And based on her preferences for monotherapy dosing once a day, that would be the niraparib on-label.

OK, let's do a second one. This is patient B. She's BRCA wildtype HRD. So, she's homologous recombination deficient, but BRCA wildtype. She had stage 3c disease, very extensive. She's 64 kg. Another young patient. So, she got neoadjuvant chemo with 3 cycles of paclitaxel and CARBO, an interval cytoreduction that unfortunately did not get it all out. She has residual disease. And then got six more cycles of chemotherapy because her provider thought she was very high risk. So, on final imaging after 9 cycles of chemo, she has responded but not as much as you want. She's a partial response. Her CA-125 has come down but is still abnormal. Baseline platelet count's 185,000. And remember, her baseline weight is 64 kg. She's done with chemo. She's had 9 cycles. She does not want any more chemo. And again, she's sort of done with us and doesn't want to come in for a lot of more procedures.

SOLO-1 is not here because it was all BRCA. This is BRCA wildtype HRD. So, what I'm showing you here is the PRIMA HRD BRCA wildtype subgroup. This is not an analytic part of the study, it's a subgroup. And so, in PAOLA BRCA wildtype HRD. These are

subgroup analysis. But they're very consistent. Hazard ratio of 0.5 and 0.43 of PARP versus no PARP. So, it does look like the benefit of PARP in this particular population, while not analytic, is pretty significant, and PAOLA really tells us again that bevacizumab alone isn't an appropriate selection in this particular patient population. And on the bottom, an icon, I'm just showing you the bevacizumab data, but really this isn't an ideal option, you know, for this patient for her molecular subtype.

This is the safety profile for niraparib versus olaparib/bevacizumab. Those are her 2 on-label options in all-comers. So, this is the patient I was showing you before just in BRCA, so this is all-comers just to show you the comparison. We've already kind of gone through the differences in interruptions, reductions, and discontinuations between PRIMA and PAOLA, but just to show it to you again.

And this is just some more granular grade 3 or higher adverse events, if you're looking at niraparib in the BRCA wildtype individualized starting dose. Remember, she's less than 77 kilograms, so she would be ISD. Her rate of thrombocytopenia grade 3 or higher could be as high as 24%, anemia is 18%, neutropenia is 16%, as compared to 2% thrombocytopenia, 17% anemia, and 6% neutropenia with the PAOLA regimen. So, the hematologic toxicities – and these are all subgroups, so there may be some influence there, but just ballparking. They are higher even with individualized starting dose. So, you have to keep that in mind to keep an eye on her.

Again, just quality-of-life here in a different population. This is specifically in the BRCA wildtype HRD population.

The quality-of-life again, showing no detriment for niraparib and similarly in PAOLA. And then I'm showing you just the bevacizumab data. We really haven't in the maintenance setting, fortunately, knock-on-wood, done anything that impairs quality-of-life, to date.

For this patient. So, she's BRCA wildtype HRD, but had a partial response. She's very high risk for recurring if you do nothing. But she may elect that. She may just feel like, I'm done, and I want you to leave me alone until I don't feel good. Some patients choose that, and that's OK. That's shared decision-making. But I wouldn't put active surveillance forward as like an equivalent option. But if the patient opts for that, of course, we honor that and take care of them.

Bevacizumab monotherapy is an option for her, though, but based on the evidence, isn't an equivalent option to a PARP inhibitor-containing therapy. So, option C and D for her are the kind of on-label options. She could get bev/olaparib, or she could get niraparib with her molecular subtype. And those would all be on-label, as would bevacizumab, but I just don't think it's an equivalent sort of option. So, that's what I would be discussing with her, either her niraparib or olaparib/bevacizumab.

And then patient C is a little older, she's 63. She's 82 kg. She has 3c disease. Had a primary surgery that was unfortunately not terrible, but they just couldn't get everything out. So, she has residual disease, not bulky, but residual disease, which we don't like. Tumor is sent off and she's homologous recombination deficiency test negative. She gets 6 cycles of chemo, still has a partial response, but she feels good, feels so much better. CA-125 is normal, platelets are 170,000. She still works. Working actually is her key to insurance. She's very worried about not being able to work. She brings a lot of ideas in for what she could come on for maintenance therapy but is interested in maintenance. She's not interested in just doing nothing, so there's a balance. But HRD test–negative is hard.

So, this is the data. PRIMA, of course, shows a moderate benefit. Hazard ratio is 0.68, so about 32% reduction in the hazard of progression in this population with niraparib versus nothing. PAOLA PARP/bev versus bev did not show any difference. So, can you say bev and PARP are equivalent? No, but it's probably not inferior. I think I'll say that without doubt. But these are probably her options, PARP versus bevacizumab monotherapy.

Safety in this group isn't any different than any of the other populations. So I'll just say that if you're going to use – compare PARP versus bevacizumab, there are significant differences in adverse events with hematologic adverse events being predominant for niraparib and then the GI, of course. And then for bevacizumab, it's hypertension. So, they're very different side effect profiles, which for her may be the way she picks, one or the other. This is really an area of clinical equipoise.

Just like everything else I've shown you, there's no difference in quality-of-life between the niraparib and placebo in the homologous recombination deficiency test-negative population, either by the FOCI, either the time to symptom worsening or the health utility index, neither of them were significantly different.

And then there was additional work done from PRIMA in this particular patient population, none of which EORTC QLQ-C30, and the rest, none of them showed any difference. Very consistent with everything else I'm showing you.

So, patient C is, a challenge. Not that we don't love her. But, she's in trouble. She has a partial response, her tumor is homologous recombination deficiency test-negative. We are very worried about it coming back, and we do not know what the best maintenance is. She doesn't want active surveillance, but she might have – she could get VEGF inhibitor monotherapy since bevacizumab. That's on-label and we have data. She cannot get VEGF inhibitor/bev plus PARP that is off-label for HRD test–negative, so that is not an option for her, nor does it make sense. She can get PARP inhibitor monotherapy with niraparib. We don't know what's better, bevacizumab or niraparib. This has not been compared. So, those would be the two options that I would be offering to her, and really it comes down, you

know, to shared decision-making.

So, in conclusion, I would say PARP inhibitor–related adverse events are generally low-grade and manageable with the exceptions that I talked about quite a bit, mainly hematologic. Around niraparib with thrombocytopenia, and with all the PARP inhibitors around anemia. So, we do have to watch for those. But really, prompt setting expectations is key, so patients are aware and have mitigation strategies. Prompt identification and management, especially around nonhematologic issues, will help with patient compliance and help them feel better. And then really remembering you can dose-interrupt over the course of therapy for a few days, and before you dose reduce – and that may really help the patient and keep them on the starting dose for as long as possible.

Shared decision-making is really important here and again, I've emphasized that through my talk, because there's just a lot of places where there's choices to be made and there's not a clear best answer. And so, the strategy is really where you can engage with your patient and help them play a role in selecting the therapy based on patient education. Then team-based collaboration and good communication will help them feel like they had control over what their maintenance option was and then their experience on that maintenance selection as well. So, really aligning the treatment planning decisions with very patient centric concerns. What are their goals, preferences? What's their understanding, what's their medical literacy, and how do you address them where they are so they can understand completely what you're talking about are really important so they can have the best outcomes possible and feel like they were part of the process.

There's a really nice guide to facilitate shared decision-making that's available to you to download, just to show you kind of what it looks like, but I would encourage you to download it. But it's actually a nice just brief what to look through with your team in your clinics just to make sure that you're doing some of the things here to facilitate shared decision-making with your patient. It's a nice kind of conversation starter for process improvement with your teams, and I would encourage you to take a look at it and we're of course submitting it to all of our participants as a reinforcement tool moving forward.

And with that, I know this was a lot of information and I talked very quickly, but I hope it was interpretable and thank you so much for watching and joining us and participating in this important educational video. Have a great day.

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