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Recent Advances in ADT: New Insights in Advanced Prostate Cancer Treatment

Announcer:
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Dr. McKay:
This is CME on ReachMD. I'm Dr. Rana McKay, and joining me today is Dr. Tanya Dorff from City of Hope. Today, we're going to discuss the recent updates in ADT and the implications to clinical practice. Androgen deprivation therapy has been the backbone of systemic treatment for patients with prostate cancer really across the continuum, from localized disease to biochemically recurrent disease and metastatic disease. And there's lots of different formulations of androgen deprivation therapy, from antagonists, agonists.

Tanya, could you give us an overview of the different agents that are out there and how you view them in clinical practice?

Dr. Dorff:
Certainly. Traditionally, we've used LHRH agonists, which we know drive testosterone up before it goes down, and we've also used these longer-lasting depot formulations. And so many of our pivotal phase 3 registrational trials were really built around those agents. However, more recently, the injectable antagonist degarelix and now the oral antagonist relugolix have become FDA-approved agents for androgen deprivation.

And so there've been some questions about whether all of our foundational trials would need to be repeated or is the fact that they are very good at suppressing testosterone enough of an endpoint to allow them to be incorporated in all the different places we use ADT for prostate cancer.

And I certainly fall into the camp that the goal of the testosterone-lowering agent is to lower testosterone. So whether it's an agonist or an antagonist, if it does that effectively, it should be something that we can use. But that's sort of where some of the discussion has been, and these agents are now incorporated into NCCN Guidelines for use as the ADT backbone, but some questions remain. One question being the duration of the testosterone suppression. So we know with the oral antagonist relugolix, that testosterone recovery is much more rapid.

And so where, traditionally, we gave ADT for a certain amount of time, we knew there was this lag before testosterone recovery that made that time period actually a little bit longer than what we were prescribing. And so that's one challenge with replacing the LHRH agonist depot injections with these more rapidly reversing agents.

What are your thoughts on that, Rana? How are you incorporating these in those kind of fixed-duration approaches?

Dr. McKay:
Quite honestly, I think the sweet spot for utilization of the antagonist is actually when you intend to use short-course ADT, where the risk of actually death from prostate cancer is low and the risk of death from alternate causes or cardiovascular disease or other things like that may even be higher. So I think the sweet spot is actually when the intention is to use short-course therapy, whether for 6 months in

the intermediate setting, intermediate-risk setting with radiation, or in the salvage setting or even if intention to give 2 years of therapy.

But I agree with you that there is a lag with T recovery with the agonist compared to the antagonist, which can potentially have a theoretical impact on efficacy that has not exactly been quantified. So I think it's a balancing act between efficacy and safety.

And maybe, Tanya, you can give us a little bit of overview about the safety. What are the implications between the agonists and the antagonists?

Dr. Dorff:
Well, the HERO trial really provided the clearest data. That was a trial comparing relugolix to the traditional LHRH agonist depot leuprolide, and that did show a better cardiovascular safety profile. So fewer major cardiovascular events, particularly in patients who had preexisting cardiovascular disease or cardiovascular risk.

So theoretically, these antagonists may be safer in that setting. However, you do have to check for drug-drug interactions when you're using the oral agent, especially some cardiac anticoagulant-type medications. You have to be careful to make sure that those can be administered concurrently. There are real-world data that call into question whether there is a difference in cardiovascular safety.

There was a prospective trial that was designed trying to address, with really rigorous collection of data and involvement of cardiologists for the patients, which of this class of drugs had the better cardiovascular safety profile, and that trial actually closed because of such a low number of cardiovascular events. And I think that the take-home from that experience was that if we involve our patients' cardiologists or internists and really manage their cardiovascular risk factors, that that enhances the safety of androgen deprivation regardless of whether we're using an agonist or an antagonist.

Dr. McKay:
Yeah, I couldn't agree with you more about the proactive assessment of cardiovascular risk in the context of patients that are initiating ADT, identifying who needs to be referred to cardiology. There's some individuals that may even benefit from starting an aspirin or beta-blockers or statin. And so I think it's critically important to make sure that that's assessed.

On the heels of these ADT-targeting agents, testosterone-lowering agents, the other stipulation that has come out has just been around compliance with an oral agent versus with an injectable. And with an injectable, they may be – not to say easier to give. Patients come into the clinic. They get their shot, whether it's given on a 1-month, 3-month, 4-month, 6-months formulation, and then you can guarantee compliance.

Any thoughts about that from a patient perspective regarding being on an oral agent versus an injectable?

Dr. Dorff:
There were certainly a lot of concerns about compliance, and in the HERO trial, they took some extraordinary measures with the pill bottle that would beep if it hadn't been opened in 24 hours. And we don't have those safeguards in the real world when we're prescribing, but my own personal experience has been that patients are actually very able to comply. It's a once-a-day medication that they can take sort of any time of day, whichever they'll remember best consistently.

And also, reassuringly, the occasional patient I have who does miss some doses, let's say because they are traveling and they forgot to bring it with them, I have not seen a lot of testosterone breakthrough, so that makes me feel a little bit more comfortable that even if a patient is not 100% compliant, we are still able to keep the testosterone suppressed, which is the goal.

And I think once we get into doublets and we're adding another agent, that makes it even less of a concern because the patient's got to take that AR-pathway inhibitor; that's an oral agent. And so having 2 oral agents is not necessarily going to compromise their compliance in that context.

Have you had any concerns with your patients?

Dr. McKay:
Honestly, I have not. I think it's very much a choice. There are some patients that prefer the injectables; there's some patients that prefer the orals. I do have to say that with the orals, I am a little bit more stringent with my testosterone monitoring. When patients are coming in for their PSA, also checking the testosterone and make sure that levels are suppressed appropriately.

And I think you bring up the good point of now, across the spectrum, we're also utilizing the androgen receptor pathway inhibitors in the localized setting for high-risk individuals, now also in the BCR setting, certainly in the metastatic hormone-sensitive setting. So there's a lot of drugs that are out there; there's 4 that are now available for use at different contexts.

Wonderful. Well, thank you so much for joining us today with CME on ReachMD.

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