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Personalizing Long-Term mCSPC Treatment Decisions

**Dr. Turck:**
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me today to discuss key decision-making factors in the long-term management of metastatic castration-sensitive prostate cancer is Dr. Bilal Siddiqui. He's an Assistant Professor in the Department of Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Siddiqui, welcome to the program.

**Dr. Siddiqui:**
Thank you very much for having me.

**Dr. Turck:**
Well, to start us off, Dr. Siddiqui, when you are putting together a patient's care plan, how do you think about tolerability from the outset, especially given that many patients with this disease will be receiving treatment for a long time?

**Dr. Siddiqui:**
So, when we're meeting a patient for the first time with metastatic hormone-sensitive disease, exactly like you said, we expect these patients to be receiving their initial treatment for several years. And so it's important that we counsel that patient right from the beginning about the side effects that they are going to experience, because they may be experiencing them for a number of years.

And these events can become more consequential over time. Many of the effects of androgen suppression—for example, hot flashes and fatigue—can become quite intolerable to patients as they start reaching years two, three, and beyond. So we really try to counsel our patients early, right from the beginning, on what they can expect in terms of fatigue, their cognitive effects, cardiovascular risk, even skin toxicities.

And one of the things that I always counsel my patients on is just how important their baseline health and lifestyle are. I always tell my patients, the most important thing that you can do to mitigate a lot of the toxicities is physical exercise and physical activity. I have patients who are able to keep their muscle mass. But it takes work. And counseling those patients from the beginning, I think, really helps.

**Dr. Turck:**
To build off of that, I'd like to talk about one type of treatment in particular. Across the available androgen receptor targeted, or AR targeted options, what tolerability differences are most important to keep front of mind? And how do issues like fatigue, CNS effects, and cardiovascular or dermatologic considerations factor into your selection?

**Dr. Siddiqui:**
So there are four androgen receptor pathway inhibitors that we use in this setting: apalutamide, enzalutamide, darolutamide, and abiraterone with prednisone. And these all have their own shared, but also somewhat distinct, tolerability profiles that factor into our decision-making.

So, for example, going to that last one you mentioned—the skin toxicity issues. These are most commonly observed with apalutamide. And we counsel our patients on what to expect with these. And, certainly, for patients with certain medical histories and predispositions—for example, a patient who has a history of psoriasis—it may be a drug that we wish to avoid in that patient. Although, for the vast majority, it tends to be quite tolerable. And there are resources for managing those skin toxicities and on how to counsel our patients.

Fatigue, cardiovascular, and CNS issues oftentimes can be quite significant. So, for example, with a drug like enzalutamide that crosses

the blood-brain barrier, that's known to have CNS and memory issues. We discuss that very, very carefully with our patients. I can think of one case I saw very recently who comes to mind, of a patient who was a lawyer. And for him, paramount was maintaining his mental sharpness as much as possible. And that helped shape our decision in which of those drugs to use.

In terms of cardiovascular considerations, this is a very strong issue in particular with abiraterone. As it's given with prednisone, we worry about that in patients with a history of heart failure or a history of arrhythmias. We will sometimes avoid abiraterone in those patients.

So all of these issues factor into which drug we choose for our patients.

**Dr. Turck:**
We know that many of these patients have often been managed primarily in urology and often have multiple comorbidities. So, with that being said, how do you assess and manage polypharmacy and drug-drug interactions when adding an AR targeted agent to their medication list?

**Dr. Siddiqui:**
That's exactly right. So these are older patients. Many of them will be on antihypertensives and on anticoagulants. It's very common for them to be experiencing polypharmacy. Where possible, we find it to be extremely helpful to collaborate with primary care physicians and to collaborate with pharmacists to really help manage those.

So, for example, when we're starting a patient on darolutamide, as just one example, we will have drug interactions with statins. And so having a collaborative relationship with a pharmacist or with their primary care physician lets us make sure that they are on a safe lipid-lowering agent that they can remain on while they're on these therapies.

But collaboration really is key.

**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. Bilal Siddiqui about practical decision-making in the long-term management of metastatic castration-sensitive prostate cancer.

So, Dr. Siddiqui, now that we've talked about tolerability and interactions, let's shift gears and discuss the financial side of things. What do we know about the cost effectiveness of AR targeted therapies, and is there a disconnect at all between their modeled value and real-world affordability?

**Dr. Siddiqui:**
This is a really important point, because financial toxicity is real, and it can directly affect patient adherence and persistence. It's important to note that when a lot of these cost-effective analyses are being run and performed, these reflect population-level value. And so they may not fully reflect the burden or the value that's being delivered to the individual patient.

The out-of-pocket costs, the insurance coverage, and the patient assistance programs vary significantly across these drugs. It is something that we inevitably take into account for every patient. In some cases, we will choose the drug that is generic. For example, abiraterone is available in a generic formulation. And that often guides our decision-making as well.

So the short answer to the question is that yes, there may be a disconnect between their modeled value and their real-world affordability. And we take a pragmatic approach to what we can get to this patient, because we know that these drugs ultimately improve outcomes for our patients, and we need to do what we can in order to get them access to these drugs.

**Dr. Turck:**
Speaking of that, if we focus on access and formulary constraints for just a moment, how do those shape your treatment conversations with patients?

**Dr. Siddiqui:**
So, unfortunately, it is part of the conversation that we have with essentially all of our patients as we're discussing. And when we talk about the shared decision-making that is a part of this, increasingly, we have to talk about cost as well as efficacy and safety.

I would say, probably, the majority of my patients, when I introduce these drugs and we talk about them, one of the first questions that they ask is, what is this going to cost? And is this going to be covered by insurance? So having these conversations early is really important to ensure that they're able to receive their medications and avoid interruptions down the road.

And we discuss this early—that there may be some formulary restrictions, for example. Your insurance company may prefer this drug versus that drug. And we try to take that into account because, ultimately, as I said, we want to be able to ensure these patients get

access to second-generation anti-androgens, because we know there is a clear clinical benefit to patients receiving them.

**Dr. Turck:**
Before we go, Dr. Siddiqui, I'd love it if you would walk us through a sample patient case. Let's imagine a 68-year-old man with newly diagnosed metastatic castration-sensitive prostate cancer. He has controlled hypertension, mild cognitive concerns, and multiple chronic medications.

How would you balance disease characteristics, tolerability, drug-drug interactions, lifestyle, and cost to ultimately choose the best treatment for him?

**Dr. Siddiqui:**
This is a very, very common scenario. So the conversation that I have with my patient as they're coming in with newly diagnosed metastatic castration-sensitive disease is, of course, the backbone of treatment is androgen deprivation therapy. We are decreasing the body's levels of testosterone and that starves the cancer, but also, on its own, comes with a number of potential side effects. These include hot flashes, night sweats, fatigue, memory issues, fat gain, muscle loss, and bone thinning. And so the way that I counsel my patients is, we start with our initial androgen deprivation. We see how they tolerate it. And that helps guide how we're going to do the next step of intensification, and how we're going to select the appropriate drug for these patients.

So all of the ARPIs, will, to some degree, affect blood pressure—they will cause hypertension. I tend to be a little bit cautious with using abiraterone in patients with hypertension, but it's not a strict contraindication. Similarly with the cognitive issues, there is some evidence to suggest that perhaps darolutamide may be a preferred option here, as it does not cross the blood-brain barrier in contrast to enzalutamide or apalutamide.

And then, in terms of the other medications that the patients are on, we would make our decision, our choice, based on which specific drugs those are. So, for example, if he is on a particular statin, and we are choosing darolutamide or one of the other amides, we may need to switch that. And we'd be working with the patient's PCP and our pharmacists to do that. We'd also take a look at if there are any formulary preferred options for that patient, and what the relative costs are going to be.

There's also a consideration given to pill burden. I talk to my patients. Four tablets of abiraterone plus prednisone, four tablets of enzalutamide, or two tablets of darolutamide in the morning and two tablets in the evening can sometimes be burdensome for patients. The standard dosing of apalutamide is typically four tablets, but there is a single tablet formulation that is attractive to certain patients. So that is sometimes a factor that that plays in as well.

And then, ultimately, we try to be very patient centered and flexible with it. I tell my patients, whichever drug we choose, these are the potential side effects. But I'll see you in very short course. I'll see you a few weeks after you start it. And if you start to experience intolerable side effects, just stop the drug and let us know. We have alternatives we can switch you to. There's no reason that you need to suffer. So we're in an era where we have multiple, very good options to choose from, and that really allows us to tailor our treatments to our patients.

**Dr. Turck:**
Such insightful perspectives for us to consider as we wrap up today's discussion. And I want to thank my guest, Dr. Bilal Siddiqui, for joining me to discuss how safety, drug interactions, and cost can shape long-term treatment decisions in metastatic castration-sensitive prostate cancer. Dr. Siddiqui, it was great having you on the program.

**Dr. Siddiqui:**
Thanks so much. It was great to be here.

**Dr. Turck:**
You've been listening to *Project Oncology* on ReachMD. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.