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Applying Clinical Trial Data in mCSPC Care

Dr. Jackson:

This is *Project Oncology* on ReachMD, and I'm Dr. Steve Jackson. Joining me to discuss strategies for applying trial data in metastatic castration-sensitive prostate cancer care are Drs. Jahan Aghalar and Ulka Viashampayan. Dr. Aghalar is an Adjunct Assistant Professor at NYU Grossman Long Island School of Medicine. Welcome to the program, Dr. Aghalar.

Dr. Aghalar:

Thank you very much.

Dr. Jackson:

And Dr. Ulka Viashampayan is a Professor of Internal Medicine at the University of Michigan Medical School in Ann Arbor. She's also the Director of the Phase One Program and co-founder of the Translational and Clinical Research Program at the Rogel Cancer Center. Dr. Viashampayan, it's great to have you with us as well.

Viashampayan:

Thank you, Steve.

Dr. Jackson:

Well, I'd like to start with you, Dr. Aghalar. When you step back and look at the data we have for metastatic castration-sensitive prostate cancer, or mCSPC for short, where do you think clinicians tend to struggle most when trying to make sense of it all?

Dr. Aghalar:

We're a victim, in a good way, of having better data that has been generated over the last 10 years. Back when I was a fellow, I always say it used to be a very straightforward decision. You have metastatic prostate cancer, you go on hormone therapy. And over the last 10 years-plus, we've seen broadening therapeutic options for this clinical state with various mechanisms of action—with taxane therapies and androgen receptor pathway inhibitors using different mechanisms of action.

And, in addition to that, there's also been newer treatment strategies. We don't necessarily have to rely on systemic therapy alone. We can also consider using metastasis-directed therapy for oligometastatic disease—even the concept of irradiating the primary prostate tumor with metastatic prostate cancers now has become more of an accepted standard of care, specifically for those patients with low volume disease.

So the challenge that we face now is, how do we use the data that we have through numerous randomized trials in real world patients? In addition to that, the clinical trial participants that allow us to generate such data are not necessarily reflective of the actual patient that's sitting in front of us in the examination room, due to age and comorbidities and, perhaps, lower performance statuses in the real world.

Of course, all these trials have their own limitations with their design. In addition to that, how do you choose what's the best particular option, as head-to-head comparisons are lacking in helping us decide what is the best treatment option within this clinical state? So synthesizing the data that's available to us with what we're actually facing in the clinic is probably a challenge that all of us face is when we see these patients in the clinic.

Dr. Jackson:

And Dr. Viashampayan, looking across key studies, how do differences in trial design and eligibility criteria shape the way you interpret outcomes? And what should we be most mindful of when reviewing these data?

Dr. Viashampayan:

I think there have been multiple clinical trials in metastatic castration-sensitive prostate cancer, and the results are mighty intriguing. But the thrust of it is that all of them have shown that either doublet or triplet therapy improves overall survival. So just androgen deprivation therapy can no longer be considered standard.

It is important to at least consider every patient with metastatic disease as they present to you for some kind of intensification of therapy. The challenges, of course, are all these studies have looked at similar endpoints. The majority of them have had androgen deprivation or ADT alone as the control arm, and then have added an oral agent: either abiraterone, enzalutamide, apalutamide, or darolutamide—any of these. And they have each shown benefit over androgen deprivation therapy. So, clearly, we do not know as of now whether one is better than the other or whether we should specifically choose one over another for a specific type of patient with metastatic prostate cancer.

Now the other question, of course, is can we consider and when do we consider chemotherapy? Chemotherapy with docetaxel was there before some of these oral agent studies were available, and the addition of docetaxel for six cycles maximum did show a survival benefit. The majority of the patients in that study had bulky disease, and chemotherapy did show survival benefit. The question, however, is if we do the doublet therapy with ADT with an oral agent, does the addition of chemotherapy add anything on top of the doublet therapy?

And that is something we do not have—the more contemporary piece. Three types of studies have shown that addition of an oral agent to ADT plus chemotherapy does show both progression-free survival and overall survival benefit.

Dr. Jackson:

Coming back to you, Dr. Aghalar, let's extend this discussion even more into endpoints. How do you assess their relevance for treatment decisions in practice?

Dr. Aghalar:

Right. So, of course, we always do hold overall survival and life expectancy as a primary goal, of course. But it's not the necessarily the be all end all. So, when evaluating these studies, the biggest question a lot of us ask ourselves is, is there an overall survival signal or not? And sometimes that's not such a straightforward question to answer, depending on when the trial was conducted and under which context.

So, for example, the latest trial that has shown benefit in terms of using doublet therapy in metastatic castrate-sensitive prostate cancer is the ARANOTE study, combining ADT with darolutamide in combination in comparison to ADT plus placebo. And this was a study that did show, PFS benefit. However, to date, there's no overall survival benefit. And many question whether or not this is due to the fact that the data is not yet mature, or whether or not there's truly an overall survival benefit in using darolutamide in combination with ADT in the doublet setting. Or, perhaps, this could be reflective of the fact that this was a study that was done a little bit later on compared to the older trials that showed a benefit in adding on an ARPI to ADT, and these patients, more likely than not, upon a progression, did avail themselves to more novel therapies that we know also further improve overall survival. So, therefore, is overall survival a fair endpoint to judge whether or not such a combination would be appropriate for the patient?

Dr. Jackson:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Doctors Jahan Aghalar and Ulka Viashampayan about interpreting mCSPC trial data and integrating it into routine care.

So, Dr. Viashampayan, another element of this conversation is making cross trial comparisons, which can be tempting without many head-to-head studies. But, from your perspective, where do you see clinicians getting into trouble doing this, and what are some strategies to avoid common pitfalls?

Dr. Viashampayan:

I think cross-trial comparisons are unavoidable, especially when you don't have head-to-head comparison data for, specifically, the oral agents in metastatic castration-sensitive prostate cancer. I think the best cross-trial comparison, which actually can be clinically helpful, would be from a toxicity standpoint, as well as drug interactions—because those are different for each of these agents—or if there is one that is better tolerated in a specific situation. For instance, cardiac disease or older patients do not do so well on abiraterone and prednisone. So that may be something to consider when you are trying to make a choice of which agent to use in the patient.

I think the things that you do need to look at when doing cross-trial comparisons is the proportion of patients who are elderly who have bulky disease. The other things that we don't typically get information on is what other therapies they had available after progression on the control arm, as well as, what kind of discussion they had about the toxicity monitoring and patient quality of life. Patient-reported

outcomes can also be an important thing to look at, especially if there is a symptomatic patient population. But again, those are the things I would caution against, because you don't sometimes know the proportion of patients with the, for instance, *HRR* mutations, or the proportion of patients with symptomatic disease when they enrolled on the study.

Dr. Jackson:

Before we come to the end of our program, I'd like to ask each of you one more question. Starting with you, Dr. Aghalar, we know that some patients seen in routine practice may have different characteristics from those enrolled in clinical trials. So, with that being said, how do factors like age, comorbidities, or disease presentation influence how you apply trial evidence?

Dr. Aghalar:

I think that definitely has a large influence. I wouldn't say necessarily chronological age has an impact, but more physiologic age, as has been pointed out, depending on what kind of comorbidities the patient has, whether or not they have any fall risks, and whether or not they are on any other medications that can potentially have serious drug interactions with some of the ARPIs. That does have an influence in terms of making treatment decisions. Disease presentation also does have a tremendous impact in terms of deciding whether or not we may think about using chemotherapy, as has been pointed out. Trials that have shown benefit in using chemotherapy particularly have been seen in those patients that have bulky disease or perhaps even visceral organ involvement.

And then I think, nowadays, it's also very important to understand the genomic signatures of these diseases that we're facing. So with the next-generation sequencing and germline profile, we are now recognizing specific gene signatures that we can predict will have more aggressive biology, such as *TP53*, *RB1*, and *PTEN* loss. We know that those patients typically will not do well prognostically and perhaps will portend earlier castrate resistance and whether or not usage of chemotherapy in that context would be more beneficial. Of course, we need more data to support such a move, but that's another consideration to have when you're dealing with more aggressive biology.

And then lastly, I think also, with the usage of gene signature profiling, hopefully we'll have more targeted therapies being developed under and currently under investigation in clinical trials that will help us decide whether or not targeted therapies within the context of mCSPC would be appropriate.

Dr. Jackson:

And before we go, Dr. Viashampayan, I'd like you to give us the big picture here. How can clinicians best use MCSPC data to create effective individualized treatment plans for their patients?

Dr. Viashampayan:

I think all of us, when we are assessing a metastatic prostate cancer patient, are thinking about both the patient's characteristics as well as the disease characteristics. And both are going to factor importantly into your treatment decisions and the life expectancy of the patient. I mean, there are a number of our patients with metastatic disease who are dying off other comorbid conditions. So it is important to take that into account when you're making a treatment decision.

The sites of disease and the overall patient status, both from a performance status—symptomatic—as well as disease bulk, each of these will factor in. I would say as you factor those in and you make the decision for the patient, maintaining the patient on that therapy and monitoring them closely are important things that we should be paying attention to.

In addition, the duration of the therapy. Unfortunately, none of our clinical trials tell us exactly, can we stop the therapy after a certain duration? Especially if our patients are having significant adverse events, or even if they're not, in the interest of their long-term health, are we able to discontinue safely therapy?

So that has made metastatic castration-sensitive prostate cancer a wide spectrum of disease ranging from a year or so median survival to all the way for decades. So that is something that you have to take into consideration and re-stratify the patients.

Dr. Jackson:

Those are great comments for us to think on as we come to the end of today's program. And I wanna thank my guests, Dr. Jahan Aghalar and Ulka Viashampayan, for joining me to discuss how clinical trial evidence can translate into everyday metastatic castration-sensitive prostate cancer treatment. Dr. Aghalar, Dr. Viashampayan, thank you both for being here today.

Dr. Viashampayan:

Thank you.

Dr. Aghalar:

Thank you very much.

Dr. Jackson:

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