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Redefining First-Line Therapy in mCSPC: Applying Evidence in Practice

Dr. McDonough:
This is *Project Oncology* on ReachMD, and I'm Dr. Brian McDonough. Joining me to discuss the evolution of treatment intensification in metastatic castration-sensitive prostate cancer, or mCSPC for short, is Dr. William Oh. He's a Professor of Internal Medicine at Yale School of Medicine in New Haven, Connecticut. He's also the Director of Precision Medicine for the Yale Cancer Center and Smilow Cancer Hospital, and the Gene and David W. Wallace Medical Director of Smilow Cancer Hospital at Greenwich Hospital. Dr. Oh, it's great to have you with us.

Dr. Oh:
Thanks a lot for inviting me. I'm happy to be here.

Dr. McDonough:
So, before we dive in, Dr. Oh, let's get some context. Can you give us an overview of how the management of mCSPC evolved from androgen deprivation therapy alone to combination approaches at diagnosis?

Dr. Oh:
I'd like to remind the audience that we have targeted therapy in prostate cancer. We have had it for decades and decades—really ever since we recognized that androgen stimulates the growth of prostate cancer. And ADT, of course, was first accomplished with bilateral orchiectomy and then subsequently, with drugs like leuprolide and other LHRH agonists.

But really what we didn't really do was improve upon androgen deprivation therapy until the last decade or so, when we've learned that we can enhance outcomes, including overall survival, by adding additional drugs, whether that's chemotherapy or androgen receptor pathway inhibitors, to the ADT backbone.

And part of this, of course, is that even though ADT's very successful at inducing remission—the vast majority of patients will have a PSA and clinical response—most patients actually progress within a few years to castration resistance, which was kind of the precursor to, unfortunately, dying of prostate cancer.

Dr. McDonough:
With that in mind, I'd love to look at some key trials that have shaped the treatment landscape. To start, the CHAARTED trial demonstrated that adding six cycles of docetaxel to androgen deprivation therapy significantly improved overall survival, particularly in patients with high-volume disease.

From your perspective, how did this study impact the way we approach newly diagnosed metastatic patients?

Dr. Oh:
I've been in this field now, Dr. McDonough, for several decades. It's scary how fast time goes by. But what really we learned when I was a young doctor was that there were actually no treatments that improved overall survival in metastatic castration-resistant prostate cancer. And the first treatment that we actually found in that setting that improved overall survival was, in fact, docetaxel.

So, as oncologists, of course, the first thing we do is, once we find a treatment that improves overall survival in more advanced patients, we move it to earlier disease settings. And that's exactly what we did in the CHAARTED trial. And what the CHAARTED trial did, of course, was it took men with mCSPC and added six cycles of docetaxel to standard ADT. And it showed a significant survival benefit with giving six cycles of docetaxel.

And this was a really important milestone, because it was the first time we showed that we could improve on ADT with a combination of

two treatments.

But I think, even though this was the beginning of this journey, it wasn't, certainly, the end, and it really reminded us that early use of combination therapy or intensification of treatment was going to improve overall survival, which is, of course, our key goal.

Dr. McDonough:
Soon after CHAARTED, the LATITUDE trial showed that adding abiraterone to androgen deprivation therapy significantly improved both overall survival and radiographic progression-free survival. Subsequent androgen receptor pathway inhibitor trials later reinforced this benefit across subgroups. So what did these consistent survival signals tell us about targeting the androgen receptor pathway more completely from the start?

Dr. Oh:
Well, for a long time we thought ADT was enough to block androgen signaling, and in fact, as I mentioned earlier, it's a very effective treatment. But these patients all progressed within a couple of years, and so we realized that perhaps we weren't suppressing the androgen signaling pathway enough.

So both the LATITUDE trial, which was done internationally, as well as STAMPEDE, which was done primarily in the UK, showed that by adding abiraterone acetate—which is, basically, a lyase inhibitor that blocks the small additional amount of adrenal androgen that's made in the body—that is, by taking the testosterone level from low to ultra low, you could improve overall survival.

And in fact, the benefit was not small. It was up to a 40 percent improvement in overall survival, which is really quite dramatic. And the analogy I sometimes use is that these cancers go into remission—the easy, hormone-dependent cancers go into remission—but there's a subset of cancer cells in prostate cancer that are relatively immune to the testosterone suppression. And, actually, it's like a cactus growing in the desert. You might need to drop that last little bit of testosterone and you can put that additional cancer cell into remission. Unfortunately, we cannot cure patients with this combination, but what we saw was up to a 40 percent improvement in overall survival.

So, in fact, this was a landmark because both the LATITUDE and the STAMPEDE trial showed that most patients with mCSPC should be receiving, at least, a combination of two drugs. And, of course, because CHAARTED showed that chemotherapy was a benefit, and LATITUDE showed that ARPI treatments—or androgen receptor pathway inhibitors improved overall survival, we now had two different classes of drugs that might, in fact, improve overall survival. So the standard of care really has shifted so that doublet, what we call a doublet or double therapy—ADT plus an ARPI or an ADT plus chemotherapy—should be the standard of care.

Dr. McDonough:
For those just tuning in, you're listening to *Project* Oncology on ReachMD. And I'm Dr. Brian McDonough. I'm speaking with Dr. William Oh about how frontline therapy has evolved in metastatic castration-sensitive prostate cancer.

Now, Dr. Oh, I have one more trial I'd like to touch on, and that's ARASENS. This demonstrated that adding darolutamide to androgen deprivation therapy and docetaxel significantly reduced the risk of death compared with androgen deprivation therapy and docetaxel alone. So how has this data influenced your thinking about selecting patients for more aggressive therapy upfront?

Dr. Oh:
I think ARASENS, and also the PEACE-1 trials, both showed that, as I mentioned, doublet therapy is very good, but could triplet therapy be even better? And ARASENS showed that if you combined ADT—androgen deprivation therapy—plus an ARPI, in this case, darolutamide, plus chemotherapy—so three drugs—would you get an even more significant benefit? So ARASENS randomized patients to the triplet—darolutamide, ADT, plus docetaxel—versus the doublet of ADT plus docetaxel, and really showed something really important: that there was a continued improvement in overall survival with the triplet therapy compared to just the doublet of ADT plus chemotherapy.

Now, this suggested that the benefit of chemotherapy and of an ARPI like darolutamide were independent in terms of how they worked. And this was important, because although giving a patient three drugs may be more intensive than giving them only two, the survival benefit justified the combination of three drugs.

Now, not everyone is a candidate for chemotherapy, but we know that many men walk in with a very good performance status and can tolerate this treatment. Remember, it's only six cycles of docetaxel chemotherapy, and the addition of a drug like darolutamide on top of ADT, we've learned—since ARASENS was first published—is very well tolerated. In other words, even though you're adding another androgen pathway inhibitor, it doesn't seem to have a significant increase in the ADT-type side effects, like hormonal side effects that we see with ADT.

Dr. McDonough:

So, with all of this being said, emerging data presented at ASCO GU, ASCO, and ESMO in the past few years have provided longer-term follow-up and subgroup analyses. How are these updates refining your interpretation of durability, sequencing, and patient selection?

Dr. Oh:
Well, of course, we have more than one ARPI. We talked about abiraterone. We talked about darolutamide. There are two additional ones, enzalutamide and apalutamide. All of the randomized trials have shown benefit from these combinations, whether as doublets or triplets. So the bottom-line important factor is really that combination therapy with ADT, plus a second and/or a third agent improves overall survival.

Now, whenever we see early data from randomized trials, we are excited by it. We see it in meetings like ASCO or ESMO. But what we want to see in subsequent follow-up studies is longer-term evidence of continued benefit. Why? Because, of course, patients who go on clinical trials may not be the same as patients that we see in clinic, right? So we want to be sure that we're not losing the benefit over time. So, as you point out, long-term durability of these results is really confirming their benefit, and also, the tolerability of continuing those treatments. And that's what the longer-term follow-ups have shown.

In addition, we really start to look at subgroups as a way of understanding if there are patients who may benefit more or less from treatment. When CHAARTED was first performed, it was done in all comers, but then we realized that patients with fewer than four bone metastases did not seem to benefit as much from chemo. So I avoid chemotherapy in patients who have what we call oligometastatic disease, or fewer than four bone mets.

There are ongoing conversations in the medical literature about how these drugs should be sequenced. In particular, if you're giving chemo upfront and the patient subsequently progresses, when should you give chemo again? What are the other types of treatments that we should be giving?

And one thing we've learned over the last few years is prostate cancer is quite heterogeneous. So we want to understand, with biomarkers, better ways of identifying optimal patients for each approach.

Dr. McDonough:
Before we wrap up our discussion, Dr. Oh, let’s look at the big picture here. Given everything we’ve discussed, what do you think are the most important principles clinicians should keep in mind when applying treatment intensification strategies in everyday practice?

Dr. Oh:
So there were some real-world evidence studies that suggest that many patients are not receiving at least two treatments, if not three treatments, in the setting of mCSPC. Some of the studies suggested only about half of the men who are candidates for doublet or triplet therapy are receiving a second drug, much less a third drug.

So you can't look at it as a PSA effect. We know ADT will make PSA go down. That's not the purpose of a second drug. The purpose of a second or third drug is to keep that man alive longer, and we're looking at 30, 40 percent improvements in overall survival. That's a very significant benefit that most patients would want.

Of course, you have to individualize therapy. You have to look at the patient in front of you. Not everyone's going to be able to tolerate doublet or triplet therapy. But, on the other hand, I think it's always better to default to the side of trying to achieve that survival benefit. And if you have to, you can reduce the dose, you can adjust the dose, et cetera. But we should default on the idea that most men want to live longer with metastatic CSPC, and we should try to give them the benefit of the doubt.

But of course, in the end, it's always important to have shared decision-making. It's important to speak to the patient and his family and really understand what their goals in life are. But don't be afraid of adding a second or third drug if you understand that the survival benefit is quite profound.

Dr. McDonough:
That is a great comment for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. William Oh, for joining me to discuss recent evidence influencing first line therapeutic decisions in metastatic castration sensitive prostate cancer.

Dr. Oh, thanks so much for being here today.

Dr. Oh:
Thank you very much for the time.

Dr. McDonough:
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