Testosterone Replacement in the Treatment of Advanced Prostate Cancer - Sam Denmeade and Michael SchweizerSam Denmeade and Michael Schweizer join Charles Ryan at the 2019 Prostate Cancer Foundation Retreat (PCF 2019) to discuss testosterone replacement in advanced prostate cancer. The three discuss the impact of testosterone on prostate cancer cells, recent clinical trials involving testosterone replacement and the risks and benefits of adding this therapy to one's treatment plan for prostate cancer patients.

Biographies:

Sam Denmeade, MD, Co-Director Prostate Cancer Program, Professor of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

Michael Schweizer, MD, Physician, Assistant Professor, Seattle Cancer Care Alliance, University of Washington School of Medicine, Fred Hutchinson Cancer Research Center.

Charles J. Ryan, MD, The B.J. Kennedy Chair in Clinical Medical Oncology at the University of Minnesota and Director of the Division of Hematology, Oncology, and Transplantation.

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Charles Ryan: Hello from PCF 2019. Today, we're going to talk about testosterone replacement in the context of advanced prostate cancer. And I have two people doing the research on that issue with me now. The first is Sam Denmead, who's from Johns Hopkins where he's a Professor of Oncology and the Director of the Genito-Urinary

Oncology Program there. And then Mike Schweizer is an Assistant Professor at the University of Washington in Seattle. And so you're both doing clinical trials with testosterone as sort of the foundation of the treatment. And these are in men essentially with castration-resistant prostate cancer. So Sam, start with telling me why we would think about doing this. What's the rationale and how did you get to this point?

Sam Denmeade: In the laboratory, it's been known for a long time that if you take prostate cancer cells from patients that can grow in a dish and give testosterone, paradoxically instead of growing better, they can be growth inhibited. And there was a lot of research in that area, but nobody ever did really any clinical work. And so we decided based on a small grant that we received from a grateful patient to do a trial and we did a pilot trial and not expecting really much to happen. And to our great surprise, a number of patients had really good responses. Their tumors shrunk, their PSA tests went down. And that allowed us to kind of apply for funding and get some grants. And now we've done some larger studies to try to establish how does it work, how well does it work? What's actually going on there.

Charles Ryan: So what do you think mechanistically is actually happening in the cancer cell?

Sam Denmeade: Well the testosterone does a lot of different things to the cell. We have some evidence that it can cause breaks in the DNA that might be a mechanism. It changes the cell replication. It affects a lot of different survival pathways that are important. It's probably a combination of things that it's doing cause it does so many profound things to the cell that...

Charles Ryan: What do patients actually do? Are these patients who are getting LHRH analog shots and then taking testosterone at the same time? Or do you do discontinue their LHRH, Mike, and then have them take it? How do they do it?

Mike Schweizer: Well, the way that we've modeled it in the clinic was this idea that we tried to cycle the testosterone between extremes. The idea being that if you have a high dose of testosterone, that's going to be a therapeutic liability for cells that are adapted to survive low testosterone conditions. And then after a period of time of it being exposed to the high testosterone conditions, we switch it up and allow the testosterone to fall back to castrate again. Again, trying to stay ahead of that adaptation that can lead to cell survival. And so the way we've modeled this is bipolar androgen therapy. So we keep patients on LHRH analog therapy to clamp androgenous testosterone and then we give them monthly injections of high dose testosterone. So you get these rapid fluctuations between sort of super physiologic to near castrate levels.

Charles Ryan: So for those listening, a man who's on an LHRH therapy is likely to have a testosterone level, let's say 35 nanograms per deciliter or something like that. A normal situation for a 65-year-old would be 350, about 10 fold. So when you give super physiologic, what do the levels go up to?

Mike Schweizer: They go up to above the upper limit of the assay. So over 1500 typically speaking.

Sam Denmeade: Two to 3000 usually.

Charles Ryan: Well, that's high.

Sam Denmeade: The way that they get a shot, it goes two to 3000 and then over a week or two it starts to come down. And by the end of the cycle, we're back close to castrate again.

Charles Ryan: How are patients feeling when you're doing this?

Sam Denmeade: Initially I thought it would be an emotional wreck by going high and low over and over again. But most men don't notice that change. A lot of the guys feel really good. Some of the guys, they get a lot of their libido back. Some folks can have return of their sexual function, so most of the guys feel kind of a boost, an energy boost. Not everybody, but a lot of the guys are very happy. Sometimes they don't want to come off the therapy because they feel so good.

Charles Ryan: Any toxicity, like standard toxicity we would think of with this?

Sam Denmeade: Yeah. The one thing we've tried to avoid is... there was some prior data and then we've had some experience where, if you give a testosterone injection to men who have pain from prostate cancer, it can make the pain get worse very quickly. So we've tried very hard to avoid anybody with symptoms from pain. The main toxicity though, it's been pretty well tolerated. I would say more than we even thought. People get a little bit of swelling they feel it in their legs. They feel a little achy sometimes. A little bit of sexual side effects, they can get tenderness in their breast, maybe a little hot flashes, but they're really not very much.

Mike Schweizer: There are rare thromboembolic events associated with some of the testosterone. That's something to be cognizant of.

Charles Ryan: Do you exclude patients with a prior history of thromboembolic phenomena?

Mike Schweizer: If they're on sort of stable anticoagulation, then I think it's likely safe. In some of my studies we've excluded patients who think are at high risk for those types of events.

Charles Ryan: You've now completed the TRANSFORMER study, which is a study that included bipolar androgen therapy and enzalutamide and we're waiting for those results to be readout. And that's going to look at progression-free survival. I believe in the castration.....

Sam Denmeade: The trial was looking at men progressing after abiraterone who had castrate disease and we compared head-to-head testosterone and enzalutamide, kind of a strange design. Sort of the exact opposite treatments. We've got all the data now, we've got a manuscript prepared and we expect in the next few months to at least submit that manuscript, hopefully. We've been disseminating the information at meetings and talking about it. And we've seen some interesting things and we're excited to build on this data and kind of go forward with the next step.

Charles Ryan: So before we talk about the next two trials. People hearing these data thinking, okay enzalutamide is out there, I can get testosterone, my patients might feel better. Is this something people should be doing off of a clinical trial or where are we there?

Sam Denmeade: That's a challenging question. I get a lot of emails about this from all over the world. And my response has been, I can't say no because you can do it. I try to educate the docs about this is what we're doing, caution them that people with symptoms shouldn't get this. Kind of giving them my experience, I've even written a little blurb to send to folks about this. It's kind of what we've seen cause they get so many emails. So I haven't given it to patients off trial at Hopkins, partly because we have trials. I think we've proven it's safe. And I think we've proven there's some efficacy and some potential for re-sensitizing. I think if folks wanted to do it and they, educated themselves a bit about, what's in the literature. If they wanted to email me and talk to me about it. I think it would be a reasonable thing.

Charles Ryan: So tell us about what you're doing next. You've got a couple of combination studies, one with immunotherapy briefly. What's the rationale for combining immunotherapy and where are you?

Sam Denmeade: In the process of doing the trials, we noticed a couple men after being on testosterone and enzalutamide kind of hormonal sequencing. We had some guys end up on immunotherapy for various reasons. We had a couple of men respond very dramatically to that immunotherapy. And we thought, well maybe there's something about the testosterone. And then in the laboratory, we've been doing some

research to look at that. And what we found in the lab is that some prostate cancer cells, when you give testosterone, activate an immune response. They turn on pathways that would stimulate the immune system. So based on that we thought there's enough here that maybe we should try this in combination. And we were fortunate enough that one of the pharmaceutical companies that makes an immunotherapy, kind of agreed to go and sponsor a trial for us. And so we've opened a trial where we give testosterone for a couple of doses and then we add, in this case it's nivolumab, the immunotherapy drug. We have a couple of other ideas about how to build on that also. But so, for now, that's the trial we have at Hopkins that's ongoing. About halfway through.

Charles Ryan: And you're doing a study of testosterone with PARP inhibition.

Mike Schweizer: That's right. So as Sam mentioned earlier, one of the mechanisms that we think underlies these effects is the ability of testosterone to induce DNA damage. And so we had some preclinical models that showed that when you combine testosterone with PARP inhibitors, you can actually increase the ability for testosterone to kill cancer cells. Interestingly, testosterone also down-regulates *BRCA* and other related proteins. That's sort of the rationale for it. And I think from the clinical side, we've actually observed that in men that have mutations in homologous recombination genes, we actually see higher response rates to testosterone. And so it starts to build this rationale for maybe doing the combo trial. And we're making good headway in accruing that.

Charles Ryan: Good. Well, good luck in your trials. It's great to hear about this interesting work and different mechanistic probabilities or possibilities for how a testosterone supplementation in this setting can help patients and serve as a platform really for a combination of approaches. So thank you for taking the time to sit with us today and I enjoyed your presentations here at PCF, and we're looking forward to seeing your data.

Mike Schweizer: Thank you so much, Chuck.