Understanding First- and Second-Generation Hormone Therapy

Tomasz Beer, MD, FACP
Deputy Director, OHSU Knight Cancer Institute
Oregon Health & Science University

Celestia (Tia) S. Higano, MD
Director, Prostate Cancer Clinical Research Group
Seattle Cancer Care Alliance

Jeff Folloder:
Dr. Beer, can we discuss a little bit the landscape of hormone therapy, and what are the mechanisms that are involved, and what are some of the tools that are used in hormone therapy?

Dr. Beer:
Sure. So, hormone therapy is really the backbone of medical treatment for prostate cancer. It's been around since the 1940s in various forms, and it was born of the recognition that prostate cancer is unique. It comes from a gland, the prostate—which is highly dependent on the male hormone testosterone for its growth and function—and the cancer retains that need for testosterone in almost all patients, initially.

So, the mainstay of therapy that targets hormonal therapy are methods to reduce the male hormone testosterone. That can be achieved with a surgical approach—removal of the testicles, which make over 90 percent of testosterone in men — or with medications, and I think on the slide, the audience is seeing some of the commonly used injectable medications that lower testosterone.

There are also medications that block the testosterone or the androgen receptor, and nowadays, we're really moving more and more towards more intensive hormonal therapy as we've developed new and more potent drugs, and I suspect we'll be talking about that as the discussion wears on.

Jeff Folloder:
Probably so. That would be a safe bet. Let's differentiate between the first-generation anti-androgens and the second-generation anti-androgens. We'd like to think that medical science is always improving. So, the first generation—glutamide, biclutamide (Casodex)—I can't pronounce all these things.

Hormone therapy—you've got a lot of tools in the toolbox, and the slide here shows a host of different things. What's the difference between first- and second-generation?

Dr. Beer:
So, there are three drugs in the United States that we think about as first-generation anti-androgens. I'll pronounce them for you. It's glutamide, biclutamide and nilutamide (Nilandron). And, all three of those drugs work by attaching to the androgen receptor, which is the main gateway, if you will, for testosterone to do its work inside a cancer cell, reducing the ability of testosterone to bind and act. As it turns out, these drugs are not complete blockers of the androgen receptor.

And so, the newer generation—enzalutamide is currently approved and available on the market—are much more potent agents in terms of their availability to block that androgen receptor. You're also seeing a couple of investigational drugs—apalutamide and darolutamide—and abiraterone acetate (Zytiga) is often lumped into that group. It actually works by reducing testosterone levels even lower – perhaps 10 times lower than the injectable drugs—so it's a little bit of a different mechanism, but it produces similar results to enzalutamide.

Jeff Folloder:
I see. Are there third generations coming?

Dr. Beer:
Not that I'm aware of. I suspect there will be someone who would like their agent to be classified as a third-generation, but we're really—as clinicians, I think we're looking for major advances before we call something a next-generation drug, so I don't think there are third-generation drugs out there. Tia, do you –?

Dr. Higano:
I think there probably will be, but I'm not aware of any. The point is we have an excellent second-generation one that's been FDA approved, and we can prescribe to our patients, which is the enzalutamide—or, Xtandi is how you say the trade name.