

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Daniel J. George, MD

Bipolar Androgen Therapy in the Treatment of Prostate Cancer



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H&O What is bipolar androgen therapy (BAT)?

SD BAT consists of the administration of a high dose of androgen—also called testosterone—in an effort to control prostate cancer in men whose tumors are progressing on androgen deprivation therapy (ADT). This causes the levels of testosterone in the blood to alternate between the polar extremes of very high and very low during a treatment cycle (Figure).

H&O How can the intermittent administration of high-dose testosterone produce an antitumor effect?

SD We know that testosterone can initially stimulate the growth of prostate cancer when the cancer is still hormone-sensitive, which is why castration is used to inhibit prostate cancer growth. For many years, however, published research has described a paradox in which supraphysiologic levels of androgens also seem to inhibit prostate cancer growth—particularly in prostate cancer cells that have adapted to growing in low levels of testosterone—and cause the tumor cells to die. How can this be?

The answer may lie with the androgen receptor. Prostate cancer cells are highly dependent on or perhaps even addicted to the activity of the androgen receptor—the cells must regulate and degrade the androgen receptor if they are to proliferate. As a strategy for survival in the low-testosterone environment of ADT, prostate cancer cells adapt to produce far more androgen receptor, which allows them to capture every possible molecule of testosterone. Androgen

receptors also may mutate so that they function even the absence of testosterone. The result is that prostate cancer is highly responsive to ADT initially but over time becomes resistant and continues to grow.

In BAT, a very high dose of testosterone saturates the androgen receptors, making them more resistant to degradation by the prostate cancer cells. This degradation is required for each cell to go through its normal cycle and produce daughter cells. In other words, we are taking advantage of the cell's adaptive increase in androgen receptor, which makes it vulnerable to the shock of a high level of testosterone.

The other beneficial aspect of this approach is that when the testosterone level drops again, some of the prostate cancer cells will be resensitized to the low level. This occurs in prostate cancer cells that were able to survive the spike in testosterone by downregulating their androgen receptor.

We want to be able to target all the prostate cancer cells—the ones with very high levels of androgen receptor, which will be sensitive to high levels of testosterone, and the ones with very low levels of androgen receptor, which will be sensitive to the rapid return of low levels of testosterone.

H&O What treatment regimen is used?

SD We use ADT throughout treatment to suppress endogenous testosterone production. We then inject the patient with a US Food and Drug Administration (FDA)–approved dose of generic testosterone that is somewhat high—usually 400 mg—and results in a very high level

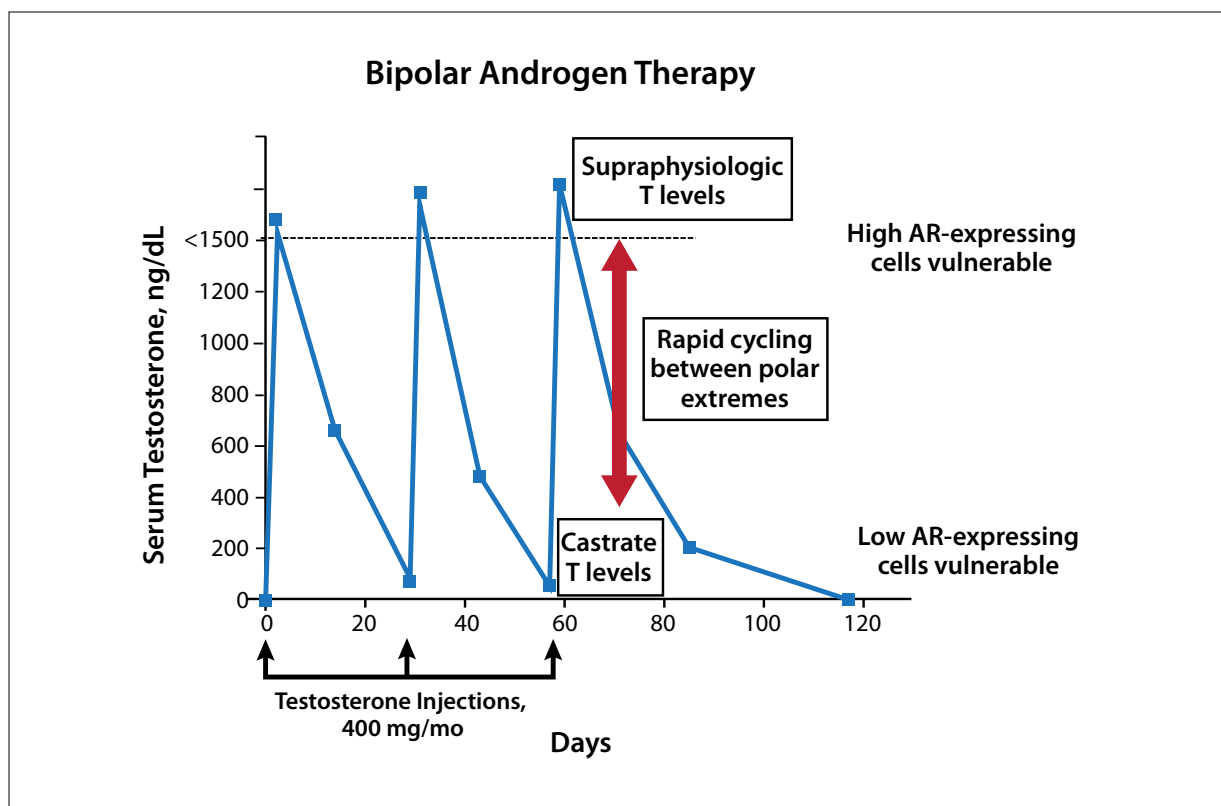


Figure. Alterations in serum testosterone in bipolar androgen therapy.

AR, androgen receptor; mo, month; T, testosterone.

of testosterone within the first few days. This level is about 5- to 10-fold higher than the normal testosterone level for a 70-year-old man, and almost 100- to 200-fold higher than the castrate level of testosterone. Over approximately 1 month, the level drops back to close to the castrate range. We use the term *bipolar androgen therapy* because the testosterone level cycles between these polar extremes.

The data we have suggest that the extra-high levels of testosterone are what is important, which is why we use the word *supraphysiologic*. In laboratory studies in vitro or in vivo, supraphysiologic levels of testosterone have been shown to be much more effective than normal levels at inhibiting cancer growth. Compared with low levels of testosterone, high levels also differentially affect the genes that are turned on in prostate cancer cells. In addition, in 2 small clinical studies (conducted by Morris and colleagues and by Szmulewitz and colleagues), men whose testosterone level was in the castrate range were given enough testosterone to get the level back to normal—approximately 300 or 400 ng/dL. Neither of those studies showed much of an effect from normal levels of testosterone, suggesting that the extra-high level is needed.

H&O Is there a rationale for simply boosting the testosterone level instead of alternating testosterone with ADT?

SD It would be interesting to do a trial with a cycling arm and a sustained arm. What would happen if we got the testosterone level up to 2000 ng/dL and left it there? But for now, we are focusing on BAT because experiments in animals have shown that cycling between high and low levels of testosterone produces a good antitumor effect.

H&O Could you describe your research on BAT in men with castration-resistant disease?

SD Our group has conducted 3 studies in this area. Our pilot study was sponsored by the One-in-Six Fund, which was started by a patient of mine to support prostate cancer research. The study, whose results appeared in *Science Translational Medicine* in 2015, was conducted in 14 men with castration-resistant prostate cancer (CRPC), who received a monthly testosterone injection (400 mg) and 2 weeks of daily etoposide (100 mg) while continuing to undergo ADT. After 3 cycles, the men whose prostate-

specific antigen (PSA) level had decreased continued to receive BAT. We found that BAT was well tolerated, with PSA declines and radiographic response seen in half the patients we treated. Treatment with antiandrogen therapies after BAT resulted in a decrease in PSA levels in all patients.

Our second study, called RESTORE (Re-sensitizing With Supraphysiologic Testosterone to Overcome Resistance; NCT02090114), is an open-label phase 2 study that is looking at men with CRPC that has stopped responding to enzalutamide (Xtandi, Astellas/Medivation) or abiraterone acetate (Zytiga, Janssen Biotech). We wanted to see whether the administration of high pulses of testosterone could resensitize these men to the drug they were taking, whether enzalutamide or abiraterone. The study also includes a group of men who are newly castrate-resistant and have not taken enzalutamide or abiraterone; the goal is to see whether these drugs might be more effective when given at an earlier stage.

We recently published results in *Lancet Oncology* for the 30 men taking enzalutamide. We found that a PSA response to BAT, defined as a drop of 50% or more, occurred in nearly one-third of the men. In addition, approximately one-half of the men had an objective response, defined as shrinkage of lymph nodes by 50% or more. The majority of patients with metastases to bone, where tumor response is difficult to image, were categorized as having stable disease during testosterone treatment. Overall, treatment was extremely safe. We have not yet published results specifically for the abiraterone arm, but preliminary analysis suggests a similar effect to what we saw in the enzalutamide arm.

The third study that we are conducting, called TRANSFORMER (Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance; NCT02286921), is a large trial sponsored by the Department of Defense Prostate Cancer Research Program. It is taking place at 17 sites around the country, and accrual was recently finished. We have enrolled 194 men (97 per treatment arm) whose prostate cancer was progressing on abiraterone and randomly assigned them to either BAT or enzalutamide. At the time of radiographic or clinical progression, the men are allowed to cross to the other arm. We are looking to answer such questions as whether giving testosterone before enzalutamide is better than giving testosterone first.

H&O What other important studies of BAT are being done?

SD We are beginning a study called COMBAT-CRPC, in which men receive 3 cycles of BAT followed by monthly

testosterone and nivolumab (Opdivo, Bristol-Myers Squibb). The idea for this study is based on findings in 2 patients in our RESTORE study who had received numerous doses of testosterone—10 doses in one patient and 12 doses in the other. These patients had received additional treatments after progression—other hormonal agents and chemotherapy—before being enrolled in separate trials in which they received a checkpoint inhibitor. Although most of the patients in these 2 trials did not respond to the checkpoint inhibitor, both of these men had a dramatic response—drops in their PSA levels of approximately 95% and 99%, and in one case complete disappearance of disease. We were intrigued to see that the only 2 patients who responded that well to checkpoint inhibition were the 2 patients who had received testosterone. We know that testosterone can cause DNA breaks and gene rearrangements, which means that it has the potential to produce neoantigens—new proteins that can stimulate an immune response. Could testosterone alter the immune system in such a way that men would respond better to checkpoint inhibition? COMBAT-CRPC will be based at Johns Hopkins and will begin enrolling patients this year. We are exploring other possibilities in the laboratory, trying to identify various agents to combine with testosterone. For example, one of my former fellows has discussed the possibility of opening a trial combining testosterone with a poly(ADP-ribose) polymerase (PARP) inhibitor.

H&O What are the potential risks of BAT?

SD I expect that most of the therapies I provide will either work or not work. With bipolar ADT, there is always the concern that it will make the tumor worse. We have treated a large number of patients at this point, and the disease of some of the patients who receive testosterone progresses, but the rate of tumor progression in these men does not seem to be accelerated by testosterone treatment.

The side effects of BAT that we see are the ones we would expect to see with testosterone treatment—breast tenderness, hot flashes, increases in hematocrit level, and edema, particularly in the lower extremities. One of the patients in RESTORE had a pulmonary embolism and another had a myocardial infarction; however, a man in the enzalutamide group also had a pulmonary embolism, so there is no indication that testosterone increases these risks. These are older men with cancer, so we are not surprised to see some of these events.

Another potential problem with testosterone injections is that in older studies from the 1970s, worsening, sometimes severe pain developed in some men within hours after they had received their first shot. We have limited enrollment in our trials to asymptomatic men, and we have not seen pain develop in these patients

during testosterone treatment. However, a few men with baseline pain that we presumed was arthritic pain have experienced flares of pain with testosterone that on re-evaluation were determined to be exacerbations of the pain caused by underlying bone metastases. The pain usually occurred after they returned home from the clinic and lasted for about a week. Some of these men have been willing to receive a second injection, and in those cases they did not have pain—it seems to be a flare that occurs only with the first shot. I recommend that care be taken in administering BAT to men with underlying pain and would not use this approach in men who clearly have pain caused by prostate cancer.

H&O What are some of the positive effects of testosterone?

SD A lot of men feel as if they have more energy, which is hard to quantify because researchers are used to evaluating negative side effects, not positive ones. Men often experience a dramatic increase in libido, which is generally positive but can also be frustrating for those who are experiencing erectile dysfunction as a result of their surgery or radiation—they have the desire but are unable to have erections.

ADT appears to affect cardiovascular function, so is it possible that testosterone could improve cardiovascular function? We have not studied that question. We also know that ADT can significantly affect cognitive function, which is something that tends to receive less attention than it should. There is a chance that testosterone might help reverse some of the side effects caused by long-term ADT.

H&O What other studies should be done in this area?

SD Studies in the laboratory have led us to believe that this approach works best if we can rapidly alternate between very high and very low testosterone levels during a cycle of therapy. One of the shortcomings of the

currently available injectable testosterone preparations is that they produce a rapid increase in blood testosterone to a very high level, but this level is not sustained for very long. In addition, the levels decline slowly over a month, without the sharp drop-off that we would prefer to see. The daily administration of testosterone gels effectively provides a normal physiologic or replacement level of testosterone, but it does not provide enough testosterone to produce a supraphysiologic level. A better approach might be to develop a cream or other preparation containing a much higher level of testosterone that would give us better control over the blood level of testosterone. We are currently exploring ways to develop such a testosterone cream for use in a clinical trial.

We also want to learn the optimal timing of testosterone therapy. Should patients receive testosterone as soon as they are castrate-resistant? Should they receive it in sequence with other hormonal therapies, such as abiraterone and enzalutamide? Could testosterone be combined with other drugs that would make it more effective? More studies are required to answer these questions.

Disclosure

Dr Denmeade has no conflicts of interest to disclose.

Suggested Readings

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