

Androgen Deprivation Therapy (ADT) Following Recurring Prostate Cancer Or When Androgen Deprivation Becomes The Necessary Therapy

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I was diagnosed in 1992 with Gleason Score 3+4=7. Following failure three years after radical prostatectomy and external beam radiation, I have been an androgen deprivation therapy patient and have maintained continuous research and study of this disease, focusing on appropriate androgen deprivation therapy, since 1996.

This “observation” is an attempt by this layman prostate cancer patient to provide a reasonable explanation of the controversies in Androgen Deprivation Therapy (ADT) for the treatment of recurrent prostate cancer. I am one of those patients. Herein are my personal conclusions; some readers may consider them as more confusing rhetoric.

It is obvious that many physicians administer ADT in different manners. The question by too many patients has become “what do I do?” Those who have researched ADT have found that there are several differing reasons as to why this physician or that physician has his or her “preference” and why they use different drugs in ADT treatment. Such patients may be left floundering and confused.

Testosterone (T) is the male hormone or androgen that comprises most of the androgens in a man’s body. Testosterone, by itself, plays a small part in driving prostate cancer (PC) growth. **5Alpha Reductase (5AR) enzymes on prostate cells convert T to as much as ten times a more potent metabolite, dihydrotestosterone (DHT), that profoundly stimulates cancer cell growth.** 5AR consists of two enzymes, type 1 and type 2, that are present on prostate cancer (PC) cells. Both are involved in the conversion of T to DHT. T has more difficulty accessing androgen receptors (AR) on prostate cancer cells, and it is when T comes upon the 5AR enzymes and is converted to dihydrotestosterone (DHT) that has a better propensity to access the AR, that there is a much more profound stimulation of PC cell growth. Antiandrogens are administered to block the AR from T access and the consequent conversion to DHT, yet it is difficult to entirely block all AR. LHRH agonists down-regulate the pituitary hormone LH, and consequently LH no longer stimulates Leydig cell testosterone synthesis

secretion. However, they do not diminish T production from the adrenal glands. Thus, to provide yet another safeguard to prevent PC cell growth, a 5AR inhibitor (dutasteride/Avodart or finasteride/Proscar) is administered to inhibit the conversion of T to DHT. With finasteride/Proscar only known to inhibit 5AR type 2, while dutasteride/Avodart is known to inhibit both types 1 and 2, many physicians, as well as advocates with experience with ADT3, opt for dutasteride/Avodart as the third medication in triple hormonal blockade. And with other trials/studies having determined that dutasteride fills a role in PC cell apoptosis as well as inhibiting cell proliferation, dutasteride/Avodart has gained more acceptance. There have been studies that have determined that 5AR type 1 is even increased and type 2 somewhat decreased during development of prostate cancer. And both type 1 and type 2 expression is increased in recurrent and metastatic cancers, supporting the concern that both enzymes are involved in the development and progression of prostate cancer and require inhibition.

Orchiectomy (surgical castration) removes the testicles that produce the majority of testosterone in men. T can also be reduced by chemical castration with administration of an LHRH agonist as part of Androgen Deprivation Therapy (ADT). Both methods reduce the production of testosterone in an attempt to starve or kill prostate cancer growth; neither method has the ability to stop the production of DHT nor to reduce the amount of androgens produced by the adrenal glands; in fact, both routes may stimulate adrenal androgen production which the prostate cells can convert to T and then to DHT. **Both of these routes are called ADT, which was historically correct, but they should be called Testosterone Reducing Therapy (TRT).**

As noted earlier, Chemical castration is done by LHRH agonists down-regulating the pituitary hormone LH, and consequently LH no longer stimulating Leydig cell testosterone synthesis secretion. LHRH agonists include (leuprolide acetate (Lupron), goserelin acetate (Zoladex), triptorelin acetate (Trelstar), leuprolide acetate in atigel (Eligard) and two longer lasting agonists, leuprolide acetate implant (Viadur) and histrelin acetate implant (Vantas). A recent addition is Degarelix. a gonadotropin-releasing hormone receptor antagonist that binds reversibly to the pituitary gonadotropin-releasing hormone receptors, reducing the release of testosterone. The end product is a diminution of Leydig cell T. T production can also be slowed by agents that are LHRH antagonists called Abarelix and Centrix. The loss or lowering of T effects most cells in the body, especially brain, bone, and muscle.

Prostate cell growth is stimulated by T or DHT attaching to androgen receptors in prostate cells. These receptors are also activated by many other androgenic substances. **Androgen receptors in the prostate cell** (and unfortunately elsewhere in the body) **are hopefully blocked** by androgen receptor blockers, or anti-androgen as bicalutamide (Casodex), flutamide (Eulexin), nilutamide (Nilandron), or cyproterone acetate (Androcur). Androcur also blocks LH. All these substances seem to act primarily on prostate cells.

As noted earlier, **the conversion of testosterone to DHT can be inhibited** by 5-AR inhibitor finasteride (Proscar) or even more completely by dutasteride (Avodart). When this conversion is inhibited, T levels in the body usually rise to try to make up for the difference. Thus the rest of the body is not deprived of the effect of T. **Of particular additional importance** - it was reported at the February 2007 annual meeting of ASCO (the American Society of Clinical Oncology - the organization for physicians who treat cancer) that dutasteride (Avodart) had been found to upregulate the gene IGFBP3 and down regulate genes TMPRSS2 and TFF3, thus causing PC cell apoptosis and inhibiting cell proliferation. In my opinion, this is documented evidence that dutasteride (Avodart) should be prescribed in all androgen deprivation therapy.

Some of the above drugs seem to kill old prostate cells or to cause what is called Apoptosis. Apoptosis seems to occur best with a combination of drugs. To just slow down PC growth is buying time, but causing Apoptosis can kill cancer. When cancer is slowed down, it seeks another source of feeding materials by mutating or forming new clones. Some of the new clones are Androgen Independent Prostate Cancer (AIPC) and some are just more aggressive prostate cancer.

The accepted treatment of metastatic PC (invasive and growing by itself away from the prostate) has been to block continued PC development by starting with surgical or chemical castration with either orchiectomy or an LHRH agonist (ADT) and reserving Casodex or other antiandrogens (ADT2) and Avodart or Proscar (inhibitors of 5AR) (ADT3) for future use should PSA and/or testosterone levels rise to indicate continued growth of PC, despite the ADT.

This fails to make sense to me based on much recent evidence. Experts are becoming more knowledgeable about the need to stop or kill cancer as quickly as we can and before it has had time to multiply and form more invasive clones. Thus, I believe that when it is obvious that ANY prostate cancer is present, it appears logical and rational that ADT3 – a full blockade against the growth of prostate cancer cells – should be initiated. My

reasoning is why wait for *a change* to occur, which would mean you held back a therapy that may have served to kill cancer cells in their earlier stages and could have prevented that change or made them stay dormant for many years? This reasoning has been shown to be extremely important in Breast Cancer.

Modern thinking physicians who have followed many persons on LHRH agonists (Lupron and Zoladex) have determined how detrimental it is for patients to be on continuous Androgen/Testosterone Deprivation; they have determined that Intermittent ADT (IADT) (stopping use of the LHRH agonist and antiandrogen) can be as beneficial as continuous therapy as long as the individual has been able to obtain and maintain for 1 year a PSA level that is “undetectable” or <0.05 ng/ml and a “castrate” testosterone level <32 ng/dl (but preferably <20 ng/dl) before considering IADT. During any IADT interval, “maintenance” with Avodart or Proscar should be considered to continue inhibition of 5AR activity. This allows T to slowly recover but still inhibits the conversion of T to DHT so as to interfere least with the good effects of T on the rest of the body and probably to delay the onset of Androgen Insensitive PC clones.

The National Comprehensive Cancer Network (NCCN) statement indicates there is currently no clinical data to support the addition of antiandrogen blockade and 5-AR blockade additions to ADT. This is because clinical trials were not presented to the Federal Drug Administration (FDA); largely because the drugs were already in use and their patents about to expire. Clinical trials require huge financial support of the pharmaceutical firms to get the studies into the pipeline. Now that newer drugs like Androcur and Avodart are available, and their patents have many years of protection, studies are underway. But it will still be years before this information gets to NCCN or guys like us; in the meantime the older drugs will be ignored. Interesting in the NCCN guidelines is they acknowledge that with ADT failure, androgen receptors are still active, and state ADT must still be continued. It is difficult to comprehend how they can recognize that androgen receptors are “active” while at the same time ignoring that both LH/testicular testosterone and adrenal gland androgen precursors can access those receptors, come in contact with 5AR, and convert to the more powerful DHT stimulant to PC cell growth.

However, data in peer reviewed literature has been validated and there is a nucleus of physicians specializing in prostate cancer treatment (those at the annual National Prostate Cancer Conferences like Strum, Scholz, Myers, Lam, Tucker, Leibowitz, et al) whom have applied this combination therapy with the older drugs and published results. They have established its

effectiveness in blocking the androgen receptors and inhibiting the conversion of T to DHT, and in so doing, increasing the effectiveness of ADT. The important report to ASCO noted previously regarding dutasteride (Avodart) playing a role in PC cell apoptosis and inhibiting PC cell proliferation should no longer be ignored.

Obviously, by this writing, I support the importance of what is called three level ADT (ADT3). It should be noted that the NCCN recognizes that patient preference is to be included as a part of the treatment decision. Every patient should study and understand their treatment options in order to be able to validate their treatment preference. Here is the specific "Summary" statement in the National Comprehensive Cancer Network Prostate Cancer Guidelines:

"SUMMARY The intention of these NCCN Prostate Cancer Guidelines is to provide a framework on which to base treatment decisions. Prostate cancer is a complex disease, with many controversial aspects of management and with a dearth of sound data to support treatment recommendations. Several variables (including life expectancy, disease characteristics, predicted outcomes, **AND PATIENT PREFERENCES** (my highlighting)) must be considered by the patient and physician in tailoring prostate cancer therapy to the individual patient."

In another area of the NCCN Guidelines regarding "Treatment" for advanced prostate cancer are these words:

"Before deciding on treatment, **YOU** and your doctor must consider:

- The risk (likelihood) of a cancer recurrence, which is predicted by [stage](#), [Gleason score](#), and [PSA](#) level. Advanced prostate cancer typically has a high risk of coming back;
- Your general health, including other diseases you may have that may make certain treatments risky or unnecessary;
- Potential side effects of treatment;
- **YOUR PERSONAL PREFERENCES.**"

(again, my highlighting)

Please note, again, "YOUR PERSONAL PREFERENCES."

The use of 5AR (Alpha Reductase) inhibitors such as dutasteride/Avodart or finasteride/Proscar is NOT UNETHICAL. Despite many physicians commenting that their use "has not been proven" (because they have not

taken the time to do their own research), if the patient chooses to have the medication prescribed as part of his androgen/hormonal deprivation therapy (ADT), it should be honored by the physician. The NCCN guidelines even question the necessity of antiandrogens if the LHRH agonist effectively brings down the testosterone and PSA levels, despite the knowledge that antiandrogens block prostate cancer (PC) cell androgen receptors, thus hopefully blocking all such receptors from testosterone accessing the prostate cancer cell. They apparently choose to ignore that the adrenal glands can still produce testosterone and thus access prostate cancer cells, or they hold off these important medications "until they become necessary," a somewhat ridiculous reason when one considers that if they become important and appropriate when "they become necessary," then they certainly should be important and appropriate early on. And since any testosterone accessing the prostate cancer cell (that can occur even while taking antiandrogens since it is unlikely that every single androgen receptor is blocked) can then be converted to the much more powerful stimulant to prostate cancer cell growth, dihydrotestosterone (DHT), a 5AR inhibitor becomes a necessary safeguard to inhibit that conversion.

And, despite the remark by many physicians that androgen deprivation therapy is not a "curative" therapy, ADT can cause PC cell apoptosis as well as inhibit PC cell proliferation. There are no therapies that can definitely be claimed to be "curative." My personal opinion is that the word "cure" should not be part of the vocabulary of cancer. We hope for "cure," but once diagnosed with any cancer, we must ever more be vigilant.

I recognize that the choice of therapy can be driven by the cost of that therapy. All ADT drugs are expensive. Medicare, as do most insurers, pays for drugs requiring injection in the physician's office like LHRH agonists that must be injected in a medical setting. Medicare only pays for drugs taken orally like Casodex, Eulexin, Avodart, Proscar, Androcur, etcetera to the limits of its Plan D. Those moved to pursue this therapy should be prepared to pay for the added medications or to find out if their physicians or the drug companies are able to obtain these drugs in clinical trials, samples, or a price reduction for those with financial need. Many medications are available to military veterans at a Veteran's Administration medical facility.

When physicians are ready to insist and support their reasoning to insurers the necessity of providing coverage for these drugs that are available to save lives, and when pharmaceutical companies can afford to make them available at reasonable cost, we may begin to see patients extending their lives in immeasurable years rather than in numbered months.

The foregoing described my research, study, and personal experience since 1996 as a patient required to be prescribed androgen deprivation therapy. However, I would be remiss if I did not make mention of an alternative androgen deprivation therapy - the use of estradiol patches, creams, or gels. Estradiol products are less expensive than conventional LHRH agonists and anti-androgens. My understanding is that estradiol treatment with patches, creams, or gels does not cause osteoporosis and is less risky than oral estrogen that has been known to cause blood clots. Many physicians will not prescribe estradiol therapy because of their awareness of oral estrogen side effects or their lack of knowledge regarding this option. Of importance if seeking this form of androgen deprivation is doing your own personal research and study, then finding a physician with understanding and experience in its administration as to proper dosage and close monitoring.

Please note that when prescribed an anti-androgen it is recommended that prior to the first administration the patient consider daily radiation to the breast area at 300 to 400 cGy for four days to prevent otherwise likely gynecomastia (breast enlargement). Or, alternatively, the medications recommended in this next remark by Medical Oncologist Stephen Strum: “Actually, the cause of the gynecomastia is due to estrogen production that is caused by high levels of testosterone resulting from single agent therapy with Casodex or any anti-androgen monotherapy or even SAB (sequential androgen blockade) using anti-androgen plus 5 alpha reductase inhibitor. The way to prevent gynecomastia is by blocking the aromatase enzyme that converts testosterone to estradiol. The drugs available to block this are Arimidex (anastrozole) or Aromasin (exemestane). So, using Tamoxifen extinguishes part of the process causing this side effect but it would not be the only remedy that I would use.” Though we note that Dr. Strum describes the cause of gynecomastia because of “single agent therapy Casodex” or any anti-androgen as monotherapy, my initial ADT therapy was dual medication hormonal blockade with Lupron and Casodex (not monotherapy with only Casodex), and with my urologist failing to advise me of the possibility of gynecomastia, I had significant breast enlargement. Thus, treatment to avoid this condition is recommended. Side effects and drug interactions/reactions of ADT treatment that can include hot flashes, muscle weakness, fatigue, osteoporosis, and others that require regular physician/laboratory monitoring can be reviewed here: <http://tinyurl.com/5snxzx>. Though these are separate issues, they are very important to be aware to discuss with as well as question their physician.

Disclaimer: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. The comments or recommendations I make are not intended to be the procedure for you to now follow; rather, they are to be reviewed along with the comments or recommendations of others for your own further research, study, and discussion with the physician providing your prostate cancer care to come to your own, personal conclusion.