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Testosterone Inactivating Pharmaceuticals

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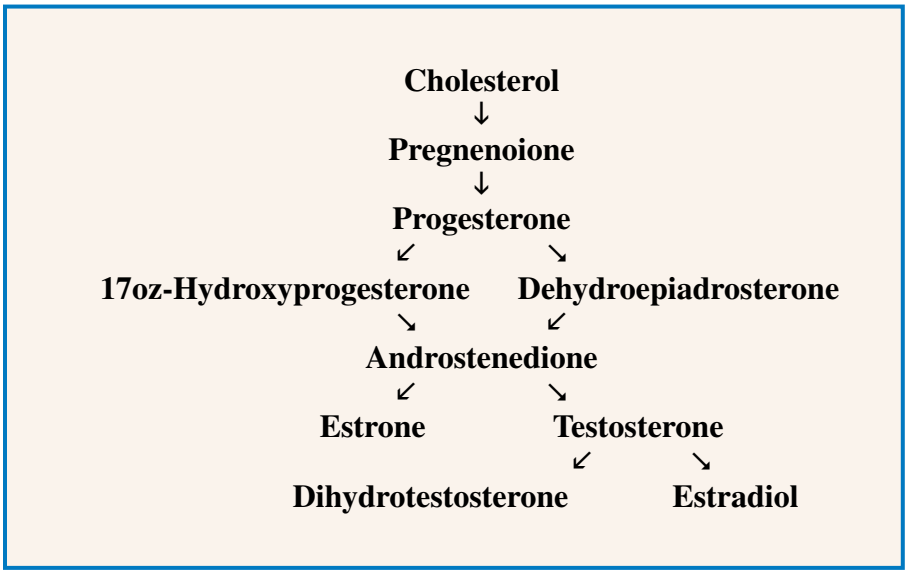
Prostate cancer needs testosterone to survive. Blocking testosterone is proven to prolong life in randomized prospective trials. Testosterone Inactivating Pharmaceuticals (TIP), otherwise known as androgen deprivation or hormone blockade, are FDA approved medicines used either alone or with radiation to treat various stages of prostate cancer. Despite widespread experience, there are many controversies about the optimal way to use TIP. Probably the biggest issue is side effects. TIP impacts quality of life. So there is an art to picking the *right amount* of TIP for each individual. The goal is to continue TIP long enough to get the job done, but stop before going too long. The optimal methodology for using TIP varies from situation to situation because prostate cancer comes in a spectrum of "stages" ranging from low-risk which can be safely monitored without immediate treatment, to metastatic castrate-resistant disease. Between these two extremes are intermediate-risk, high-risk, seminal vesicle invasion (stage T3b), PSA-relapse and lymph-node metastasis (Stage D1). For more details about low, intermediate and high risk disease, see the article titled *What's Your Type* available at www.pcri.org.

Testosterone

Testosterone, the most common androgen in men, is manufactured intracellularly from cholesterol and progesterone, mainly in the testicles. Dihydrotestosterone (DHT), a substantially more potent form of testosterone, is converted from testosterone by the enzyme 5-alpha reductase which is located in the prostate and the liver. Dehydroepiandosterone (DHEA) and androstenedione (ANDRO), weaker androgens, are synthesized in the adrenal glands, located above each kidney. The adrenal glands are where other common hormones such as cortisone and adrenaline are created. DHEA and ANDRO are synthesized from cholesterol and progesterone just like testosterone (see figure 1).

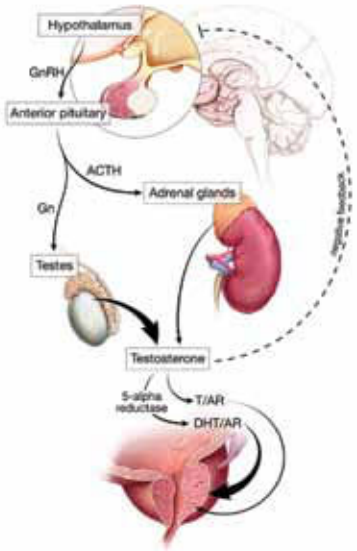
Figure 1: Synthetic Pathway of Testosterone



Prostate cancer can't survive without testosterone. The prostate gland is a vestigial nubbin until after puberty when it blossoms into a walnut sized gland to manufacture semen. After puberty, if testosterone is removed, the gland involutes and atrophies. Prostate cancer cells are derived from the prostate gland so they also need testosterone to survive. Prostate cancer cells grow and proliferate when testosterone is present; they shrivel and die when testosterone is absent. When testosterone levels in the blood drop, the cancer cells "commit suicide" through a process called *apoptosis*.

Testosterone Inactivating Pharmaceuticals

There are different varieties of testosterone inactivating pharmaceuticals. They fall into three main categories. In the first category are the LHRH agonists such as Lupron, Zoladex, Eilgard, and Vantas. These medicines are administered by injection on a monthly, quarterly, semi-annual or yearly basis. They work by suppressing the pituitary gland (at the base of the brain) which in turn sends a suppressive hormonal signal to the testicles.



The Hypothalamic-Pituitary-Gonadal Axis

In the second category are the anti-androgens such as Casodex, Eulexin and Nilutamide. These pills work at the molecular level to block testosterone from activating the androgen receptor (the switch in the cell that enhances cell growth when its turned on).

In the third category are the 5-alpha-reductase inhibitors such as Proscar and Avodart. They work by blocking the conversion of testosterone into its more potent analogue, DHT.

Combinations

These medications can be used together in combination to attain more complete testosterone suppression and thus increase the anti-cancer effect. However, urologists throughout the world more commonly employ single-drug therapy with LHRH agonists alone. This policy is rooted in studies done back in the 1990's. These studies showed that anti-androgens added to LHRH agonists only enhanced survival by a couple months[1] Also many urologists at that time were concerned about the high cost of Casodex. Unfortunately this policy of using LHRH agonists without Casodex persists even though these days Casodex is generic and much more affordable.

Adding medicines from the third category, the 5-alpha reductase inhibitors like Proscar or Avodart, is often justified with the rationale that, "It can't hurt, and it might help." While using drugs from all three categories is popular in some circles, clinical studies are lacking. There are a number of studies, however, confirming that Proscar and Avodart have an anticancer effect. For more details about using 5-alpha reductase inhibitors to treat prostate cancer, see the article titled *Proscar and Avodart* at www.pcri.org.

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TABLE 1: Studies Showing Survival Advantage with TIP

Author	Reference Number	Comparison Group	Treatment Group	Better Survival	Fewer Relapses
Bolla	4	No TIP	36 mo. TIP	yes	
Horwitz	5	4 mo. TIP	24 mo. TIP	yes	
Zeliadt	6	No TIP	Any TIP	yes	
Granfors	7	No castration	castration	yes	
Crook	8	3 mo. TIP	8 mo. TIP		yes
D'Amico	9	No TIP	6 mo. TIP		yes

Casodex by Itself

Clinicians with experience using Casodex as a single agent, so called anti-androgen monotherapy, have the general sense that: "Casodex monotherapy is about 70% as effective as the LHRH agonists but with only 30% of the toxicity." Anti-androgens have been studied in prospective randomized trials as stand-alone therapy[2] and combined with radiation.[3] Overall, compared to LHRH agonists, side effects are certainly less. And compared to placebo, they clearly retard prostate cancer growth. The only caveat is a higher risk of breast growth. This can be partially or completely prevented with prophylactic breast radiation or an estrogen blocking pill called Femara. For more details on using Casodex by itself see the article titled *Anti-Androgen Monotherapy* available at www.pcri.org.

TIP Added to Radiation Improves Survival

The most convincing proof that TIP enhances survival is from studies of men with intermediate-risk, high-risk and Stage T3b disease (seminal vesicle invasion) who are undergoing radiation. In the studies, little or no TIP is compared with TIP administered for a more prolonged period. The two groups are monitored over time to determine if one group has superior survival. The results from several such trials are listed in Table 1.

As can be seen in Table 1, longer periods of TIP prolong survival more that shorter periods. However, the *optimal* duration of TIP is still unknown since treatment periods between 8 and 24 months are yet to be tested to see if more than 8 months but less than 24 months would yield comparable benefit. This is an important unanswered question because the side effects of TIP can be notable. At the present time our policy is to aim for somewhere between 12-18 months of therapy, depending on how well treatment is tolerated. If side effects are not excessive, a full 24 months of therapy can be considered. For more details on the side effects of TIP see the article *Preventing the Side Effects of TIP* available at www.pcri.org.

Even without radiation, TIP as a sole modality can effectively control prostate cancer for many years. In a prospective trial in men with proven lymph node spread (stage D1), better long-term survival was seen when TIP was started immediately as compared to TIP initiated at the time of cancer progression.[10] However, in another prospective trial with locally advanced prostate cancer (seminal vesicle invasion or stage T3b), better survival occurred when radiation was *added* to TIP, compared to men who were treated with TIP alone.[11]

To summarize — when the disease is aggressive, TIP and radiation together appear best, but only up to a point. Once the disease becomes metastatic, TIP alone is considered standard. At the other end of the spectrum are the men with intermediate-risk disease. For the more "favorable type" of intermediate risk disease, combination treatment is overkill. These men should be treated with one treatment or the other, not both. Men with the more "unfavorable type" of intermediate risk disease should consider combination treatment, but only with *short-term* TIP for three or four months.

PSA Relapse

Medical experts continue to debate the advisability of starting TIP immediately in men with PSA relapse. The debate is likely to continue because there are no prospective trials, only less definitive retrospective trials.[12] The situation is also complicated by differences between patients — some men have relapses that are very slow-paced whereas others have a type of disease that moves faster. And many studies confuse matters by inappropriately jumbling both groups' together, making outcomes difficult to interpret. Not surprisingly, studies incorporating men with slowly-paced disease show no benefit with starting TIP right after relapse. Such men will do well whether they have TIP or not.

Despite all these conflicting reports, several studies confirm that there is a benefit for starting TIP before the onset of bone metastasis.[13,14] This is seen most clearly in studies done in men with faster PSA-doubling times (less than 6-9 months).[15,16] So more and more experts recommend that TIP be started before the onset of bone metastasis. Recommendations vary when it comes to selecting a predetermined PSA threshold to begin treatment. Numbers like 5, 10 or 20 are suggested as the trigger for starting TIP but other factors, including Gleason score and PSA doubling time, also need to be taken into account. PSA alone fails to portray the whole picture. For example, Johns Hopkins has reported that one-fourth of men with PSA relapse develop bone metastasis with PSA levels under 10.[17]

Intermittent TIP

To reduce side effects, TIP is often given intermittently.[18] The idea of stopping and taking a holiday from TIP was first floated in the early 1990's. Back then, discontinuing treatment seemed crazy. However, our initial experience with TIP for men in PSA relapse had made us feel pretty upbeat about its effectiveness. PSA levels almost always dropped to zero. With PSA levels so low the question arose, "Have we cured the disease?" The only way to find out was to stop the treatment and see. As it turned out, cure was rare. PSA levels started rising once testosterone in the blood recovered. Even so, we and others were gratified to learn that TIP could be restarted a second time with a high likelihood that the PSA would again drop zero.[19]

Our ensuing experience using TIP intermittently was published in the Journal of Urology.[20] We discovered that a longer initial treatment period (up to about 12 months) induced a longer holiday period. Proscar was also shown to further extend the holiday. More recently, we have shown that the off-period can be prolonged further using medicines that work by stimulating the immune system, medicines such as Leukine, low-dose cytoxan, Celebrex and Revlimid.[21] For more details, see the article titled *Immune Treatment for PSA-Relapsed Prostate Cancer* available at www.pcri.org.

Intermediate-Risk Disease

In the United States, most men with intermediate-risk disease are treated with surgery or radiation. When radiation is used, adding four to six months of TIP gives better cure rates than radiation by itself.[8,9] However, the intermediate-risk category is a broad with predicted post-radiation relapse rates that vary between 10 and 50% depending on the primary Gleason Grade (4 vs. 3), the degree of PSA elevation, and the extent of disease on biopsy. Men with the more "favorable" type of intermediate-risk disease might consider either TIP alone (see below) or radiation alone. Men with the "unfavorable" type of intermediate-risk disease should probably consider using a short-course of four months of TIP *plus* radiation.

TIP Without Radiation

I believe that TIP is a reasonable, stand-alone treatment for men with intermediate-risk disease. While there are limited studies documenting its effectiveness (ref), at Prostate Oncology Specialists we have treated 120 men with 12 months of TIP followed by a color doppler directed biopsy of the previously documented cancer site. The biopsy was clear of cancer in 80% of the men.

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We have also recently submitted an article for publication detailing the twelve-year outcome of 73 men with an average age of 67 initially treated with TIP alone. The average PSA for all the men was 9. The average Gleason score was seven. Most had a nodule that could be felt on digital rectal examination. Treatment was started back in the 1990's before the advent of the modern D'Amico staging system (separation of men into low, intermediate and high-risk categories). When we went back and assigned risk-categories (during the process of preparing the publication) men from all three risk-categories were represented.

Twenty-one of these men (29%) never needed any further therapy; a single course of TIP kept their PSA suppressed indefinitely. Twenty-four men (33%) required periodic retreatment with TIP (intermittent TIP) to keep their PSA levels under five. Twenty-eight men (38%), rather than continuing on intermittent TIP, decided to have local therapy such as surgery, seeds or radiation. Their local therapy was performed, on average, five and a half years after the first cycle of TIP. Of these 28 men who had delayed local therapy, only three developed a PSA relapse and none have developed metastasis.

So clearly, TIP as primary therapy is effective. The problem (as is the case for all prostate cancer treatments) is side effects. Fortunately, after treatment is stopped, testosterone recovers and side effects wear off. Since it is now becoming standard policy to monitor *biopsy-positive* low-risk disease in a standardized approach called *active surveillance*, we question why active surveillance techniques can't be used to monitor men with TIP-induced, *biopsy-negative* disease? Criticisms of using TIP as primary therapy for intermediate-risk disease seem to be based solely on an unwillingness to deviate from "the way things have always been done" rather than any justifiable logic.

The Final Word — Quality of Life

Testosterone deprivation is one of the most potent treatments ever known for cancer. Breast cancer is the only other hormonally responsive cancer and the anti-hormones for breast cancer are only 20% as effective as TIP is for prostate cancer.

Despite TIP's potency, quality of life considerations are critical. The side effects of TIP can be severe. When long-term suppressive TIP is indicated, intermittent treatment helps. Men who have locally advanced disease who are taking TIP with radiation for cure, still face uncertainties about the optimal treatment time. The best we can do is weigh impact of the side-effects in each individual and balance them with the known ability of TIP to improve cure rates.

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