

## HORMONE THERAPY FOR MANAGEMENT OF PROSTATE CANCER

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### ABSTRACT

Hormone therapy is another form of systemic therapy. It is most often used as an adjuvant therapy to help reduce the risk of the cancer coming back after surgery, but it can be used as neoadjuvant treatment, as well. Hormone therapy or androgen deprivation therapy is a form of treatment used to control prostate cancer. Testosterone is the primary male hormone. It helps develop and maintain typical male characteristics such as muscle mass, erectile function and sexual desire. A normal testosterone level is necessary and does not cause problems. However, when cancer cells are in the prostate, testosterone can make them grow faster. In other words, testosterone feeds prostate cancer. If testosterone is stopped, the cancer cells will shrink, no matter where they are in the body. Hormone therapy does not cure cancer. It helps stop the body from producing testosterone or stop it from getting into the cancer cells. It must be used with other treatments like surgery or radiation. However, hormone therapy can temporarily slow the growth of prostate cancer and shrink existing tumours, reducing symptoms and prolonging life. Treatment of prostate cancer varies depending on the stage of the cancer and may include surgical removal, radiation, chemotherapy, hormonal manipulation or a combination of these treatments.

**Keywords:** prostate cancer, hormonal therapy, androgen deprivation therapy.

### INTRODUCTION

Benign prostatic hyperplasia (BPH) is a pathologic process which may contribute to lower urinary tract symptoms in aging men. A common problem among males over 50 years, its prevalence increases with age. Histologically, BPH is characterized by an increased number of both epithelial and stromal cells in the periurethral area of the prostate. There is controversy as to whether this increase is secondary to epithelial and stromal proliferation or impaired apoptosis leading to cellular accumulation. Testosterone in males is produced primarily in the testicles, but also in the adrenal glands. The majority of testosterone in the body is bound to sex hormone-binding globulin (SHBG), a protein produced in the liver that transports testosterone through the bloodstream, prevents its metabolism, and prolongs its half-life. Once it becomes unbound from SHBG, free testosterone can enter cells throughout the body. In certain tissues, notably

the scalp, skin, and prostate. Testosterone is converted into 5 $\alpha$ -dihydrotestosterone (DHT) by the enzyme 5 $\alpha$ -reductase. DHT is a more powerful androgen than testosterone (as it has approximately 3-10 times the potency at the androgen receptor, the site of action of the androgen hormones), so 5 $\alpha$ -reductase can be thought to amplify the androgenic effect of testosterone in the tissues in which it's found. Nevertheless, it is understood that androgens, growth factors, neurotransmitters and other cell interactions play a role in the development of this condition.

Prostate cancer is the most commonly diagnosed solid tumor in men and the second leading cause of cancer death in males. Prostate cancer will continue to become an increasingly important healthcare issue in the coming years. Traditionally hormonal therapy has been used only for metastatic diseases, new applications that utilize hormonal therapy in earlier stages appear to be making a difference in Prostate

cancer. The hormone responsive nature of prostate carcinoma provides an additional strategy to primary therapy alone by which clinical management may lead to improved long-term outcomes. Randomized, controlled, phase III clinical trials have examined the efficacy of immediate androgen deprivation therapy (ADT) as adjunctive therapy to prostatectomy and radiation therapy in men with unfavorable localized or Locally advanced Prostate cancer with generally improved outcomes. National data sets such as Cancer of the Prostate Strategic Urologic Research Endeavor (Prostate cancer SURE) support the fact that there has been an increasing use of strategies such as early hormone therapy in nonmetastatic disease. Given emerging data about the potential harms of ADT, the need is growing to define the optimal duration of ADT plus external beam radiotherapy for patients with locally advanced Prostate cancer. Testimony to the evolution in the treatment of locally advanced Prostate cancer is apparent through the impetus of designing randomized trials, as the urologic field pushes on to practice evidence-based medicine. The focus of this article is to highlight those trials that may help the clinician to develop the optimal regimen for the patient diagnosed with locally advanced Prostate cancer.

#### **Types of Prostate cancer**

**Locally advanced prostate cancer** has spread beyond the gland but not to other parts of the body. Hormone therapy is the standard treatment for this stage of cancer because it treats cancer cells throughout the body. Locally advanced prostate cancer cannot be treated with radical prostatectomy because the cancer is not contained within the prostate gland.

**Advanced prostate cancer** has spread to other parts of the body. Hormone therapy cannot cure the cancer but may be used to keep it under control for some time.

#### **Forms of hormonal manipulation and hormonal suppression**

Male hormones (called androgens), particularly testosterone and dihydrotestosterone, determine male secondary sex characteristics and stimulate prostate cell growth. When prostate cells, both healthy and cancerous, are deprived of androgens, they no longer proliferate and eventually die.

Androgen deprivation therapy (also called androgen suppression therapy or hormone therapy) uses drugs or surgery to suppress or block male hormones, particularly testosterone and dihydrotestosterone that stimulate the growth of prostate cells. Androgen deprivation

therapy is not a cure for prostate cancer, but it can help control symptoms and disease progression. Hormone therapy or androgen suppression therapy (AST), allows for a decrease in serum testosterone in an effort to slow down the growth of Prostate cancer. Multiple medications and strategies have been used to induce castrate serum levels of testosterone or to interfere with its function. Androgen deprivation therapy is used for advanced and metastatic cancer and may be used if treatment for localized prostate cancer has failed and cancer recurs.

There has been some debate about when to start androgen deprivation therapy. In 2007, the American Society of Clinical Oncology (ASCO) published clinical guidelines for androgen deprivation therapy in patients with recurrent, progressive, or advanced prostate cancer. The guidelines recommend that hormone therapy should, in general, be delayed until patients begin to experience symptoms from their cancer. However, when therapy is deferred, patients should regularly visit their doctors every 3 - 6 months for careful monitoring of their condition. ASCO recommends either removal of both testicles (bilateral orchiectomy) or injections with luteinizing hormone-releasing hormone (LHRH) as initial androgen deprivation treatments. Combining antiandrogen drug therapy with orchiectomy or LHRH may also be considered.

When prescribing hormone therapy drugs, some doctors recommend periodically stopping and restarting treatment (intermittent therapy). This approach may help men avoid the loss of sexual function. More research needs to be conducted to determine the effectiveness of intermittent therapy.

#### **1. Orchiectomy**

Orchiectomy is the surgical removal of the testicles (surgical castration). It is the single most effective method of reducing androgen hormones, but because it is permanent it is not suitable for intermittent or temporary androgen deprivation. Orchiectomy plus radical prostatectomy may delay progression in patients with cancers that have spread only to the pelvic lymph nodes.

Men who have orchiectomy have reduced sexual function and desire. Patients do not experience a reversal of sex characteristics and the voice does not change. Like all androgen deprivation therapies, orchiectomy increases the risk for osteoporosis. Surgical castration results in an effective reduction of circulating testosterone within a few hours, and still remains an

underutilized method in the treatment of advanced Prostate cancer.

## 2. The introduction of the luteinizing hormone-releasing hormone (LHRH) agonists

The two most commonly used in studies discussed are Leuprolide and Goserelin, revolutionized the treatment of advanced Prostate cancer. After an initial surge of luteinizing hormone (LH) or follicle-stimulating hormone (FSH) and subsequently testosterone, constant exposure to treatment by LHRH agonists results in down regulation of receptors in the pituitary gland. As a consequence, a decrease in testosterone production is observed from inhibition of FSH and LH release. Monotherapy with LHRH androgen deprivation results in a decline of 90% of circulating testosterone. Ten per cent of circulating testosterone is still present in castrated men due to peripheral conversion of circulating adrenal steroids to testosterone. To achieve maximal androgen blockade (MAB), combined therapy with nonsteroidal antiandrogens (NSAAs) bicalutamide, flutamide, and nilutamide has also become an accepted option. NSAAs work by blocking the action of testosterone through the inhibition of the prostatic nuclear uptake of androgen. Ketoconazole also has been shown to be a useful second-line treatment in patients with advanced Prostate cancer, but its widespread use is limited by concerns regarding liver toxicity.

### The Mechanism of Action of GnRH Agonists

GnRH agonists have the same effect on gonadotropin release after binding the type I receptor as native GnRH. The main difference of GnRH agonists used in clinical practice, in comparison with native GnRH, is that the half-life time and the bioavailability are prolonged, due to increased lipophilicity. The extensive development of GnRH agonists over the past three decades resulted in seven analogues, which have become approved for clinical use. The potency was increased by the replacement of glycine at position 6 by D-amino acids and the replacement Gly-NH<sub>2</sub> at the C-terminus by NH<sub>2</sub>-ethylamide binding to the proline at position 9, resulting in nonapeptides. The continuous administration of GnRH agonists (daily or depot application) initially causes LH and FSH hypersecretion (flare-up), which is followed after a period of about 10 days by desensitization of the pituitary and profound suppression of LH and FSH. This results in the inhibition of ovarian steroidogenesis and

follicular growth. This "medical hypophysectomy" has shown to be beneficial in reproductive steroid-dependent disorders and during IVF treatment to prevent a premature LH surge.

### 3. Gonadotropin-releasing hormone antagonists or Anti-androgens

Degarelix is one of the new, modified gonadotropin-releasing hormone antagonists. Unlike the standard LHRH agonists, degarelix is a direct LHRH antagonist, and thus avoids the flare phenomenon. This compound was recently compared with leuprolide in a phase III randomized trial. Testosterone levels were suppressed significantly faster with degarelix than with leuprolide, with nearly all patients achieving castrate levels by day 3 of treatment. In addition, degarelix resulted in a significantly faster reduction in PSA level. Long-term disease control rates are not yet available.

### The Mechanism of Action of GnRH Antagonists

Unlike GnRH agonists, the antagonists do not induce an initial hypersecretion of gonadotropins but instead cause an immediate and rapid, reversible suppression of gonadotropin secretion. The principal mechanism of action of GnRH antagonists is competitive occupancy of the GnRH-receptor. The first-generation antagonists, containing replacements for His and Trp at positions 2 and 3, respectively, had low suppressive activities. The potency in the second generation was increased after the incorporation of a D-amino acid at position 6 but resulted in increased anaphylactic reactions due to the increased histamine-releasing activity. These problems were resolved in the third generation by the replacement of D-Arg at position 6 by D-ureidoalkyl amino acids. Examples of third-generation GnRH antagonists are cetorelix, iturelix, azaline B, ganirelix, abarelix, and antarelix. Their administration results in the suppression of LH (about 70%) and FSH (about 30%) serum levels after about 6 hours. GnRH antagonists may also be used in disorders or treatments in which the initial gonadotropin surge caused by GnRH agonists is undesirable. This drug is given in pill form and may be used alone or with orchiectomy or LHRH. **Cyproterone acetate (CPA)** is a steroidal, progestational antiandrogen that blocks the androgen-receptor interaction and reduces serum testosterone through a weak antigonadotropic action. CPA is also associated with a high rate of cardiovascular complications.

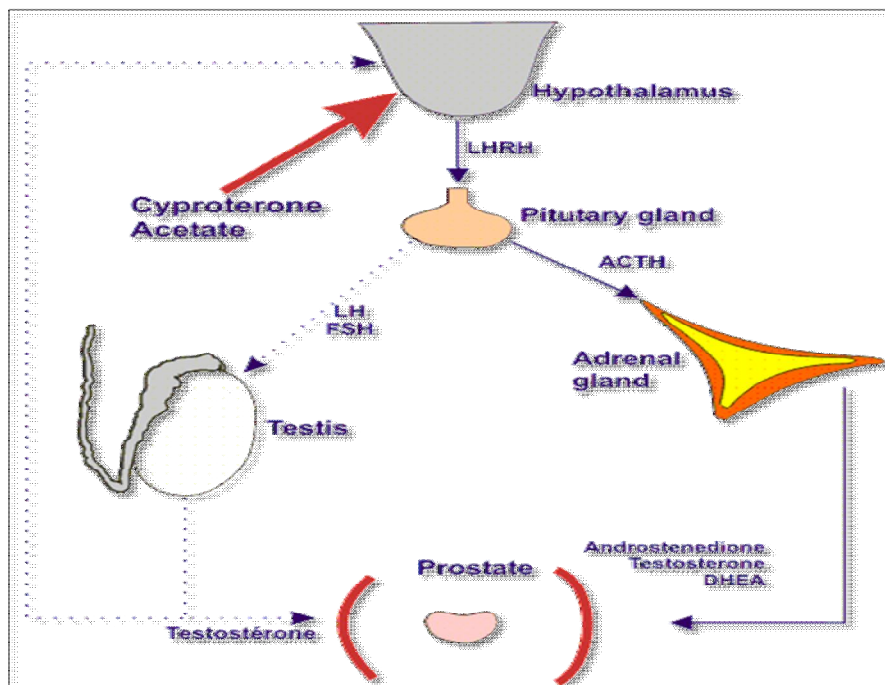


Fig. Mechanism of action of antiandrogens

#### 4. Estrogen

Estrogen is a female sex hormone that can be used in a man-made form to control the release of testosterone in men with prostate cancer. It works in two ways

- It stops the brain from telling the testicles to release testosterone.
- It acts directly on cancer cells, slowing their growth and killing some cancer cells.

Several nonsurgical options exist in achieving hormonal suppression.

Diethylstilbestrol (DES), a semisynthetic estrogen compound, was one of the first nonsurgical options for the treatment of Prostate cancer. At one time a first-line hormonal therapy, its widespread use has been limited due to significant cardiovascular and thromboembolic toxicity

#### 5. 5-Alpha reductase inhibitors [5-ARI] Drugs for Prostate Cancer Prevention

Normal and abnormal growth of the prostate is dependent on the presence of hormones and growth factors. The most important of these is testosterone which is converted within the prostate into its more active metabolite, dihydrotestosterone (DHT), by 5 $\alpha$ -reductase, a nuclear-bound steroid enzyme localized primarily in the prostatic stromal cell. This cell plays an important role in androgen-dependent prostatic growth. Two isoenzymes have been identified, each encoded by a separate gene. The

predominant enzyme in extraprostatic tissue such as the skin or liver is type one is 5 $\alpha$ -reductase. Conversely, the predominant prostatic enzyme is type two 5 $\alpha$ -reductase. This latter enzyme is critical to normal development of the prostate and hyperplastic growth later in life. Type two 5 $\alpha$ -reductase is extremely sensitive to inhibition by both finasteride as well as dutasteride, a dual type one, type two 5 $\alpha$ -reductase inhibitor. Given that several studies have demonstrated identical prostate size reduction between patients treated with finasteride as well as dual type 1, type 2 inhibitors (such as dutasteride), the role of type one derived DHT is unlikely to be clinically meaningful.

As a competitive inhibitor of type two 5 $\alpha$ -reductase, finasteride prevents the conversion of testosterone to DHT, thereby lowering both serum and intraprostatic DHT levels. A study by Norman and colleagues revealed that finasteride reduced intraprostatic DHT level by 91.4%. However, finasteride does not reduce DHT levels to castrate levels since circulating testosterone is converted to DHT by the type one isoenzyme existing in the skin and liver.

Testosterone in males is produced primarily in the testicles, but also in the adrenal glands. The majority of testosterone in the body is bound to sex hormone-binding globulin (SHBG), a protein produced in the liver that transports testosterone through the bloodstream, prevents its metabolism, and prolongs its half-life. Once it becomes unbound from SHBG, free testosterone

can enter cells throughout the body. In certain tissues, notably the scalp, skin, and prostate, testosterone is converted into 5 $\alpha$ -dihydrotestosterone (DHT) by the enzyme 5 $\alpha$ -reductase. DHT is a more powerful androgen than testosterone (as it has approximately 3-10 times the potency at the androgen receptor, the site of action of the androgen hormones), so 5 $\alpha$ -reductase can be thought to amplify the androgenic effect of testosterone in the tissues in which it's found. Finasteride, a 4-azasteroid and analogue of testosterone, works by acting as a potent and specific, competitive inhibitor of one of the two subtypes of 5 $\alpha$ -reductase, specifically the type II isoenzyme.<sup>36</sup> In other words, it binds to the enzyme and prevents endogenous substrates such as testosterone from being metabolized. 5 $\alpha$ -reductase type I and type II are responsible for approximately one-third and two-thirds of systemic DHT production, respectively.

Other 5 $\alpha$ -reductase substrates include progesterone, androstenedione, epitestosterone, cortisol, aldosterone, and deoxycorticosterone. The entire physiologic effect of their reduction is unknown, but likely related to their excretion or is itself physiologic. Beyond being a catalyst in the rate-limiting step in testosterone reduction, 5 $\alpha$ -reductase enzyme isoforms I and II reduce progesterone to dihydroprogesterone (DHP) and deoxycorticosterone to dihydrodeoxycorticosterone (DHDOC). In vitro and animal models suggest subsequent 3 $\alpha$ -reduction of DHT, DHP and DHDOC lead to steroid metabolites with effect on cerebral function by enhancing gamma-aminobutyric acid (GABA)ergic inhibition. These neuroactive steroid derivatives enhance GABA at GABA(A) receptors and have anticonvulsant, antidepressant and anxiolytic effects, and also alter sexual and alcohol related behavior. 5 $\alpha$ -dihydrocortisol is present in the aqueous humor of the eye, is synthesized in the lens, and might help make the aqueous humor itself.<sup>39</sup> Allopregnanolone and THDOC are neurosteroids, with the latter having effects on the susceptibility of animals to seizures. 5 $\alpha$ -dihydroaldosterone is a potent antidiuretic agent, although different from aldosterone. Its formation in the kidney is enhanced by restriction of dietary salt, suggesting it may help retain sodium as follows

$$\text{Substrate} + \text{NADPH} + \text{H}^+ \rightarrow 5\alpha\text{-substrate} + \text{NADP}^+$$

5 $\alpha$ -DHP is a major hormone in circulation of normal cycling and pregnant women.

By blocking DHT production, finasteride reduces androgen activity in the scalp. In the prostate, inhibition of 5 $\alpha$ -reductase reduces prostate volume, which improves benign prostatic hyperplasia (BPH) and reduces risk of prostate cancer. 5 $\alpha$ -reductase inhibition also reduces epididymal weight, and decreases motility and normal morphology of spermatozoa in the epididymis.

Although the pathophysiology of clinical BPH is not considered to be dependent on prostate size, reducing the prostate's volume is thought to decrease the constant component of bladder outlet obstruction. Furthermore, men with a prostate volume of 30 cm<sup>3</sup> or more have been shown to be 3.5 times more likely to have moderate-to-severe lower urinary tract symptoms and acute urinary retention. Therefore, by actively decreasing the size of the prostate through reduction of intraprostatic DHT, finasteride arguably plays an important role in the reduction of long-term risk of progression.

In 2009, the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA) issued a joint guideline recommending that doctors discuss the pros and cons of the use of 5-ARIs for prostate cancer prevention with men who:

- Have a PSA score of 3.0 or below
- Are being screened yearly for prostate cancer
- Do not yet show signs of prostate cancer.

ASCO/AUA also recommended that patients who already take finasteride or dutasteride for controlling urinary symptoms of BPH should talk with their doctors about continuing to take the drug for prostate cancer prevention.

The guideline is the first to recommend drug therapy for preventing prostate cancer. It was based on results of a large 7-year clinical trial that showed that finasteride reduced the overall relative risk of developing prostate cancer by about 25%. However, in this study, a few more men who took finasteride developed a high-grade aggressive form of prostate cancer than the men who did not take finasteride. More recent studies have suggested that 5-ARI drugs may not increase the risk of developing aggressive cancer. It is still unclear if finasteride is an appropriate preventive approach, and not all doctors agree with the ASCO/AUA guideline.

Finasteride and dutasteride may cause reduced sexual drive and problems with erection during the first 1 - 2 years of use. It is not yet known what the long-term effects of 5-ARIs are if they are taken for longer than 7 years.

**Pros and cons of hormone therapy**

Hormone Therapy	Pros	Cons
<b>Orchiectomy</b>	<ul style="list-style-type: none"> <li>• Controls prostate cancer as effectively as LHRH.</li> <li>• Less likely to cause breast swelling than anti-androgens/estrogens.</li> <li>• Provides permanent solution (not reversible), for those who desire it.</li> </ul>	<ul style="list-style-type: none"> <li>• Not reversible, so side effects are permanent.</li> <li>• Side effects include erectile dysfunction and hot flashes.</li> <li>• Requires surgery and local or general anaesthetic.</li> </ul>
<b>LHRH agonists</b>	<ul style="list-style-type: none"> <li>• Controls prostate cancer as effectively as orchiectomy.</li> <li>• Less likely to cause breast swelling than anti-androgens/estrogens.</li> <li>• Side effects may be lessened by switching to a different drug, or reversed by stopping treatment.</li> </ul>	<ul style="list-style-type: none"> <li>• When treatment starts, may cause a testosterone 'flare'</li> <li>• Side effects include erectile dysfunction and hot flashes.</li> <li>• Visits to GP or hospital needed every 1 to 3 months.</li> </ul>
<b>Antiandrogens</b>	<ul style="list-style-type: none"> <li>• Side effects may be improved by switching to a different drug, or reversed by stopping treatment.</li> <li>• Since testosterone is still being produced, it may be possible to maintain erections.</li> <li>• Less likely to cause osteoporosis than LHRH.</li> </ul>	<ul style="list-style-type: none"> <li>• Must be taken daily.</li> <li>• Can cause breast swelling and erectile dysfunction.</li> <li>• Less effective than LHRH in treating cancer that has spread elsewhere in body.</li> </ul>
<b>Estrogens</b>	<ul style="list-style-type: none"> <li>• If other hormone drugs are no longer effective, it is suitable for treating advanced prostate cancer.</li> <li>• Side effects may be improved by stopping treatment.</li> <li>• Less likely to cause osteoporosis and hot flashes than LHRH.</li> </ul>	<ul style="list-style-type: none"> <li>• Must be taken daily.</li> <li>• Not suitable for men with heart/ circulation problems, due to increased risk of blood clots in lungs and legs.</li> <li>• Causes erectile dysfunction and breast swelling or tenderness.</li> </ul>

**Summary**

Treatment of Prostate cancer is a challenge for both patients and clinicians. Hormonal therapy has traditionally been used for treatment of patients with distant metastases. More recently, hormone therapy has been added to radiotherapy to improve the efficacy of treatment. The general rationales for combining external radiation therapy and hormone therapy are numerous: decreasing prostate gland volume, diminishing the number of cancer cells by inducing apoptosis and eliminating distant and regional micrometastases at the time of definitive radiotherapy. Over the last 20 years several randomized clinical trials have positive results of combined hormone therapy and localized therapy in the form of RP or radiation therapy have been performed. Although the data for the use of HT with radiation therapy in low-risk Prostate cancer is not convincing, in the group of patients with high risk of relapse (T3 or GS >7 or PSA >20 ng/ml), combined hormone therapy and radiation therapy improves treatment results and should be highly recommended. Further support of the concept of combining hormonal therapy with radiation therapy in high-risk disease has been supported

by organizations such as the American Urological Association. The optimum duration of hormone therapy with radiation therapy will continue to be an area of research study.

Lastly, continuous hormonal therapy has been the norm for advanced disease. Concerns over the long-term effects of hormonal therapy in the older male have opened the possibility of 'hormonal holidays', technically known as intermittent hormonal therapy. A growing body of literature supports this concept with several smaller trials indicating at least equivalence with long-term hormonal therapy in terms of disease control. The ultimate treatment plan is an informed decision between the healthcare provider and the patient. The factors to consider in the early use of hormonal therapy are the documented and potential clinical benefits, potential toxicity and cost. It is recognized that more research is needed to guide the choice, duration, and schedule of hormonal deprivation therapy, and the impact of long-term hormone therapy with regard to toxicity and the patient's quality of life.

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