The goal of hormone therapy in men, also called androgen deprivation therapy (ADT) is to lower levels of the male hormones in the body, in order to affect the growth of cancer. Androgens, such as testosterone, which are produced mainly in the testicles, can actually stimulate prostate cancer cells to grow. ADT improves disease-free and overall survival in various clinical settings for men with prostate cancer. Lowering androgen levels can usually make a prostate cancer diminish in size or slow its growth (Smith, Egerdie, Toriz, Feldman, R., Tammela, Saad, ... & Leder, 2009).

**Hormone therapy does not cure prostate cancer and is not a substitute for curative therapy**

Hormone therapy may be used in several situations:

- As first-line therapy if an individual is not able to have surgery or radiation or cannot be cured with these treatments because the cancer has already spread beyond the prostate gland
- After initial treatment, with surgery or radiation therapy, if the cancer remains or recurs
- As an adjuvant (added to enhance medical effectiveness) to radiation therapy as initial treatment in certain groups of men at high risk for cancer recurrence
- As neo-adjuvant therapy (given prior to other treatments), in an attempt to shrink the cancer and make other treatments, such as, surgery or radiation more effective
- ADT is also commonly used in patients with an increasing prostate-specific antigen (PSA) level after primary therapy (smith, et al, 2009).

**I. Types of Hormone Therapy**

There are several methods used for androgen deprivation therapy

**Orchiectomy:**

Androgen-deprivation therapy (ADT) is the standard first-line therapy for metastatic prostate cancer and can be achieved through bilateral orchiectomy or a medical methodology. Androgen-deprivation therapy improves disease-free and overall survival in various clinical settings. Orchiectomy is a relatively simple procedure with minor surgical risks. Despite its low physical morbidity, orchiectomy has fallen out of favor given its psychological impact and viable medical alternatives for androgen deprivation, such as treatment with gonadotropin-releasing hormone (GnRH) agonists (Smith, 2009). In an orchiectomy, the surgeon removes the testicles where more than 90% of the androgens are produced. With the source of androgen production removed, most prostate cancers shrink. Orchiectomy, done as outpatient procedure, is the least expensive and least complex method to reduce androgen production. However, it is permanent, and many men have trouble accepting the removal of their testicles. For those men who elect to have the procedure, silicone prostheses that resemble testes can be inserted into the scrotal sac if they wish.
Possible side effects of orchiectomy are generally related to changing levels of androgen hormone in the body. About 90% of men who have had this operation have reduced or absent libido & impotence.

Some men also experience:

- Hot flashes
- Breast tenderness and growth of breast tissue
- Osteoporosis leading to bone fractures
- Anemia
- Decreased mental acuity
- Loss of muscle mass
- Weight gain
- Fatigue
- Decrease in HDL ("good") cholesterol
- Depression

Many of these side effects can be treated. Occasionally, the hot flashes will be improved by treatment with a group of antidepressants known as SSRI inhibitors (Alibhai, Gogov, & Allibhai, 2006). Most significantly ADT increases bone resorption, reduces bone mineral density, and increases the risk of osteoporosis and fracture in men with prostate cancer. The risk of fracture increases with increasing duration of androgen-deprivation therapy and is an important contributor to the morbidity associated with this treatment. Several drugs, including bisphosphonates (Aredia, Zometa, Fosamax) and selective estrogen-receptor modulators, have been utilized to prevent bone loss associated with androgen-deprivation therapy (Smith, et al, 2009). Denosumab, a fully human monoclonal antibody, has been found to significantly increase bone mineral density and decrease new vertebral fractures in men receiving androgen deprivation therapy for prostate cancer. In Smith, et al (2009) it was found that Denosumab significantly and consistently increased bone mineral density at all skeletal sites and in every subgroup, including men at greatest risk for bone loss and fractures.

Some approaches that may help to slow or prevent osteoporosis include:

- Taking calcium and vitamin D.
  - The recommended daily intake of calcium is 1,200 mg to 1,500 mg, and 400 to 800 IU of vitamin D.
- Exercising.
  - Regular physical activity, especially weight-bearing exercises such as jogging, dancing and stair-climbing, can help prevent bone loss. Resistance exercises, such as weight lifting, have been shown to strengthen bones.
- Use of bisphosphonates.
  - Bisphosphonates usually taken by intravenous infusion (but sometimes by mouth) can stop or even reverse osteoporosis due to hormonal therapy for
Exercise is a good way to reduce the loss of muscle mass, combat fatigue, and decrease weight gain. Resistance exercise can significantly improve muscle mass, strength, physical function, and balance in hypogonadal men. Resistance exercise regimens are usually well tolerated and should be recommended for patients undergoing ADT as an effective countermeasure to these common treatment-related adverse effects (Galvão, Taaffe, Spry, Joseph, & Newton, 2010).

Androgen deprivation therapy has been associated with numerous adverse effects, and one of the most predictable consequences of ADT is the development of anemia. Although anemia caused by ADT is rarely severe, ADT is often given to frail, elderly men with increased susceptibility to anemia due to multiple comorbid conditions. ADT associated anemia may contribute to fatigue and reduced quality of life and is an independent risk factor of mortality in men with prostate cancer. It is not known whether treatment of ADT associated anemia alters clinically important outcomes, or whether treatment affects mortality. Awareness of the phenomenon of ADT-induced anemia should avoid unnecessary work-up in mild cases of normocytic normochromic anemia as typically anemia associated with the decreased androgen level is mild and many patients remain asymptomatic. Routine CBC monitoring is suggested (Grossmann, Zajac, 2012).

**Luteinizing hormone-releasing hormone (LHRH) agonists:** Even though LHRH agonists are more expensive and require more frequent doctor visits, most men choose this method over orchiectomy. These drugs lower testosterone levels as effectively as orchiectomy by decreasing the production of androgens (Heidenreich, Bastian, Bellmunt, Bolla, Joniau, van der Kwast,... & Mottet, 2014).

Some LHRH agonists are injected or placed as small implants under the skin. They are given monthly or every 3, 4, 6, or 12 months. Some LHRH analogs currently available in the United States include:

- Leuprolide
- Goserelin
- Triptorelin

When LHRH agonists are initiated, testosterone production increases briefly before decreasing to very low levels. This effect is called a “flare” and results from the complex way in which LHRH analogs work. Men whose cancer has spread to the bones may experience bone pain. If the cancer has spread to the vertebrae, even a temporary increase in growth could compress the spinal cord and cause pain or paralysis. Flare can be avoided by giving anti-androgens (see below) prior to starting treatment with LHRH analogs and continue for the first weeks of therapy.

**Antiandrogens:**
Antiandrogens block the body's ability to use any androgens. Even after orchiectomy or during treatment with LHRH analogs, a small amount of androgen is still produced by the adrenal glands. Antiandrogens are used to block this production.

Drugs of this type:
- Flutamide (Eulexin)
- Bicalutamide (Casodex),
- Nilutamide (Nilandron),
- Enzalutamide (Xtandi)

Enzalutamide is a newer agent and has been found to have approximately a 5-to-8-fold higher binding affinity for the androgen receptor (AR) - making it a significantly more potent and effective antiandrogen in comparison to the other agents. Unlike with the earlier non-steroidal antiandrogens, there has been no evidence of hepatotoxicity or elevated liver enzymes in association with Enzalutamide treatment in clinical trials. Possible side effects of LHRH analogs are similar to those of orchiectomy, and are largely due to changes in hormone levels (Keating, 2015).

Combined androgen blockade (CAB): Some oncologists treat patients with both androgen deprivation (orchiectomy or an LHRH agonist) plus an anti-androgen. Some studies have suggested this may be more helpful than androgen deprivation alone. Most doctors are not convinced there's enough evidence that this combined therapy is better than starting with one drug alone when treating metastatic prostate cancer. (American Cancer Society (ACS), 2016).

An antiandrogen may be added if treatment with orchiectomy or an LHRH analog is no longer working by itself. If hormone therapy including an antiandrogen becomes ineffective, some men seem to benefit for a short time from simply stopping the antiandrogen. This is called the "antiandrogen withdrawal" effect, and it is uncertain why it happens. Side effects of antiandrogens in patients already treated with orchiectomy or with LHRH agonists are usually not significant. Diarrhea is the major side effect, although nausea, liver problems, and fatigue can also occur. The major difference from LHRH agonists is that antiandrogens have fewer sexual side effects (ACS, 2016).

Libido and potency can be maintained on the anti-androgens if they are used alone

Other androgen-suppressing drugs:
Estrogens, such as diethylstilbestrol (DES), were once the main alternative to orchiectomy for men with advanced prostate cancer. Because of their side effect profile which includes the potential for blood clots and breast enlargement, estrogens have been largely replaced by LHRH analogs and anti-androgens, although estrogens may be tried if androgen deprivation is no longer effective (ACS, 2016).

Current Controversies in Hormone Therapy

Many issues surrounding hormone therapy are not yet resolved, such as the best time to start and stop it and the best method of administration. Studies addressing these issues are now underway.
Treating early-stage cancer: Some oncologists have used hormone therapy instead of watchful waiting or active surveillance in men with early stage prostate cancer who do not want surgery or radiation. Studies have not found that these men live any longer than those who don’t get any treatment until the cancer progresses or symptoms develop. Because of this, hormone treatment is not usually advised for early-stage prostate cancer (ACS, 2016).

Early versus delayed treatment: For men who need (or will eventually need) hormone therapy, such as men whose PSA levels are rising after surgery or radiation or men with advanced prostate cancer who don’t yet have symptoms, it’s not always clear when it is best to start hormone treatment. Some oncologists think that hormone therapy works better if it’s started as soon as possible, even if a man feels well and is not having any symptoms. Some studies have shown that hormone treatment may slow the disease down and perhaps even help men live longer. But not all agree with this approach. Some are waiting for more evidence of benefit. They feel that because of the side effects of hormone therapy and the chance that the cancer could become resistant to therapy sooner, treatment shouldn’t be started until a man has symptoms from the cancer. This issue is being studied (ACS, 2016).

Intermittent versus continuous hormone therapy: Most prostate cancers treated with hormone therapy become resistant to this treatment over a period of months or years. Some oncologists believe that constant androgen suppression might not be needed, so they advise intermittent (on-again, off-again) treatment. The hope is that giving men a break from androgen suppression will also give them a break from side effects like decreased energy, sexual problems, and hot flashes. In one form of intermittent hormone therapy, treatment is stopped once the PSA drops to a very low level. If the PSA level begins to rise, the drugs are started again. Another form of intermittent therapy uses hormone therapy for fixed periods of time – for example, 6 months on followed by 6 months off. At this time, it isn’t clear how this approach compares to continuous hormone therapy. Some studies have found that continuous therapy might help men live longer, but other studies have not found such a difference (ACS, 2016).

Conclusion:
Prior to beginning androgen deprivation therapy (ADT), all patients should be counseled about the associated side effects, and these should be considered in the treatment planning decision-making for prostate cancer, especially in men at high risk for cardiovascular events or fractures, and for indications where a survival benefit of ADT has not been established. ADT associated adverse effects are diverse, and management of patients with prostate cancer receiving ADT should consist of an individualized, multidisciplinary approach by clinicians with specific expertise and in this area of practice. This could include experts in endocrinology, urology, radiation and medical oncology, geriatric medicine, dietetics, exercise physiotherapy, sex therapy and psychology.
References


