Hormone Therapy for Prostate Cancer

What are male sex hormones?

Hormones are substances that are made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs.

Androgens (male sex hormones) are a class of hormones that control the development and maintenance of male characteristics. The most abundant androgens in men are testosterone and dihydrotestosterone (DHT)

Androgens are required for normal growth and function of the prostate, a gland in the male reproductive system that helps make semen. Androgens are also necessary for prostate cancers to grow. Androgens promote the growth of both normal and cancerous prostate cells by binding to and activating the androgen receptor, a protein that is expressed in prostate cells (1). Once activated, the androgen receptor stimulates the expression of specific genes that cause prostate cells to grow (2).

Almost all testosterone is produced in the testicles; a small amount is produced by the adrenal glands. Although prostate cells do not normally make testosterone, some prostate cancer cells acquire the ability to do so (3).

How does hormone therapy work against prostate cancer?

Early in their development, prostate cancers need androgens to grow. Hormone therapies, which are treatments that decrease androgen levels or block androgen action, can inhibit the growth of such prostate cancers, which are therefore called castrate-sensitive prostate cancer. Such cancers may also be described as being androgen dependent, androgen sensitive, castration sensitive, or hormone sensitive.

Most prostate cancers eventually stop responding to hormone therapy and become castration (or castrate) resistant. That is, they continue to grow even when androgen levels in the body are extremely low or undetectable. In the past, these tumors were also called hormone resistant, androgen independent, or hormone refractory; however, these terms are rarely used now because the tumors are not truly independent of androgens for their growth. In fact, some newer hormone therapies have become available that can be used to treat tumors that have become castration resistant.

What types of hormone therapy are used for prostate cancer?

Hormone therapy for prostate cancer can block the production or use of androgens (4). Currently available treatments can do so in several ways:

- reducing androgen production by the testicles
- blocking the action of androgens throughout the body
- blocking androgen production (synthesis) throughout the body including by prostate cancer cells

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Androgen production in men. Drawing shows that testosterone production is regulated by luteinizing hormone (LH) and luteinizing hormone-releasing hormone (LHRH). The hypothalamus releases LHRH, which stimulates the release of LH from the pituitary gland. LH acts on specific cells in the testes to produce the majority of testosterone in the body. Most of the remaining androgens are produced by the adrenal glands. Androgens are taken up by prostate cells, where they either bind to the androgen receptor directly or are converted to dihydrotestosterone (DHT), which has a greater binding affinity for the androgen receptor than testosterone.

Treatments that reduce androgen production by the testicles. These treatments are the most commonly used hormone therapies for prostate cancer and the first type of hormone therapy that most people with prostate cancer receive. This form of hormone therapy, which is called androgen deprivation therapy, or ADT, includes:

- **Orchiectomy, a surgical procedure to remove both testicles.** Removal of the testicles, called surgical castration, can reduce the level of testosterone in the blood by 90% to 95% (5).
- **Drugs called luteinizing hormone-releasing hormone (LHRH) agonists, which prevent the pituitary gland from secreting a hormone called luteinizing hormone.** LHRH agonists, which are sometimes called LHRH analogs, are synthetic proteins that are structurally similar to LHRH and bind to the LHRH receptor in the pituitary gland. (LHRH is also known as gonadotropin-releasing hormone or GnRH, so LHRH agonists are also called GnRH agonists or GnRH analogs.)

Normally, when androgen levels in the body are low, the hypothalamus releases LHRH. This stimulates the pituitary gland to produce luteinizing hormone, which in turn stimulates the testicles to produce androgens. LHRH agonists, like the body's own LHRH, initially stimulate the production of luteinizing hormone. However, the continued presence of high levels of LHRH agonists actually causes the pituitary gland to stop producing luteinizing hormone. As a result, the testicles are not stimulated to produce androgens.

Treatment with an LHRH agonist is called medical castration or chemical castration. But unlike surgical castration (orchiectomy), medical castration is reversible. Once treatment is stopped, androgen production usually resumes.

LHRH agonists are given by injection or are implanted under the skin. LHRH agonists that are approved to treat prostate cancer in the United States include leuprolide (Lupron Depot, Eligard, Camcevi), goserelin (Zoladex), and triptorelin (Trelstar).

When patients receive an LHRH agonist for the first time, they may experience a phenomenon called "testosterone flare." This is a temporary increase in testosterone level that occurs because LHRH agonists briefly cause the pituitary gland to secrete extra luteinizing hormone before blocking its release. The flare may worsen clinical symptoms (such as bone pain, ureter or bladder outlet obstruction, and spinal cord compression).

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- **Drugs called LHRH antagonists, which are another form of medical castration.** LHRH antagonists (also called GnRH antagonists) prevent LHRH from binding to its receptors in the pituitary gland. This in turn prevents the secretion of luteinizing hormone, which stops the testicles from producing androgens. Unlike LHRH agonists, LHRH antagonists do not cause a testosterone flare.

  LHRH antagonists that are approved to treat advanced prostate cancer in the United States include degarelix (Firmagon), which is given by injection, and relugolix (Orgovyx), which is a pill that is taken by mouth.

Treatments that block the action of androgens in the body, called antiandrogen therapies, androgen receptor blockers, or androgen receptor antagonists. Such treatments work by competing with androgens for binding to androgen receptors. By keeping androgens from binding to androgen receptors, these treatments reduce the ability of androgens to promote prostate cancer cell growth.

Androgen receptor blockers are typically used together with ADT (orchiectomy or an LHRH agonist) because the combination both reduces androgen levels and keeps any remaining androgen from binding to androgen receptors. The combination is often referred to as combined androgen blockade, complete androgen blockade, maximal androgen blockade, or total androgen blockade. In addition to being used as hormone therapy for prostate cancer, androgen receptor blockers are sometimes used for a few weeks at the start of ADT to prevent testosterone flares.

Androgen receptor blockers that are approved in the United States to treat prostate cancer include the "first-generation" drugs flutamide, bicalutamide (Casodex), and nilutamide (Nilandron), and the "second-generation" drugs enzalutamide (Xtandi), apalutamide (Erleada), and darolutamide (Nubeqa). The second-generation drugs bind to and block the androgen receptor more strongly and specifically than the first-generation drugs (6). Darolutamide is the only androgen receptor blocker that does not cross the blood-brain barrier in humans, which may result in fewer central nervous system–related side effects. Androgen receptor blockers are given as pills to be swallowed.

Treatments that block the production of androgens throughout the body, known as androgen synthesis inhibitors. Like ADT, androgen synthesis inhibitors prevent androgen production by the testicles; unlike ADT they also prevent androgen production by the adrenal glands and prostate cancer cells. Even though only small amounts of androgens are produced outside the testicles, the low levels that are still produced can be enough to support the growth of some prostate cancers.

Androgen synthesis inhibitors lower testosterone levels to a greater extent than any other known treatment. They do so by inhibiting an enzyme called CYP17. This enzyme, which is found in testicular, adrenal, and prostate tumor tissues, is necessary for the body to produce testosterone.

Androgen synthesis inhibitors approved in the United States include abiraterone (Yonsa, Zytiga) and ketoconazole. Both are given as pills to be swallowed.

Abiraterone is used in combination with prednisone to treat metastatic prostate cancer, both castration-sensitive and castration-resistant. Ketoconazole is approved for indications other than prostate cancer but is sometimes used off-label as second-line treatment for castration-resistant prostate cancer, although such use is rare given the availability of second-generation androgen receptor blockers.

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How is hormone therapy used to treat castration-sensitive prostate cancer?

Hormone therapy may be used in several ways to treat castration-sensitive prostate cancer, including for:
Early-stage prostate cancer with an intermediate or high risk of recurrence. Men who are having radiation therapy to treat early-stage prostate cancer that has an unfavorable intermediate or high risk of recurrence often receive ADT as well. And ADT may be used after prostatectomy in men who have high-risk node-positive disease (7, 8).

Relapsed/recurrent prostate cancer. Hormone therapy is often used alone for people who have a recurrence of prostate cancer after earlier treatment with radiation or surgery. Hormone therapy is standard treatment for those who have a symptomatic recurrence (as documented by CT, MRI, PSMA PET scan, or bone scan) and may also be recommended for some people who have a "biochemical recurrence" (a rise in prostate-specific antigen [PSA] level after treatment with surgery or radiation), especially if the PSA level is rising rapidly.

Advanced or metastatic prostate cancer. ADT used alone was for many years the standard treatment for men who, at the time of their initial prostate cancer diagnosis, are found to have castration-sensitive metastatic disease (i.e., disease that has spread to other parts of the body) (9). Now, such men are treated with ADT plus another type of hormone therapy (abiraterone, enzalutamide, or apalutamide) or ADT plus the chemotherapy drug docetaxel (Taxotere) and a second-generation androgen receptor blocker, such as abiraterone or darolutamide. Some of these men, especially those with extensive metastases, may be treated with ADT plus chemotherapy plus another type of hormone therapy (10).

Although hormone therapy can delay progression of metastatic disease and may extend survival, it can also have side effects. Men should discuss the risks and potential benefits of hormone therapy with their doctors and potential ways to reduce some side effects.

Palliation of symptoms. Hormone therapy is sometimes used alone for palliation or prevention of local symptoms in men with localized prostate cancer who are not candidates for surgery or radiation therapy (11). Such men include those with a limited life expectancy, those with locally advanced tumors, and/or those with other serious health conditions.

How will I know that my hormone therapy is working?

Doctors cannot predict how long hormone therapy will be effective in suppressing the growth of any individual man's prostate cancer. Therefore, men who take hormone therapy for more than a few months are regularly tested to determine the level of PSA in their blood. An increase in PSA level may indicate that a man's cancer has started growing again or become resistant to the hormone therapy that is currently being used.

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How is castration-resistant prostate cancer treated?

Treatments for castration-resistant prostate cancer include:

- Complete androgen blockade—that is, androgen deprivation therapy plus an androgen receptor blocker (flutamide, bicalutamide, nilutamide, apalutamide, darolutamide, or enzalutamide).
- Androgen synthesis inhibition with abiraterone.
- Chemotherapy, most commonly with docetaxel. Another chemotherapy drug, cabazitaxel (Jevtana), is approved for the treatment of metastatic castration-resistant prostate cancer that was previously treated with docetaxel.
- Radiopharmaceuticals, including radium-223 dichloride (Xofigo) and lutetium Lu-177 vipivotide tetraxetan (Pluvicto). Radium-223 collects in areas of bone that are undergoing increased turnover (bone resorption coupled with bone formation), such as where bone metastases are forming, and gives off radiation that kills cancer cells. Lutetium Lu-177 vipivotide tetraxetan targets and binds to prostate cells and delivers radiation that kills them.
- Drugs called PARP inhibitors. The PARP inhibitors rucaparib (Rubraca), olaparib (Lynparza), talazoparib (Talzenna), and niraparib in combination with abiraterone (Akeega) are approved to treat metastatic castration-resistant prostate cancers that have certain genetic changes that disrupt DNA repair in the cancer cells.
- Immunotherapy using a cell-based vaccine called sipuleucel-T (Provenge). This vaccine uses a man's own immune cells to fight metastatic prostate cancer that has few or no symptoms.

People with castration-resistant prostate cancer who receive these treatments will continue to receive ADT (e.g., an LHRH agonist) to keep testosterone levels low, because an increase in testosterone could lead to tumor progression in some men (12).

What is intermittent ADT?

Researchers have investigated whether a technique called intermittent androgen deprivation can delay the development of hormone resistance. With intermittent androgen deprivation, hormone therapy is given in cycles with breaks between drug administrations rather than continuously, particularly in people with a biochemical recurrence. The goal of intermittent androgen deprivation is to delay the development of hormone resistance. An additional potential benefit of this approach is that the temporary break from the side effects of hormone therapy may improve a man's quality of life. No trials have compared intermittent ADT with continuous ADT.

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What are the side effects of hormone therapy for prostate cancer?

Because androgens affect many other organs besides the prostate, ADT can have a wide range of side effects (4, 13), including:

- loss of interest in sex (lowered libido)
- erectile dysfunction
- hot flashes
- loss of bone density
- bone fractures
- loss of muscle mass and physical strength
- changes in blood lipids
- insulin resistance
- weight gain
- mood swings
- fatigue
- growth of breast tissue (gynecomastia)

Antiandrogens can cause diarrhea, breast tenderness, nausea, hot flashes, loss of libido, and erectile dysfunction. The antiandrogen flutamide may damage the liver, and enzalutamide and apalutamide may cause fractures. Darolutamide may avoid some central nervous system–related side effects seen with enzalutamide and apalutamide, such as seizures and falls.

Androgen synthesis inhibitors can cause diarrhea, itching and rashes, fatigue, erectile dysfunction (with long-term use), and, potentially, liver damage.

Although the addition of ADT to radiation therapy has been shown to increase survival for men with high-risk prostate cancer, it worsens some adverse effects of radiotherapy, particularly sexual side effects and vitality (14). The risk of side effects increases the longer a person is on hormone therapy (13).

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What can be done to reduce the side effects of hormone therapy for prostate cancer?

Men who lose bone mass during long-term hormone therapy may be prescribed drugs to slow or reverse this loss. The drugs zoledronic acid (Zometa) and alendronate (Fosamax) (both of which belong to a class of drugs called bisphosphonates) can be used to increase bone mineral density in men who are undergoing hormone therapy (15, 16), as can a newer drug, denosumab (Prolia), which increases bone mass through a different mechanism (17). However, drugs to treat bone loss are associated with a rare but serious side effect called osteonecrosis of the jaw (12).

Exercise may help reduce some of the side effects of hormone therapy, including bone loss, muscle loss, weight gain, fatigue, and insulin resistance (12, 18). Several clinical trials are examining whether exercise can reverse or prevent side effects of hormone therapy for prostate cancer.

The sexual side effects of hormone therapy for prostate cancer can be some of the most difficult to deal with. Erectile dysfunction drugs such as sildenafil (Viagra) do not usually work for men undergoing hormone therapy because these drugs do not address the loss of libido (sexual desire) that is associated with a lack of androgens.

Most of the sexual and emotional side effects caused by low levels of androgens will eventually go away if a man stops taking hormone therapy. However, particularly for older men and those who received ADT for a long time, testosterone levels may not fully recover and these side effects may not disappear completely. Some physical changes that have developed over time, such as bone loss, will remain after stopping hormone therapy.

Patients should be sure to tell their doctor about all medications and supplements they are taking, including over-the-counter herbal medicines. Some herbal medicines interact with drug metabolizing enzymes in the body, which can adversely affect hormone therapy (19).

Source: *National Cancer Institute, "Hormone Therapy for Prostate Cancer";*

https://www.cancer.gov/types/prostate/prostate-hormone-therapy-fact-sheet

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