

Hormone (Androgen Deprivation) Therapy For Prostate Cancer

Hormone therapy is also called *androgen deprivation therapy* (ADT). The goal is to reduce levels of male hormones, called *androgens*, in the body, or to prevent them from reaching prostate cancer cells.

The main androgens are testosterone and dihydrotestosterone (DHT). Androgens, which are made mainly in the testicles, stimulate prostate cancer cells to grow. Lowering androgen levels or stopping them from getting into prostate cancer cells often makes

prostate cancers shrink or grow more slowly for a time. However, hormone therapy alone does not cure prostate cancer. Hormone therapy may be used:

- If you are not able to have surgery or radiation or can't be cured by these treatments because the cancer has already spread beyond the prostate gland
- If your cancer remains or comes back after treatment with

surgery or radiation therapy

- Along with radiation therapy as initial treatment if you are at higher risk of the cancer coming back after treatment (based on a high Gleason score, high PSA level, and/or growth of the cancer outside the prostate)
- Before radiation to try to shrink the cancer to make treatment

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Medical Advisors

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Thanks!

Next meeting: March 20, 2014
Pat Trozzo, Pharmacist, CC MB
Topic: PCa Drugs: What's New,
What's Approved and ... What's Coming.
Location: Main Floor Auditorium
Seven Oaks General Hospital
Leila and McPhillips
Time: 7 to 9 p.m.



The Manitoba Prostate Cancer Support Group does not recommend treatment modalities, medications, or physicians.

Thought of The Day

What was the best thing before sliced bread?

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more effective

Types of hormone therapy:

Orchiectomy (surgical castration)

Even though this is a type of surgery, its main effect is as a form of hormone therapy. In this operation, the surgeon removes the testicles, where most of the androgens (testosterone and DHT) are made. With this source removed, most prostate cancers stop growing or shrink for a time.

This is done as a simple outpatient procedure. It is probably the least expensive and simplest way to reduce androgen levels in the body. But unlike some of the other methods of lowering androgen levels, it is permanent, and many men have trouble accepting the removal of their testicles.

Some men having the procedure are concerned about how it will look afterward. If wanted, artificial silicone sacs can be inserted into the scrotum. These look much like testicles.

Luteinizing hormone -releasing hormone (LHRH) analogs

These drugs lower the amount of testosterone made by the testicles. Treatment with these drugs is sometimes called *chemical castration* because they lower androgen levels just as well as orchiectomy.

Even though LHRH analogs (also called *LHRH agonists*) cost more than orchiectomy and require more frequent doctor visits, most men choose this method. These drugs allow the testicles to remain in place, but the testicles will shrink over time, and they may even become too small to feel.

LHRH analogs are injected or placed as small implants under the skin. Depending on the drug used, they are given anywhere from once a month up

to once a year. The LHRH analogs available in the United States include leuprolide (Lupron®, Viadur®, Eligard®), goserelin (Zoladex®), triptorelin (Trelstar®), and histrelin (Vantas®).

When LHRH analogs are first given, testosterone levels go up briefly before falling to very low levels. This effect is called *flare* and results from the complex way in which LHRH analogs work. Men whose cancer has spread to the bones may have bone pain. If the cancer has spread to the spine, even a short-term increase in growth could compress the spinal cord and cause pain or paralysis. Flare can be avoided by giving drugs called *anti-androgens* for a few weeks when starting treatment with LHRH analogs. (Anti-androgens are discussed further on.)

Luteinizing hormone -releasing hormone (LHRH) antagonists

LHRH antagonists work like LHRH agonists, but they reduce testosterone levels more quickly and do not cause tumor flare like the LHRH agonists do.

Degarelix (Firmagon®) is an LHRH antagonist used to treat advanced prostate cancer. It is given as a monthly injection under the skin and quickly reduces testosterone levels. The most common side effects are problems at the injection site (pain, redness, and swelling) and increased levels of liver enzymes on lab tests. Other side effects are discussed in detail below.

Anti-androgens

Anti-androgens block the body's ability to use any androgens. Even after orchiectomy or during treatment with LHRH analogs, the adrenal glands still make small amounts of androgens.

Drugs of this type, such as flutamide (Eulexin®), bicalutamide (Casodex®), and nilutamide (Nilandron®), are taken daily as pills.

Anti-androgens are not often used by themselves. An anti-androgen may be

added to treatment if orchiectomy or an LHRH analog is no longer working by itself. An anti-androgen is sometimes given for a few weeks when an LHRH analog is first started to prevent a tumor flare.

Anti-androgen treatment may be combined with orchiectomy or LHRH analogs as first-line hormone therapy. This is called *combined androgen blockade* (CAB). There is still some debate as to whether CAB is more effective in this setting than using orchiectomy or an LHRH analog alone. If there is a benefit, it appears to be small.

Some doctors are testing the use of anti-androgens *instead of* orchiectomy or LHRH analogs. Several recent studies have compared the effectiveness of anti-androgens alone with that of LHRH agonists. Most found no difference in survival rates, but a few found anti-androgens to be slightly less effective.

If hormone therapy including an anti-androgen stops working, in some men the cancer will stop growing for a short time from simply stopping the anti-androgen. Doctors call this the *anti-androgen withdrawal* effect, although they are not sure why it happens.

Other androgen-suppressing drugs

Estrogens (female hormones) were once the main alternative to orchiectomy for men with advanced prostate cancer. Because of their possible side effects (including blood clots and breast enlargement), estrogens have been largely replaced by LHRH analogs and anti-androgens. Still, estrogens may be tried if androgen deprivation is no longer working.

Ketoconazole (Nizoral®), first used for treating fungal infections, blocks production of androgens. It is most

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often used to treat men just diagnosed with advanced prostate cancer who have a lot of cancer in the body, as it offers a quick way to lower testosterone levels. It can also be tried if other forms of hormone therapy are no longer effective.

Ketoconazole can block the production of cortisol, an important steroid hormone in the body. People treated with ketoconazole often need to take a corticosteroid (like hydrocortisone) to prevent the side effects caused by low cortisol levels.

Newer forms of hormone therapy

Researchers have developed newer forms of hormone therapy in recent years that may prove to be more effective than some of those now in use.

Abiraterone (Zytiga®): Drugs such as LHRH agonists can stop the testicles from making androgens, but other cells in the body, including prostate cancer cells themselves, can still make small amounts, which may fuel cancer growth. Abiraterone blocks an enzyme called CYP17, which helps stop these cells from making certain hormones, including androgens.

Abiraterone is used mainly in men with advanced prostate cancer that is still growing despite low testosterone levels (from LHRH agonists or orchiectomy), and who have already been treated with the chemotherapy drug docetaxel (Taxotere®). Abiraterone has been shown to shrink tumors, lower PSA levels, and help these men live longer. Doctors are now looking to see if this drug might be helpful earlier in the course of the disease as well.

This drug is taken as a pill every day. Because abiraterone lowers the level of certain other hormones in the body, prednisone (a cortisone-like drug) needs to be taken as well during treatment.

Other new drugs: Several other new medicines, including Enzalutamide, have shown promise in early studies. They are

now being tested against prostate cancer, but are only available through clinical trials at this time.



Possible side effects of hormone therapy

Orchiectomy, LHRH analogs, and LHRH antagonists can all cause similar side effects due to changes in the levels of hormones such as testosterone and estrogen. These side effects can include:

- => Reduced or absent libido (sexual desire)
- => Impotence (erectile dysfunction)
- => Hot flashes, which may get better or even go away with time
- => Breast tenderness and growth of breast tissue
- => Osteoporosis (bone thinning), which can lead to broken bones
- => Anemia (low red blood cell counts)
- => Decreased mental sharpness
- => Loss of muscle mass
- => Weight gain
- => Fatigue
- => Increased cholesterol
- => Depression

Some research has suggested that the risk of high blood pressure, diabetes, strokes, heart attacks, and even death from heart disease is higher in men treated with hormone therapy, although not all studies have found this.

Anti-androgens have similar side effects. The major difference from LHRH agonists and orchiectomy is that anti-androgens may have fewer sexual side effects. When these drugs are used alone, libido and potency can often be maintained. When these drugs are given to men already being treated with LHRH agonists, diarrhea is the major side effect. Nausea, liver problems, and tiredness can also occur.

Abiraterone does not usually cause major side effects, although it can cause joint or muscle pain, high blood pressure, fluid buildup in the body, hot flashes, upset stomach, and diarrhea.

Many side effects of hormone therapy can be prevented or treated. For example:

Hot flashes can often be helped by treatment with certain antidepressants.

Brief radiation treatment to the breasts can help prevent their enlargement, but it is not effective once breast enlargement has occurred.

Several different drugs are available to help prevent and treat osteoporosis.

Depression can be treated by antidepressants and/or counseling.

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Exercise can help reduce many side effects, including fatigue, weight gain, and the loss of bone and muscle mass.

There is growing concern that hormone therapy for prostate cancer may lead to problems with thinking, concentration, and/or memory. But this has not been studied well in men getting hormone therapy for prostate cancer. Studying

the possible effects of hormone therapy on brain function is hard, because other factors may also change the way the brain works. A study has to take all of these factors into account. For example, both prostate cancer and memory problems become more common as men get older. Hormone therapy can also lead to anemia, fatigue, and depression – all of which can affect brain function. Still, hormone therapy

does seem to lead to memory problems in some men. These problems are rarely severe, and most often affect only some types of memory. More studies are being done to look at this issue.

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New Drugs for Advanced PCa

Source: The Digital Examiner: PCCN Calgary

For many years, men with rising PSA and metastasis after primary treatment (surgery, radiation, hormone therapy, etc.) have essentially had only three options to choose from: 1) salvage radiation or surgery, 2) chemotherapy with Taxotere (docetaxel), or 3) do nothing and let their prostate cancer run its course. Since I was diagnosed with high risk advanced prostate cancer 6½ years ago and joined our PCCN-Calgary Warriors Group, I have seen men choose each of these options. Their experience and journeys have varied.

Salvage therapies are initially effective for many men with rising PSA, but often the disease recurs a second time and more aggressive treatments are needed. Taxotere was the first drug to provide a survival benefit in Prostate Cancer – albeit short – just 3 to 4 months median improvement. For some men, the survival has been much longer than 4 months. However, for others with aggressive disease, one has to wonder if there was any benefit given the short duration of effectiveness and the side effects experienced.

With recent advances in drug development, the options for men with advanced PCa have really increased and there are many new drugs on the

horizon and in clinical trial. Over the last couple of years, we've had Warriors participate in several Phase III clinical research trials through the Tom Baker Centre. Phase III trials are the final phase of testing for approval of a new drug. Typically, these Phase III trials are conducted at multiple centres around the world. Men are randomized to either the candidate drug or to a control drug or placebo. The protocol for a Phase III trial is very well defined. The trial is "blinded" so that neither the patient nor their oncologist knows who is receiving the drug versus the control. The outcomes for success are very well defined – typically overall survival, cancer specific survival, progression free survival, etc. The results of the trial are independently monitored.



A couple of years ago, several Calgary Warriors participated in a post-chemotherapy Phase 3 trial for Zytiga (also known as abiraterone). Several men had a very good response, with

reductions in their PSA and reduced bone pain. Eventually, they did develop resistance to the drug. Zytiga is now routinely available to men who have failed chemotherapy, and is increasingly being offered to men pre-chemotherapy.

In June, Health Canada approved Xtandi for the treatment of men with metastatic castration-resistant prostate cancer in the setting of medical or surgical castration and already received chemotherapy. This past week, Warriors learned of exciting news from the Independent Data Monitoring Committee (IDMC) for the Phase 3 PREVAIL Trial of Xtandi (also known as enzalutamide or MDV3100). This trial involved more than 1,700 men world-wide with metastatic prostate cancer that had progressed despite androgen deprivation therapy and who have not yet received chemotherapy.

Given the observed benefits in the PREVAIL trial's co-primary endpoints 1) overall survival and 2) radiographic progression-free survival, and 3) also considering the observed safety profile of Xtandi, the IDMC concluded Xtandi demonstrated a favorable benefit-risk ratio. The IDMC recommended the PREVAIL study be stopped and patients treated with placebo be offered Xtandi. The IDMC

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informed the companies developing Xtandi that: Patients treated with Xtandi demonstrated a statistically significant overall survival advantage compared with patients receiving placebo. Xtandi provided a 30% reduction in risk of death compared with placebo.

Patients treated with Xtandi demonstrated a statistically significant radiographic progression-free survival advantage compared with patients receiving a placebo. Xtandi provided an 81% reduction in risk of radiographic progression or death compared with placebo. Given the overall survival benefit and the observed safety profile, the IDMC considered the overall benefit-risk ratio to favor the Xtandi arm and recommended unequivocally that patients receiving placebo be offered treatment with Xtandi. Medivation, the developer of the drug, and Astellas have said they will initiate

meetings with and submissions to regulatory agencies beginning in early 2014. In the meantime, Astellas Pharma is offering men in Canada opportunity to obtain the drug through an advanced access program.

Our Calgary Warriors are truly excited about these results for Xtandi. I personally have participated in the PREVAIL trial and was lucky to be randomized to the drug. I've responded extremely well and feel great. Further good news is that several Calgary Warriors have recently qualified to receive Xtandi through their medical oncologist at the Tom Baker Centre.

Xtandi's Mechanism of Action

Xtandi is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Xtandi has been shown to competitively inhibit androgen binding to androgen receptors, and inhibit androgen receptor nuclear translocation and interaction with DNA.

Drugs in the Research Pipeline

There's even many more promising new drugs in the re-search pipeline. Over the next 3 – 5 years, I think we can safely say we will have a full armament of new drugs available pre-chemo, post-chemo, bone health, etc. The challenge for urologists and oncologists will be to figure out the most advantageous sequence for administration. Medivation, the developer of Xtandi, and Astellas Pharma, the international marketer, have said they will initiate meetings with regulatory agencies to seek approval for Xtandi in the pre-chemotherapy setting. Meanwhile, Astellas is offering Xtandi in Canada to men that qualify through an early access program.

*Submitted by Stewart Campbell,
PCCN Calgary Warriors
November 2013*

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Definition of mCRPC by Urologists and Oncologists

Source: Urological Oncology

What are the knowledge gaps regarding current approaches to the management of patients with castration-resistant prostate cancer (CRPC)? Are there practice differences among urologists and oncologists? How confident are physicians in their understanding of the best methods for identifying, treating, and managing patients with CRPC?

How do you define CRPC?

We asked 101 urologists and 104 oncologists and we found significant differences between the two specialties when it came to defining CRPC.

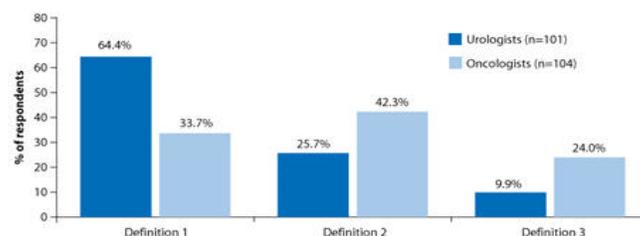
Specifically, we asked: How do you define Castration-Resistant Prostate Cancer (CRPC)?

1. Progression marked by elevation of PSA despite ongoing androgen deprivation treatment (ADT)
2. Progression marked by elevation of PSA, new metastases, progression of existing metastases despite confirmation of castrate levels of testosterone
3. Progression marked by elevation of PSA, new metastases, progression of existing metastases despite ongoing ADT

We found that almost twice as many urologists (64.45%) than oncologists (33.7%) defined CRPC as progression marked by elevated PSA levels

despite ADT. Oncologists, on the other hand, were more likely to define CRPC more narrowly, by requiring confirmation of castrate levels of testosterone (42.3% of oncologists versus only 25.7% of urologists). Only 9.9% of urologists and 24% of oncologists selected the third option, defining CRPC as progression marked by elevation of PSA, new metastases, progression of existing metastases despite ongoing ADT.

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Effect of Exercise on Prostate Cancer Patients

MONDAY, Jan. 20, 2014 (HealthDay News) - A new study offers a possible explanation of how exercise may improve outcomes for prostate cancer patients. It's known that prostate cancer patients who are more active have a lower risk of cancer recurrence and cancer death than those who get little or no physical activity, but the reasons for this are unclear.

In this study, researchers looked at 572 prostate cancer patients and found that those who walked at a faster pace before their diagnosis had more regularly shaped blood vessels in their prostate tumors than those who walked slowly.

Specifically, men with the fastest

walking pace (3.3 miles to 4.5 miles per hour) before diagnosis had 8 percent more regularly shaped blood vessels than those with the slowest walking pace (1.5 miles to 2.5 miles per hour), according to the study.

The new findings were scheduled for presentation this week at the American Association for Cancer Research - Prostate Cancer Foundation conference, in San Francisco.

"Prior research has shown that men with prostate tumors containing more regularly shaped blood vessels have a more favorable prognosis compared with men with prostate tumors containing mostly irregularly shaped blood vessels," study author Erin Van Blarigan, an assistant professor in the department of

epidemiology and biostatistics at the University of California, San Francisco, said in an AACR news release.

"Our findings suggest a possible mechanism by which exercise may improve outcomes in men with prostate cancer," Van Blarigan added. "Although data from randomized, controlled trials are needed before we can conclude that exercise causes a change in vessel regularity or clinical outcomes in men with prostate cancer, our study supports the growing evidence of the benefits of exercise, such as brisk walking, for men with prostate cancer."

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Urinary Incontinence: Embarrassing and Life-Limiting

Many men focus on erectile dysfunction as the major complication of radical prostatectomy for prostate cancer. They're wrong. Recovery of urinary control is far more important, and if that happens slowly, or never happens at all, urinary incontinence will cast a far greater shadow on their lives than impotence would. Hence, many men are surprised and embarrassed by the urinary incontinence they typically encounter following prostate surgery.

Although the urinary incontinence itself isn't life threatening, the stigma attached to wet clothing and offensive odor can have profound consequences that may lead to humiliation and social withdrawal.

How common is incontinence following a radical prostatectomy? At medical centers of excellence, incidence of serious urinary incontinence appears to be low, in the 3 percent range. However, if you look

at overall national patient survey data, the urinary incontinence numbers are dramatically higher, in the range of 50 to 60 percent.

The reason urinary incontinence develops is because the healthy tissue responsible for urinary control is at high risk during a prostate procedure due to its nearness to the prostate itself. Surgically removing the prostate entails separating the part of the urethra that passes through the prostate at the point where it joins the remaining sphincter located just downstream. It also may mean removal of part of the sphincter muscles when the tumor is extensive and possible damage to the nerves that control sphincter action if the operation is difficult to perform because of prostatic size or variations in anatomy.

Experienced surgeons are certainly aware of these technical aspects of the surgery

and generally keep this in mind when counseling patients about the relative safety of radical prostatectomy as opposed to other forms of treatment for the disease.



The good news. Most urinary incontinence, fortunately, is temporary. As the pelvic floor that supports the bladder heals and the external sphincter muscle that controls urine flow becomes more efficient, continence typically returns within a few weeks or months after catheter removal. The time frame varies, depending on the extent of the surgery, your age, and the surgeon's experience in rebuilding the urinary tract and preserving the urinary sphincter.

Source: Johns Hopkins Health Alerts, November 2013

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Cancer: Stress and Anxiety

The challenges and changes that cancer brings can make people with cancer, their caregivers or loved ones feel stressed and anxious. Anxiety is a very common response to a cancer diagnosis. When you're stressed, you may feel nervous or like you can't turn off your thoughts.

Symptoms of stress and anxiety include:

- => excessive worrying
- => muscle tension
- => trouble sleeping or getting => too much sleep
- => restlessness
- => fast heartbeat, trembling, shortness of breath, chest tightness, nausea, dizziness or high blood pressure
- => tiredness or exhaustion
- => trouble concentrating
- => irritability
- => impatience

People can have different levels of stress and anxiety, from a lower level to a higher level, depending on their situation or how they perceive it.

Anxiety may be highest when a person is waiting for test results, at the time of diagnosis or while waiting for treatment to start. People may also feel anxious:

- => when treatment needs to be changed or when it finishes
- if cancer does not respond to treatment
- => when they have physical changes or challenges because of cancer or its treatment
- => when they have severe pain
- => if they don't have enough support from others as a side effect of some medicines



These tips may help you manage stress and anxiety:

- => Try to figure out what makes you feel anxious.
- => Talk with someone you trust.
- => Spend time with people who make you laugh.
- => Think about what's important and try to manage your time by making a realistic list of things to do each day. Try to create some balance in your life. Make sure to include things that you enjoy.
- => Decide how much you want to know about your situation. Some people can ease their anxiety by learning more about cancer and its treatment. Others feel best if they just follow the plan their healthcare team gives them and don't ask extra questions.
- => Keep a journal or diary during treatment. Writing down thoughts and feelings can help relieve anxiety. A journal is also a good place to write positive feelings, so you can look at them again when you feel low.
- => Try meditation,

relaxation techniques or regular exercise to help manage stress.

=> Eat a healthy diet, get enough sleep and be active.

=> Cut down on drinks containing caffeine, such as coffee, tea or cola drinks.

Switch to decaffeinated drinks.

=> Look at support or resources available to help cope with and relieve anxiety. Sometimes talking to someone who has had a similar cancer experience can be very helpful.

The treatment for anxiety will depend on how it affects a person's daily life. Sometimes the symptoms of stress and anxiety can be very severe. Talk to the doctor or healthcare team if you feel stressed or anxious most of the time. They may:

- => suggest a class that teaches people how to manage stress
- => refer you to a social worker, counsellor or other mental health expert
- prescribe anti-anxiety drugs

Source: Canadian Cancer Society

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Credit card donations can be made by going to our website at www.manpros.org and clicking on the donate tab. Canada Helps will issue a tax receipt.



Our Support Group attends a number of Health Fairs in order to give prostate cancer information to the public. Shown here are (L to R) Bob Weiss - volunteer; Kirby Hay – MPCSG Board member; and Alan Lowe – volunteer. We appreciate the time you spent and your commitment. We especially thank Kirby for locating and carrying along all the materials to set up the table. Way to go, guys!

Email - manpros@mts.net

ALL MEMBER INFORMATION IS KEPT CONFIDENTIAL

Answering Machine - (204) 989-3433

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MEETINGS

March 20, 2014

Pat Trozzo, Pharmacist, CCMB
 Topic : PCa Drugs: What's New,
 What's Approved and ... What's Coming

April 17, 2014

Dr. Graham Glezerson, Urologist
 Topic: TBA

May 15, 2014

John Dyck
 Topic: HIFU Treatment: My Story

All meetings are held at
 Seven Oaks General Hospital Auditorium
 7-9 p.m.
 Everyone welcome

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