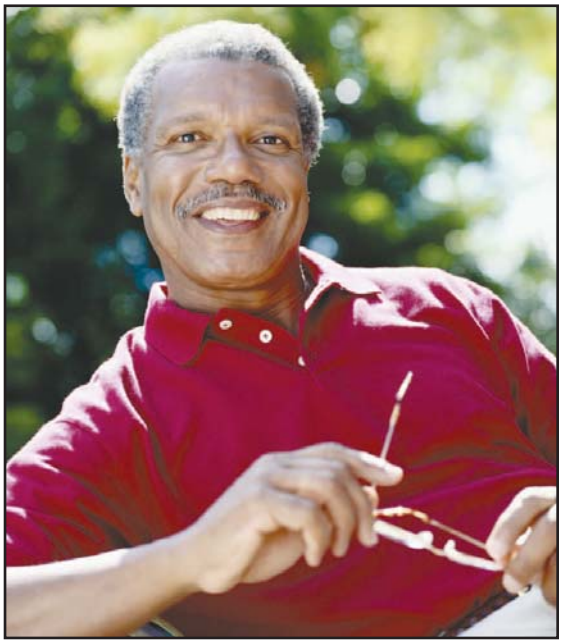
Manipulating Hormones:

Androgen Suppression in Prostate Cancer Patients



By D. Robert Siemens, MD, FRCSC

In this article:

1. How are androgens regulated?
2. What are the methods of androgen suppression?
3. What are the unanswered questions about androgen suppression?
4. What is the expanding role of hormonal manipulation in prostate cancer?

In Canada, prostate cancer is the most commonly diagnosed cancer in men with approximately 18,200 new cases diagnosed and 4,316 deaths in 2002. Although prostate specific antigen (PSA) testing allows for earlier diagnosis, still nearly 30% of newly diagnosed men will be found to have advanced cancer. At least 25% of all patients will eventually die from their disease. For more than half a century the mainstay of palliation for advanced prostate cancer has been the withdrawal of androgens. There is still no curative treatment for metastatic disease. The role of androgen suppression, however, has expanded dramatically in the treatment of prostate cancer.

Case

A 62-year old man presents with complaints of significant voiding troubles over the last few years. He has had some new onset lower back and right hip pain. On examination, he has percussion tenderness over his lumbar vertebrae. Digital rectal examination reveals a large, hard prostate. Results from a prostate specific antigen come back at 108 ng/mL.

See case discussion on page 117.

How are androgens regulated?

The synthesis of testosterone is described in Figure 1. Although the androgen receptor does have an affinity for testosterone, the androgen that plays the most dominant role in the prostate is actually 5-dihydrotestosterone (DHT). Most DHT is formed in the prostate gland by 5- α reductase.

The control of testosterone production in the testicle is coordinated through the hypothalamic-pituitary axis (Figure 2). Luteinizing hormone-

releasing hormone (LHRH) is released by the hypothalamus in a pulsatile fashion, resulting in the appropriate secretion of luteinizing hormone (LH) by the pituitary. LH then stimulates the production of testosterone in the testicle. Negative feedback to the axis is accomplished mostly by serum testosterone.

The complete testosterone pathway described in Figure 1 is present only in the human testes; however, the adrenal gland does produce dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione, which can be converted to testosterone in peripheral tissues. In some patients, high DHT levels in the prostate after castration suggest that the adrenal gland can be an important alternate source of androgens.[1]

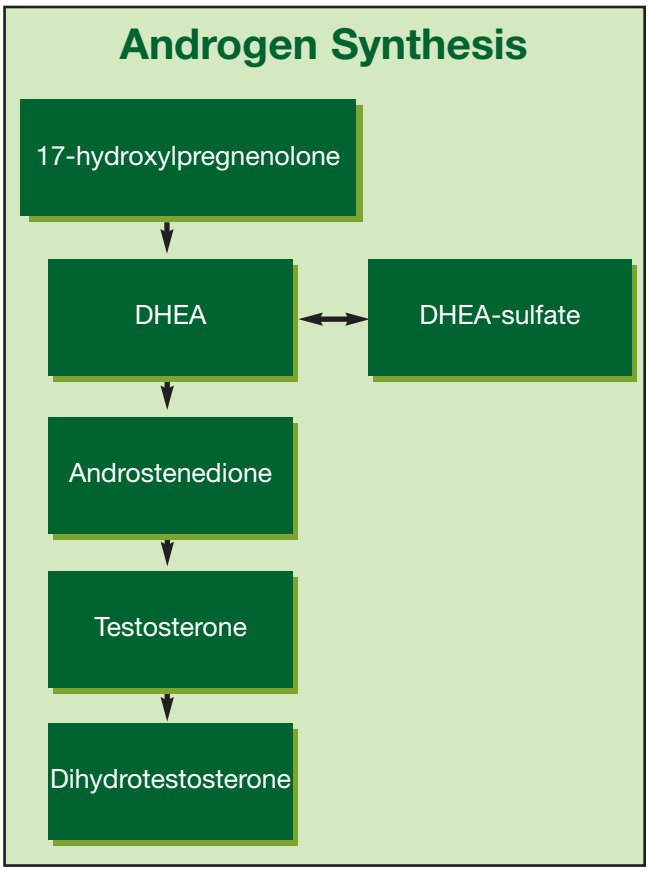


Figure 1. Androgen synthesis.

What is the role of androgens in prostate cancer?

In 1966, Charles Huggins was awarded the Nobel Prize for his observation that suppressing androgens caused regression of prostate carcinoma. Although not all prostate cells (normal or malignant) die on androgen withdrawal, castration does result in dramatic reduction of prostate size and the programmed cell death of those hormone-dependent cancer cells.[2] Metastatic deposits of cancer have been shown to decrease 40% to 80% and disappear in 5% to 10% of patients. Unfortunately, the hor-

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HPA-axis function and hematological status should be assessed periodically. Height should also be regularly monitored in children and adolescents receiving prolonged treatment with inhaled cortico\steroids.

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Reference: 1. Product Monograph of ADVAIR™, GlaxoSmithKline Inc., December 2001

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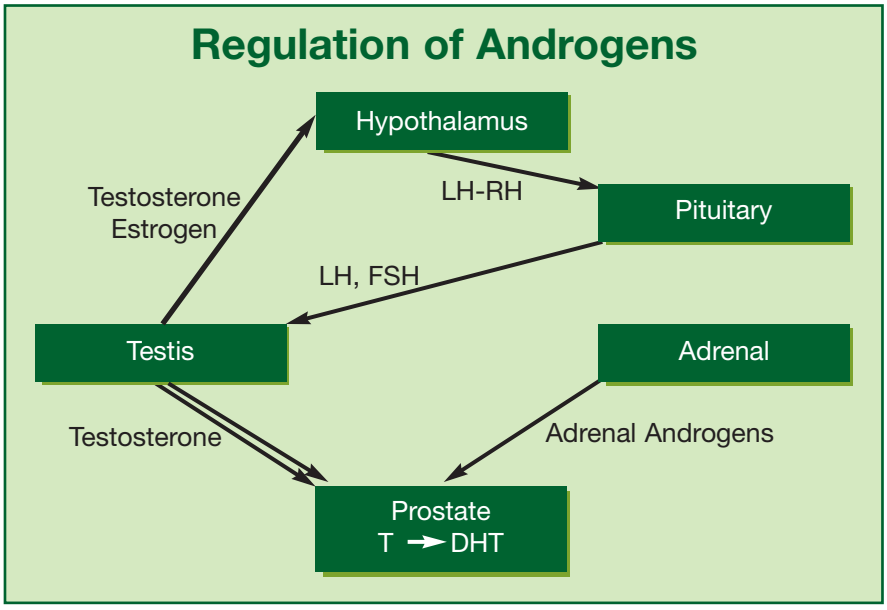

Figure 2. Regulation of androgens.

mone-independent population of cancer cells will continue to grow. Metastatic prostate cancer will always progress, and patients eventually die of their disease.

Surgical castration

Since 1941, surgical castration has been the gold standard for androgen suppression in men with advanced prostate cancer. Bilateral orchiectomy results in immediate and complete castrate levels of testosterone (~0.2 ng/mL). The advantages of surgical castration are obvious: orchiectomy can be carried out in an outpatient fashion, it is immediately effective, and there is no difficulty with compliance. Body image problems can be addressed by sub-capsular orchiectomy or placement of testicular prostheses. The side effects after bilateral orchiectomy are similar to those of any method of castration. Men describe loss of libido and potency (>75%), sweating (10%) and painful gynecomastia (~1% to 2%). Hot flashes occur in greater than half of men with castrate levels of testosterone and can be managed by progestational agents or steroidal antiandrogens. Other possible adverse effects include cardiovascular changes, anemia, weight gain, and loss of muscle mass. Increasing evidence shows that osteoporosis is strongly accentuated by castration. The incidence of osteoporotic fractures in these men have been reported as high as 5%. Several recent studies report the possible benefits of bisphosphonate therapy in men on androgen suppression.[3]

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Castration without surgery

Early medical castration was performed using estrogens to decrease the testicular production of testosterone. Its administration, however, was associated with significant cardiovascular events that limited its use. Today, medical castration is accomplished with LHRH agonists, such as goserelin acetate (Zoladex™), leuprolide acetate (Lupron™), and buserelin acetate (Suprefact™). These agonists at first cause a continuous stimulation of LH at the level of the pituitary and result in

a flare of testosterone production from the testicle. Then, due to down-regulation of the LHRH receptors and the subsequent decline of LH release, castrate levels of testosterone occur generally in three to four weeks. Some patients may experience an increase of tumour activity because of the initial flare of testosterone production. These patients should be given an antiandrogen when medical castration is initiated. All of these LHRH agonists are available in time-release formulations that permit intramuscular or subcutaneous injections every three to four months, depending on the product. Another form of medical castration using a LHRH antagonist has also been reported recently.

What are antiandrogens?

Antiandrogens are substances that counteract the effect of hormones at the level of the target cell. They act through competitive binding of the androgen receptor. Steroidal antiandrogens, such as cyproterone acetate (Androcur™), also decrease the gonadotropins (and subsequently testosterone production) because of their progestational effects. The so-called "pure" antiandrogens, such as flutamide (Euflex™), nilutamide (Anandron™), and biclutamide (Casodex™), are nonsteroidal and have no effect on gonadotropins. In fact, the nonsteroidal antiandrogens block the negative feedback mechanism of testosterone control, resulting in a self-limiting rise in serum testosterone up to 1.5 times normal. The rate of common complications of castration, such as decreased libido, erectile dysfunction, and hot flashes, has been found to be lower with the "pure" antiandrogens, when used as monotherapy. However, gynecomastia, gastointestinal complications, and hepatitis can be occasionally severe.

The adrenal gland may contribute to the failure of androgen suppression.

What about the cost issue?

Some mention of resource management is appropriate in discussing the different methods of androgen suppression, especially due to its relatively frequent use in the aging population. A conservative

Continued on page 116.

estimate for a "lifetime" cost of a bilateral orchiectomy in Canada would be less than $2,000. The annual drug costs of the LHRH analogues can range from $4,500 to $8,000 without factoring in other costs, including support staff and followup. The cost of total androgen ablation (combining medical castration and antiandrogens) could increase the cost up to $10,000 annually. One cost study from the U.S. estimated the cost of medical castration to be at least 10 to 20 times that of surgical castration. They also showed that when a 20% cost-sharing was introduced into the decision-making for their patient population, preference for medical castration over orchiectomy decreased from 70% to 26%.[4]

Intermittent therapy improves quality of life, including energy level and sexual function.

Palliation of metastatic prostate cancer

For over half a century, the standard palliation of men with metastatic prostate cancer has been through castration. Despite this history, there are still significant controversies in the optimal management of these patients. Since androgen suppression is not curative, there is some debate as to the timing of therapy. Some physicians opt for therapy as soon as advanced disease is detected, while others wait for evidence of disease progression. Unfortunately, there is conflicting laboratory and clinical data as to the benefit of starting androgen suppression therapy early in the course of metastatic prostate cancer.[5-8] Although there are no convincing data supporting early androgen deprivation in all patients with advanced prostate cancer, reviews of more modern and better tolerated hormonal therapies may suggest some advantages of immediate therapy.[9]

What is total androgen blockade?

Another controversial aspect of hormonal therapy is that of total androgen blockade (TAB). As mentioned earlier, the adrenal gland may be a significant contributor of androgens to prostate cells and may contribute to the failure of androgen suppression. The addition of antiandrogens that can block the androgen receptor may further suppress the tumour cells sensitive to the low levels of DHT found in patients after castration. Again, there are conflicting data as to the benefit of TAB. Some randomized studies show a survival benefit, while others show no significant difference. Several meta-analyses of the literature are also conflicting, with results suggesting either no survival benefit or mild benefit in some patient cohorts.[10] Although several studies show no significant benefit to adding antiandrogens after surgical castration, there may be some benefit to TAB when utilizing medical castration.

Can we improve quality of life?

Intermittent androgen suppression takes advantage of the reversibility of medical castration. A full recovery from the action of LHRH agonists upon discontinuation allows the possibility of therapy in intermittent pulses. Monitoring of cancer progression when the patient is off androgen suppression is possible with PSA. Although clinical information is lacking regarding the effect of intermittent therapy on survival compared to standard therapy, it does improve quality of life, including energy level and sexual function.[11]

Other quality of life regimens include monotherapy (antiandrogens alone) without the addition of medical or surgical castration. Although patients on monotherapy report increased physical capacity and maintained sexual function, several studies have reported earlier treatment failure compared to castration.

Expanding the role of androgen suppression

Over the last decade there has been growing evidence of the usefulness of androgen suppression as an adjuvant therapy for non-metastatic prostate cancer.

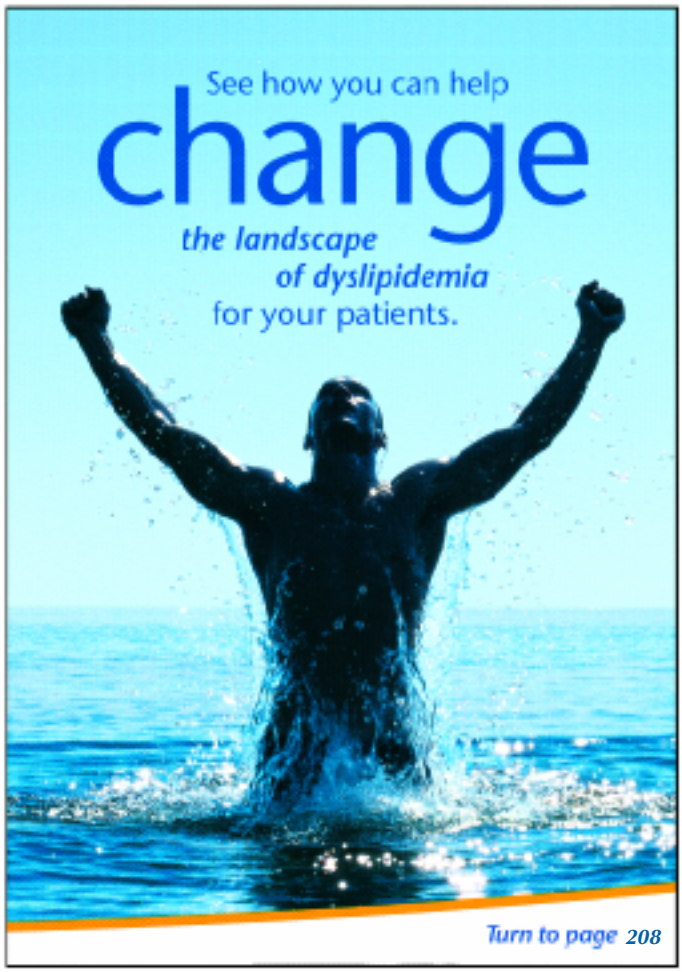
Several large randomized studies have demonstrated the benefit of hormonal manipulation when used either prior to, or concomitantly with, pelvic radiation. In 1997, Bolla et al. reported that patients with locally advanced cancer, treated with the combination of radiotherapy and three years of adjuvant androgen suppression, had better local control, as well as a survival benefit.[12] However, the relative benefit of these therapies remains unclear, as does the timing and duration of any neo-adjuvant or adjuvant therapy.

The role of androgen suppression around the time of radical prostatectomy remains less clear. A few nonrandomized studies of adjuvant androgen suppression after prostatectomy for locally advanced disease have shown some benefit, including men with lymph node positive disease.[13,14] The use of androgen suppression prior to radical prostatectomy has also been explored. Earlier studies of several months of neo-adjuvant hormone therapy suggested improved staging of the pathologic specimen. Unfortunately, this has not translated into a clinical benefit for the patient with available followup.[15] CME

Continued on page 118.

Case Discussion

After referral to a urologist, and confirmation of metastatic prostate cancer through a bone scan, the patient is placed on an oral antiandrogen. He is considering his options for treatment of his advanced prostate cancer.



Take-home message

- Hormonal manipulation is the mainstay of palliation for symptomatic patients with prostate cancer. Surgical castration remains the gold standard.
- Early androgen suppression may delay progression of those with advanced disease, but most likely does not improve survival significantly.
- The complications of androgen suppression including fatigue, hot flashes, decreased libido, and accentuating osteoporosis are significant.
- There is no overwhelming evidence to add an antiandrogen to medical or surgical castration (total androgen ablation) other than to cover the "flare" period when starting luteinizing hormone-releasing hormone agonists.
- Innovative indications for androgen suppression include adjuvant therapy for patients with high-risk disease undergoing curative radiotherapy.

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Hormonal Manipulation in Prostate Cancer Patients

1. What is the role of testosterone in prostate cancer?

Initiation and progression of prostate cancer are influenced by androgens. Androgen suppression in men with metastatic disease will result in response rates up to 80%. However, hormone-independent cells will continue to grow.

2. What is meant by medical castration?

Today, medical castration involves subcutaneous or intramuscular injections of luteinizing hormone-releasing hormone (LHRH) agonists that suppress luteinizing hormone production and, eventually, testosterone production in the testes.

3. What is total androgen blockade?

Total androgen blockade refers to the addition of oral antiandrogens (which block the androgen receptor in prostate cells) to a regimen of medical castration with LHRH agonists. These antiandrogens block any adrenal androgens that may affect prostate cancer cells despite shutting off testicular testosterone production (medical castration).

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4. When should androgen suppression be started in a man with advanced prostate cancer?

The timing of hormonal therapy is controversial. Although there is some evidence to suggest that early therapy (*i.e.,* men with advanced disease but no symptoms) may delay the progression of the disease. So far, no significant survival difference has been found.

5. What are the side effects of androgen supression?

The side effects of castration include loss of libido and potency, sweating, gynecomastia, and regularly occurring hot flashes. Other effects may include loss of muscle mass, weight gain, cardiovascular changes and exacerbation of osteoporosis.

For an in-depth article on Hormonal Manipulation in Patients with Prostate Cancer, please go to page 110.