

Integrated Healthcare Practitioners

Androgen deprivation therapy (ADT)- A framework in management of advanced prostate cancer

Case

A 76 year old male presents with a Prostate-Specific antigen (PSA) of 942ng/ml, dexamethasone results reveals a T-score of -2.5. Digital rectal examination revealed slightly enlarged prostate. Prostatic biopsy Gleason score of 8 (4 + 4) poorly differentiated adenocarcinoma in 8 of 12 specimens. Remarkable laboratory evaluation displays elevated alkaline phosphatase and normocytic anemia. CT indicates possible nodal disease and extraprostatic extension. A hormonal screen showed a total serum testosterone of 9.2 nmol/L (normal 10–28 nmol/L). Bio-available testosterone was 1.4 nmol/L (normal 2–8.6 nmol/L). The patient had a history of recent 2 year induction of vegan diet with a weight of 140lbs at 5'7".

This article submission outlines a basic framework for clinicians working with patients with advanced prostate cancer commencing androgen deprivation therapy (ADT). Integration of complementary therapies may prove to be highly effective in co-management of the side effects of ADT in these patients. Clinically, this work must involve careful monitoring of hormonal status, bone density, laboratory markers and mental/emotional status of the patient in response to ADT.

Hormonal therapy - ADT

The preferred treatment of locally confined prostate cancer is local surgery or radiotherapy. In 1941 Huggins et al, (Huggins 1941) published the first data regarding androgen dependence of prostate cancer. Dr. Charles Brenton Huggins was awarded the 1966 Nobel Prize for discovering that hormones could be used to control the spread of some cancers. Androgen-deprivation therapy (ADT) with GnRH agonist or bilateral orchidectomy has since become the main treatment for metastatic or recurrent prostate cancer. The use of ADT is increasing with the advocacy of adjuvant ADT in otherwise asymptomatic patients with locally advanced prostate cancer, and the

inclusion of neoadjuvant temporary ADT in the multimodal treatment of localized prostate cancer (Sharifi 2005).

The use of adjuvant ADT in men with locally advanced prostate cancer has resulted in decreasing recurrence and improved survival (Messing 1999). ADT has also been shown to improve survival in high-risk patients undergoing radiotherapy (Bolla 1997, Sharifi 2005).

Prostate cancer is androgen-dependent, and hormone therapy, mainly achieved by androgen deprivation therapy (ADT), has been one of the main treatment modalities in the clinical management of prostate cancer patients for more than six decades. In the 1980s, luteinizing hormone releasing hormone agonists (LHRH analogs), which reduce testosterone to castration levels, were introduced. Nonsteroidal antiandrogens and antiandrogen were subsequently developed. Since then, so-called maximum androgen blockade (MAB)/combined androgen blockade (CAB), which is a combination of surgical or medical castration and oral antiandrogens, has been developed.

More recently, novel treatment modalities have been developed, such as intermittent androgen suppression and alternative antiandrogen therapy after relapse from initial MAB/CAB

. A brief treatment of hormonal therapy aims to decrease the production of testosterone in the testes or block the uptake of testosterone. This in turn slows growth of the tumor or in some cases, arrests the growth of the tumor for several years. Additionally, a short course may be administered before radiation to decrease the volume of the tumor. In this case as a neoadjuvant agent, it may be administered by a uro-oncologist for two to eight months. Hormonal therapy is commonly used to treat cancer that has metastasized outside the prostate and pelvic region. It may also be combined with radiation treatment in locally advanced stages. Several types of hormonal therapy are often used in the treatment of prostate cancer:

Orchiectomy - Surgical removal of the testicles, decreasing approximately 95% of testosterone production (approximately 5% produced in the adrenals).

LHRH analogs or GnRH analogs (luteinizing hormone-releasing hormone analogs) - LHRH analogs consist of administering a injection and may be used in advanced disease and metastasis and may offer an alternative for patients who chooses to or cannot have orchiectomy LHRH analogs include *Zoladex* (goserelin acetate implant), *Lupron Depot* (leuprolide acetate for depot suspension) *Eligard* (leuprolide acetate) *Suprefact* (buserelin acetate) and *Trelstar* (leuprolide acetate). LHRH analogs are administered montly, bi-montly, quarterly, every four months, six months or yearly. Clinically, it is important to note that in a small percentage of patients a ‘testosterone surge’

may occur in the first month of treatment and may worsen symptoms, such as bone pain until testosterone levels begin to fall.

Antiandrogens (steroidal and non-steroidal) - Antiandrogens do not prevent the production of testosterone, instead, they block the uptake of testosterone by the prostate cells. Antiandrogens are subdivided into steroidal and non-steroidal antiandrogens. Non-steroidal antiandrogens include Casodex (bicalutamide), Euflex (flutamide) and Anandron. Steroidal antiandrogens are limited to Androcur (cyproterone acetate).

Summary – Reasons for ADT therapy

- Reduce the size of the tumor (volume reduction) to increase clinical efficacy of radiation treatment of prostatectomy.
- Delay disease progression following radiation
- Prevent cancer progression in high risk disease while waiting for definitive therapy.
- Immediately after prostatectomy or radiation

Chemotherapy – is reserved for patients with advanced prostate cancer (Stage M+) that no longer respond to hormonal therapy.

Side effects of androgen deprivation therapy (ADT)

The testes are the major source of testosterone while the remaining androgens produced by the adrenal glands are hormone precursors that are enzymatically converted to testosterone and dihydrotestosterone in prostatic and peripheral tissues (Imamoto 2008). Androgen deprivation is associated with a variety of adverse effects, including hot flushes, loss of libido, loss of muscle mass (sarcopenia), fatigue, gynecomastia, cognitive dysfunction, insulin resistance, change of lipid profile, and depression. The long-term adverse effects include osteoporosis and anemia. These adverse body composition changes may contribute to frailty, fatigue, emotional distress, and decreased quality of life (QOL) during ADT therapy.

Diabetes/Insulin resistance

ADT has been associated with a greater risk of developing DM. In a retrospective study of 29 insulin-dependent diabetic men diagnosed with prostate cancer, after starting ADT, the fasting glucose, HbA1c and insulin requirements all deteriorated over 24 months following ADT (Haider 2007). Mean fasting glucose level increased from 143 to 187 mg/dL, the mean HbA1c

increased from 6.3 to 9.3, and the daily insulin dose increased from 26 to 48 units. In addition, all cardiovascular biochemical risk markers measured, including total cholesterol, C-reactive protein, plasminogen activator and plasminogen activator inhibitor-1 deteriorated (Haider 2007).

In a small cross-sectional study, men receiving ADT had significantly higher fasting glucose and insulin levels after adjustment for age and BMI (Basaria 2006). Furthermore, in a 12-week prospective study of 25 non-diabetic men with prostate cancer started on ADT, the mean insulin sensitivity decreased by 12.8% from baseline (Smith 2006). At the same time, fasting plasma insulin levels increased by 25.9% with a small increase of HbA1c.

It should be noted that an increase of 1% in HbA1c is associated with a 28% increase in the risk of death from all causes among patients with or without diabetes, independent of age, blood pressure, serum cholesterol, BMI and smoking habit (Khaw 2001).

Metabolic Syndrome

Metabolic syndrome refers to a clustering of specific risk factors for cardiovascular disease whose pathophysiology appears related to insulin resistance. The National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) and the World Health Organization (WHO) define the metabolic syndrome using different but related criteria (Table 1).

Table 1

<p>National Cholesterol Education Program Adult Treatment Panel III</p>	<p>Any three or more of the following:</p> <ul style="list-style-type: none"> - Waist circumference > 102 cm - Serum triglycerides \geq 1.7 mmol/l - Blood pressure \geq 130/80 mm Hg - High density lipoprotein cholesterol < 1.0 mmol/l - Serum glucose \geq 6.1 mmol/l (\geq5.6 mmol/l may be applicable)
<p>World Health Organization</p>	<p>Diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance and at least two of the following criteria:</p> <ul style="list-style-type: none"> - Waist to hip ratio > 0.90 - Serum triglycerides \geq 1.7 mmol/l - Blood pressure \geq 140/90 mm Hg - Urinary albumin excretion rate > 20 μg/min or albumin-to creatinine ratio \geq 30 mg/g