

# Integrated Healthcare Practitioners

## Androgen Deprivation Therapy (ADT)- A framework in the management of advanced prostate cancer.

### Case

A 76 year old, vegetarian male (for the past two years), presents with the following history:

- Prostate-Specific Antigen (PSA) of 942 ng/ml
- DEXA results reveal a T-score of -2.5
- Digital rectal examination reveals a slightly enlarged prostate
- Prostatic biopsy Gleason score of 8 (4 + 4), with poorly differentiated adenocarcinoma in 8 of 12 specimens
- Elevated alkaline phosphatase and normocytic anemia
- CT scan indicates possible nodal disease and extra-prostatic extension
- Total serum testosterone was 9.2 nmol/L (normal 10–28 nmol/L)
- Bio-available testosterone was 1.4 nmol/L (normal 2–8.6 nmol/L)
- Weight: 140lbs, height: 5'7"

This article outlines a basic framework for clinicians working with patients who have advanced prostate cancer and who are commencing androgen deprivation therapy (ADT). Integration of complementary therapies may prove to be highly effective in co-management of the side effects of ADT. This requires careful monitoring of:

- Hormonal status
- Bone density
- Laboratory markers
- Mental and emotional status

### Hormal therapy- ADT

The preferred treatment of locally confined prostate cancer is surgery or radiotherapy. In 1941 Huggins et al, (Huggins 1941) published the first data regarding androgen dependence of prostate cancer and discovered that hormones could be used to control the spread of some cancers. 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 decreased recurrence and improved survival (Messing 1999). ADT has 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 ADT, has been one of the main treatment modalities for more than six decades. In the 1980s luteinizing hormone releasing hormone (LHRH analogs) were introduced, which reduces

testosterone to castration levels. Non-steroidal antiandrogens were subsequently developed, and then maximum androgen blockade (MAB)/combined androgen blockade (CAB), which is a combination of surgical or medical castration and oral antiandrogens.

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 slows the 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% are produced in the adrenals).

**LHRH analogs or GnRH analogs**- Injections may be used in advanced disease and metastasis, and may offer an alternative for patients who choose not 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)
- *Trelstar* (leuprolide acetate)

LHRH analogs are administered monthly, bi-monthly, quarterly, every four months, six months or yearly. 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. Non-steroidal antiandrogens include *Casodex* (bicalutamide), *Euflex* (flutamide) and *Anandron*. Steroidal antiandrogens are limited to *Androcur* (cyproterone acetate).

## Reasons for ADT

- Reduces the size of the tumor (volume reduction) to increase clinical efficacy of post-prostatectomy radiation treatments.
- Delays disease progression following radiation
- Prevents cancer progression in high risk disease while waiting for definitive therapy.
- Effective Immediately after prostatectomy or radiation

**Note: Chemotherapy is reserved for patients with advanced prostate cancer (Stage M+) who no longer respond to hormonal therapy.**

## Side effects of ADT

Side effects of ADT include:

- Hot flushes
- Loss of libido
- Loss of muscle mass (sarcopenia)
- Fatigue
- Gynecomastia
- Cognitive dysfunction
- Insulin resistance
- Lipid profile changes
- 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).

## Diabetes- insulin resistance

ADT has been associated with a greater risk of developing diabetes mellitus (DM). In a study of 29 insulin-dependent diabetic men diagnosed with prostate cancer, fasting glucose, HbA1c, and insulin requirements all deteriorated over 24 months after starting ADT (Haider 2007). Mean fasting glucose levels 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. Cardiovascular risk markers including total cholesterol, C-reactive protein, plasminogen activator and plasminogen activator inhibitor-1, all 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, ADT treated men with prostate cancer, the mean insulin sensitivity decreased by 12.8% from baseline (Smith 2006). Fasting plasma insulin levels increased by 25.9%, with a small increase in HbA1c.

**Note:** A 1% increase 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 (NCEP) - Adult Treatment Panel III (ATP III), and the World Health Organization (WHO), define metabolic syndrome using different but related criteria (Table 1).

**Table 1.**

<p><b>NCEP-ATP III</b></p>	<p>Any three or more of the following:</p> <ul style="list-style-type: none"> <li>• Waist circumference &gt; 102 cm</li> <li>• Serum triglycerides <math>\geq</math> 1.7 mmol/l</li> <li>• Blood pressure <math>\geq</math> 130/80 mm Hg</li> <li>• HDL &lt; 1.0 mmol/l</li> <li>• Serum glucose <math>\geq</math> 6.1 mmol/l</li> <li>• (<math>\geq</math>5.6 mmol/l may be applicable)</li> </ul>
<p><b>W.H.O.</b></p>	<p>Diabetes impaired fasting glucose, glucose tolerance or insulin resistance and at least two of the following criteria:</p> <ul style="list-style-type: none"> <li>• Waist to hip ratio &gt; 0.90</li> <li>• Triglycerides <math>\geq</math> 1.7 mmol/l</li> <li>• Blood pressure <math>\geq</math> 140/90 mm Hg</li> <li>• Urinary albumin excretion rate &gt; 20 <math>\mu</math>g/min or albumin-to creatinine ratio <math>\geq</math> 30 mg/g</li> </ul>

A recent cross-sectional study reported a higher prevalence of metabolic syndrome (as defined by NCEP- ATP III) in 18 men receiving a GnRH agonist than in age-matched control groups of untreated men with prostate cancer and men without prostate cancer (Braga-Basaria 2006). Men receiving GnRH agonist therapy were more likely to have:

- Increased abdominal girth
- Elevated triglycerides
- Elevated fasting plasma glucose; consistent with other prospective studies of GnRH agonist treatment (Smith 2002, Smith 2008).

In contrast to metabolic syndrome, however, prospective studies have shown that GnRH agonists preferentially increase subcutaneous rather than visceral abdominal fat and increase rather than decrease HDL cholesterol (Smith 2002, Smith 2008). Other observations suggest that GnRH agonists cause a pattern of metabolic changes that are distinct from the classically defined metabolic syndrome (Table 2).

**Table 2.**

<p><b>Metabolic changes</b></p>	<p><b>Classic metabolic syndrome</b></p>	<p><b>GnRH agonist induced metabolic changes</b></p>
<p>Waist circumference</p>	<p>Increased</p>	<p>Increased</p>
<p>Waist-to-hip ratio</p>	<p>Increased</p>	<p>No Change</p>
<p>Blood pressure</p>	<p>Increased</p>	<p>No Change</p>
<p>Triglycerides</p>	<p>Increased</p>	<p>No Change</p>
<p>HDL cholesterol</p>	<p>Decreased</p>	<p>Increased</p>
<p>Fat accumulation</p>	<p>Visceral</p>	<p>Subcutaneous</p>
<p>Adiponectin</p>	<p>Decreased</p>	<p>Increased</p>