Androgen Deprivation Therapy

A framework in the management of advanced prostate cancer.

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CASE

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

- Prostate-specific antigen (PSA) of 942ng/ml
- Dexa results reveal a T-score of -2.5 (L4,L5)
- Digital rectal examination reveals a slightly enlarged prostate
- Prostatic biopsy Gleason score of 8 (4 + 4), with poorly differentiated adenocarcinoma in eight of 12 specimens
- Elevated alkaline phosphatase and normocytic anemia
- CT scan indicates possible nodal disease and extra-prostatic extension
- Bone scan indicates metastases in lumbar vertebrae
- Total serum testosterone was 9.2 nmol/L (normal 10-28nmol/L)
- Bio-available testosterone was 1.4nmol/L (normal 2-8.6nmol/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 the following:

- 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 published the first data regarding androgen dependence of prostate cancer, and discovered that hormones could be used to control the spread of some cancers (Huggins 1941). ADT with gonadotropin-releasing hormone (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 immediate ADT in men post-prostatectomy with node-positive disease 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, GnRH analogues 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 tumour or in some cases, arrests the growth of the tumour for several years. Additionally, a short course may be administered before radiation to decrease the volume of the tumour. 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% is produced in the adrenals).

GnRH analogues
Injections may be used in advanced disease and metastasis, and may offer an alternative for patients who choose not to or cannot have orchiectomy. GnRH analogues include the following:
- Zoladex (goserelin acetate implant)
- Lupron Depot (leuprolide acetate for depot suspension)
- Eligard (leuprolide acetate)
- Suprefact (buserelin acetate)
- Trelstar (leuprolide acetate)

Luteinizing hormone-releasing hormone (LHRH) analogues 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
- To treat metastatic prostate cancer
- To treat men with biochemical recurrence post-prostatectomy or radiotherapy.
- Improves the effectiveness of radiation therapy for intermediate to high-risk prostate cancer
- May prevent cancer progression in high-risk disease while waiting for definitive therapy.

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 the following:
- 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, hemoglobin A1c (HbA1c) and insulin requirements all deteriorated over 24 months after starting ADT (Haider 2007). Mean fasting glucose levels increased from 143 to 187mg/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).

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Table 1: NCEP-ATP III and WHO criteria for metabolic syndrome

NCEP-ATP III	WHO
Any three or more of the following: • Waist circumference >102cm • Serum triglycerides ≥1.7mmol/l • Blood pressure ≥130/80mmHg • HDL <1.0mmol/l • Serum glucose =6.1mmol/l • =5.6mmol/l (may be applicable)	Diabetes, impaired fasting glucose, glucose tolerance or insulin resistance and at least two of the following criteria: • Waist to hip ratio >0.90 • Triglycerides ≥1.7mmol/l • Blood pressure ≥140/90mmHg • Urinary albumin excretion rate >20µg/min or albumin-to creatinine ratio ≥30mg/g

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, however, related criteria (Table 1).

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 the following:

- 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).

HOT FLUSHES

Significantly affecting quality of life, vasomotor hot flushes are a frequent complaint of men receiving ADT. Typical manifestation is a sudden perceived increase in temperature; specifically a feeling of warmth in the face, neck, upper chest and back, which may be seen in up to 80% of patients undergoing treatment with GnRH analogue. As many as 27% report this as the most troublesome adverse effect (Holzbeierlein 2004).

Treatment of hot flushes includes the use of hormonal (estrogens, megestrol acetate, medroxyprogesterone acetate and cyproterone acetate) and non-hormonal preparations (antidepressants, clonidine) (Holzbeirlein 2004). For a non-pharmaceutical therapy, accupuncture carries the strongest evidence (Ezzo 2000, Frisk 2008, Hirsch 2000).

OBESITY

Androgens are important determinants of body composition in men. Serum testosterone concentrations correlate positively with lean mass and negatively with fat mass in normal men (Tayek 1990). GnRH agonists significantly decrease lean body mass and increase fat mass in men with prostate cancer (Berruti 2002, Smith 2001, 2002, 2004, Tayek 1990). In two studies of men with non-metastatic prostate cancer, GnRH agonists decreased lean body mass by 2.7% to 3.8% and increased fat mass by 9.4% to 11.0% from baseline to one year (Berruti 2002, Smith 2001). Changes in body composition appear primarily as an early adverse effect of GnRH agonist treatment, with most of the treatment-related change in fat and lean body mass apparent within the first year of therapy.

Table 2: Comparison of metabolic syndrome versus GnRH agonist therapy on impact to select metabolic parameters

Changes	Classic Metabolic Syndrome	GnRH Agonist-Induced
Waist circumference	Increased	Increased
Waist-to-hip ratio	Increased	No change
Blood pressure	Increased	No change
Triglycerides	Increased	No change
HDL cholesterol	Decreased	Increased
Fat accumulation	Viceral	Subcutaneous
Adiponectin*	Decreased	Increased

*Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin is exclusively secreted from adipose tissue into the bloodstream and is very abundant in plasma, relative to many hormones. Levels of the hormone are inversely correlated with body fat percentage in adults (Diez 2003).

Table 3: Side effects of ADT therapy

Side Effect	Incidence
Hot flushes	55% to 80%
Anemia	90% show 10% drop in hemoglobin, 13% have >25% drop in hemoglobin
Impotence	50% to 100%
Increase in net weight, muscle wasting and fat deposition	Common
Depression	Common
Osteoporosis	1.4% to 2.6% per year
Hormone-related fracture	Common
Gynecomastia	13% to 70%, depending on drug used
Fatigue	13%
Changes in lipid profile	Common
Gastrointestinal symptoms	22%
General weakness	Common
Diabetes	11%
Acute myocardial infarction	5%
Sudden cardiac death	4.5%
Coronary artery disease	25%

This table has been adapted from Kumar (2005).

MUSCULOSKELETAL

Musculoskeletal side effects of hormonal therapy include osteoporosis and decrease in muscle mass. Men receiving or starting ADT should be evaluated for risk of osteoporosis including the following:

- A family history of osteoporosis
- Low body weight
- Prior fractures
- Excessive alcohol use
- Smoking
- Glucocorticoid use
- Low vitamin D status
- Other medical comorbidities

Studies over time have shown that bone density decreases by approximately 0.5% to 1% per year in healthy, elderly men (Orwoll 1990). In healthy individuals, general bone loss as a normal part of aging is slower and less visible in men than in women (Orwoll 1990). Several trials have established that BMD is significantly decreased in men receiving ADT, when compared with a control group. It was determined from one group that the prevalence of osteoporosis in patients with prostate cancer increased to more than 80% after 10 years of ADT (Morote 2007). These losses surpass bone loss in women who are in early menopause (Higano 2003). Mortality after hip fracture was also higher in men than in women (Seemean 1999).

An evaluation of more than 50,000 men from two medical databases compared the risk of fractures in men with a diagnosis of prostate cancer: ADT versus non-ADT treated (Shahinian 2005). Men treated with ADT had an increased risk of fracture starting one year after diagnosis, and the risk of fracture increased with an increase in the number of doses of GnRH analogue. Current guidelines for the prevention of osteoporotic fractures in patients receiving hormonal manipulation should address issues of lifestyle modification including smoking cessation, decreased alcohol intake, added resistance exercise, and adequate supplementation of calcium and vitamin D.

COGNITIVE AND MOOD CHANGES

There is conflicting literature on the issue of cognitive function changes in men undergoing ADT. One study that randomized 82 men to GnRH analogue versus close clinical monitoring suggested that there may have been worsening on some tests of attention and memory (Green 2002). Other data did not suggest any cognitive impairment in men being treated with ADT; however, they noted an improvement in object recall (Salminen 2003). A more recent study associated declines in verbal fluency, visual memory and visual recognition with declines in estradiol induced by ADT (Salminen 2005).

A quality-of-life study of 144 men given a choice of immediate or deferred ADT found significantly worse scores for fatigue and psychological distress when receiving ADT (Herr 2000). Men with prostate cancer surveyed at *Massachusetts General Hospital* were found to have eight times the national rate of depression. This was not associated with ADT (Pirl 2002).

Hormonal deprivation also has emotional effects, including moodiness, short temper, crying with minimal provocation, and feeling depressed and anxious (Rosenblatt 1995).

OTHER SIDE EFFECTS OF ADT

There are many side effects of ADT therapy. Table 3 provides a summary.

SUMMARY

ADT has a multitude of adverse effects; most notably, a greater risk of diabetes mellitus, cardiovascular disease and osteoporosis. Treatment-related obesity and insulin resistance appear sufficient to explain the greater risk for diabetes. Several mechanisms may contribute to greater risk for cardiovascular disease, including obesity, insulin resistance and increased serum cholesterol and triglycerides. The metabolic alterations associated with GnRH agonist therapy appear distinct from the classically defined metabolic syndrome. In the future, aggressive dietary and lifestyle changes, along with the use of other natural agents may serve as standard therapy for those trying to prevent prostate cancer, and for those with advanced disease status. Careful monitoring and treatment of the associated adverse effects of ADT are imperative when working with those with advanced prostate cancer.

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