Androgen Deprivation Therapy Impact on Quality of Life and Cardiovascular Health, Monitoring Therapeutic Replacement

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ABSTRACT

Introduction. Androgen deprivation therapy (ADT) is commonly utilized in the management of both localized and advanced adenocarcinoma of the prostate. The use of ADT is associated with several adverse events, physical changes, and development of medical comorbidities/mortality.

Aim. The current article reviews known adverse events associated with ADT as well as treatment options, where available. Current recommendations and guidelines are cited for ongoing monitoring of patients receiving ADT.

Methods. A PubMed search of topics relating to ADT and adverse outcomes was performed, with select articles highlighted and reviewed based on level of evidence and overall contribution.

Main Outcome Measures. Reported outcomes of studies detailing adverse effects of ADT were reviewed and discussed. Where available, randomized trials and meta-analyses were reported.

Results. ADT may result in several adverse events including decreased libido, erectile dysfunction, vasomotor symptoms, cognitive, psychological and quality of life impairments, weight gain, sarcopenia, increased adiposity, gynecomastia, reduced penile/testicular size, hair changes, periodontal disease, osteoporosis, increased fracture risk, diabetes and insulin resistance, hyperlipidemia, and anemia. The definitive impact of ADT on lipid profiles, cardiovascular morbidity/mortality, and all-cause mortality is currently unknown with available data. Treatment options to reduce ADT-related adverse events include changing to an intermittent treatment schedule, biophysical therapy, counseling, and pharmacotherapy.

Conclusions. Patients treated with ADT are at increased risk of several adverse events and should be routinely monitored for the development of potentially significant morbidity/mortality. Where appropriate, physicians should reduce known risk factors and counsel patients as to known risks and benefits of therapy. **Trost LW, Serefoglu E, Gokce A, Linder BJ, Sartor AO, and Hellstrom WJG. Androgen deprivation therapy impact on quality of life and cardiovascular health, monitoring therapeutic replacement. J Sex Med 2013;10(suppl 1):84–101.**

Key Words. Adverse Events; LHRH; GnRH; Antiandrogen; Morbidity

Introduction

Adenocarcinoma of the prostate is the most common visceral malignancy among U.S. males with 241,740 new cases and 28,170 deaths estimated in 2012 [1]. Several management options are available for the treatment of prostate cancer including surgical extirpation, radiation/proton therapy, high intensity focused ultrasound, and cryotherapy, among others.

Androgen deprivation therapy (ADT) is commonly utilized in cases of lymph node involvement, metastatic disease, for adjunctive use with radiation, with biochemical recurrences following initial primary treatment, and is also employed as primary therapy for localized prostate cancer [2–6]. Treatment with ADT has increased in the prostate-specific antigen (PSA) era with utilization rates in nonmetastatic prostate cancer increasing from 3.7% of patients in 1991 to 31% in 1999 among North American men and from 16,000 in 2003–04 to 23,500 in 2008–09 among Australian men [7–9].

ADT includes various treatment modalities, which reduce circulating androgen levels or block

Class of Drugs	Region of Action	Mechanism of Action
GnRH Agonists	Anterior pituitary gland	Decrease release of LH through downregulation of GnRH receptors
GnRH Antagonists	Anterior pituitary gland	Direct inhibition of GnRH receptors
Adrenal Ablating Drugs	Adrenal gland	Decrease androgen synthesis from steroid precursors through inhibition of cytochrome P450 enzymes
Androgen Receptor Antagonists	Prostate	Through competitive binding, inhibition of androgen receptor ligand-binding domain

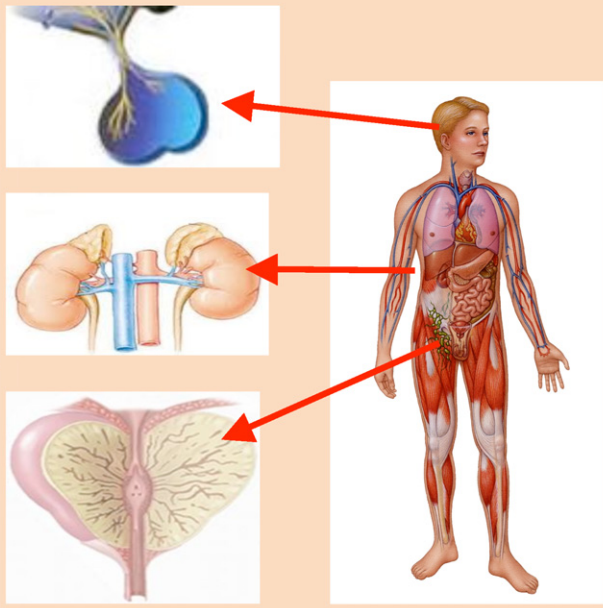

Figure 1 Summary of mechanism of action for current drug classes of androgen deprivation therapy

their effect on prostate cancer cells. Common methods of administering ADT include surgical or pharmacologic castration (administered intermittently or continuously) with both therapies demonstrating equivalent overall survival, time to treatment failure, and progression-free survival [10]. Although several medical therapies exist to reduce androgen levels, the most commonly employed agents are luteinizing hormone-releasing hormone (LHRH) or gonadotropin-releasing hormone agonists, including leuprolide, goserelin, triptorelin, and histrelin, among others.

Additional categories used alone or in conjunction with LHRH agonists include LHRH antagonists (abarelix, degarelix), antiandrogens (flutamide, bicalutamide, nilutamide), adrenal androgen inhibitors (ketoconazole), estrogens (diethylstilbestrol [DES], estradiol, polyestradiol phosphate, premarin), and abiraterone (Figure 1).

Given the prevalence of ADT, treating physicians should recognize the known adverse and long-term untoward effects and provide monitoring of patients undergoing treatment. This communication is outlined to review adverse effects of ADT as well as management options, where applicable. Discussion of the effects of testosterone therapy on the prostate and prostate cancer, including supplementation in the setting of previously treated prostate cancer, is beyond the scope of the current article, and the interested reader is referred to a recent article of this topic [11].

Adverse Effects of ADT

ADT is associated with side effects including decreased libido, erectile dysfunction (ED), vasomotor symptoms, fatigue, decreased energy, depressed mood and cognition, emotional lability, reduced quality of life (QOL), weight gain, gynecomastia, alterations in muscle mass/body fat distribution, reduction in penile/testicular size, development of osteoporosis, increased fractures, anemia, insulin resistance, diabetes mellitus (DM), and possible cardiovascular (CV) disease, among others.

Subjective Symptoms

Decreased Libido/ED

Patients treated with ADT experience diminished libido with only 13–20% maintaining sexual activity [12,13]. Compared with prostate cancer controls, patients treated with intermittent ADT (IADT) experienced reductions in libido (28% with moderate/high libido off therapy vs. 10% on therapy), masculinity (50% vs. 26%), and erectile function (46% vs. 13%), with effects beginning at 3 months and peaking at 9 months [13]. During