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A Holistic Approach to Androgen Deprivation Therapy: Treating the Cancer without Hurting the Patient

Key Words

Androgen deprivation therapy • Side effects • Prevention • Prostate cancer • Quality of life

Abstract

Introduction: Androgen deprivation therapy (ADT) for advanced prostate cancer can be associated with side effects which may negatively impact quality of life (QoL) and induce serious medical problems. **Aim:** The aim is to give practical recommendations on how to monitor and counsel patients and effectively manage side effects based on relevant original articles, review articles and abstracts. **Results:** Urologists should be aware of side effects and adapt their practice patterns to rapidly recognize these and administer appropriate treatment. Proper counseling of ADT-treated patients is needed to help them recognize and prevent and/or manage side effects. Patients should be encouraged to adopt a healthy lifestyle such as a healthy diet and physical exercise. In addition, bone mineral density and metabolic and cardiovascular parameters need to be carefully monitored. **Conclusions:** Urologists should take appropriate measures to prevent and manage ADT-related side effects to promote the general health and overall QoL of patients.

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Introduction

Androgen deprivation therapy (ADT) has confirmed benefits in the treatment of advanced (i.e. locally advanced and metastatic) prostate cancer (PCa) [1]. Recent epidemiological data also indicate that ADT is increasingly being used in asymptomatic patients in earlier disease stages, a setting in which it has not demonstrated a significant benefit and therefore should not be recommended [2]. There are also no recommendations regarding the timing of ADT in early-stage PCa, and therefore the advantages and disadvantages of ADT in early-stage PCa should be discussed with the patient. Considering this, many men with PCa will still receive ADT for a prolonged time, and although these men may benefit from ADT, they will also suffer from the side effects of this therapy. Traditionally, ADT is recognized through its acute obnoxious side effects such as loss of libido and erectile dysfunction, hot flushes, fatigue and psychological effects such as emotional instability, depression or cognitive dysfunction [3–5]. Recently, however, it has become clear that ADT-related morbidity comes mostly from long-term side effects that are mostly invisible to the patient [3]. These include accelerated bone loss leading eventually to osteoporosis and potentially fractures, as well as the induction of a ‘sarcopenic obesity’ which may lead to an increased risk of cardiovascular morbidity and mortality [4]. These side effects need to be monitored and properly treated to avoid dramatic complications.

Table 1. Practical recommendations for patients to manage hot flushes*Actions that can be taken*

- Wear natural fibers such as cotton or linen that allow the skin to breathe.
- Dress in layers so you can peel off one layer after another as you get warmer.
- Put a wet, cold cloth on your neck (not on your forehead).
- Drink a glass of cold water or fruit juice when the hot flush starts.
- Make sure the bedroom is well ventilated and cool.
- Put a can of ice water with ice cubes next to the bed at night to drink or to cool your forehead or wrists.
- Use a double set of sheets or put a towel on your bed which can easily be removed after a hot flush with sweating.
- Exercise regularly.

Actions that need to be avoided

- Avoid large temperature changes; do not put the air conditioning too low. Avoid hot tubs, saunas.
- Avoid food or beverages that trigger hot flushes, such as coffee, alcohol or spicy food.
- Avoid clothes or sheets made of synthetic fibers.
- Try to avoid stress.
- Try to stop smoking.

This review aims to give practical advice on the prevention and management of ADT-related side effects to promote the general health and overall quality of life (QoL) of patients treated with ADT.

Hot Flushes

Hot flushes (called hot flashes in the US) are described as a sudden intense and uncomfortable heat sensation in the face, neck, upper chest and back, lasting from seconds up to an hour. This side effect is one of the most common side effects of ADT, with up to 80% of patients describing it [5, 6]. Hot flushes are considered by patients as one of the most bothersome side effects of ADT that may largely disrupt everyday life. Often hot flushes are triggered by stress, heat, sudden changes in body position, or the ingestion of warm or spicy food or smoking [5]. Management of hot flushes includes informing patients about these triggering situations and advising them to avoid these. In addition, a number of practical recommendations can be given to patients in order to make it easier for them to handle their hot flushes (table 1). If hot flushes are very bothersome for patients, medical therapy can be considered. Precise evaluation of the frequency, sever-

ity and level of bother of hot flushes can be done by means of simple questionnaires, such as the Moyad questionnaire [7]. Hormonal agents such as megestrol acetate, medroxyprogesterone acetate, cyproterone acetate and low-dose diethylstilbestrol are very popular to treat bothersome hot flushes [3–5, 7]. There has been some concern regarding the use of diethylstilbestrol, as it is associated with cardiovascular complications and gynecomastia [4, 5]. More recently, research is focusing on new antidepressants, such as venlafaxine or citalopram [8, 9]. However, their efficacy is inferior to hormonal treatment as demonstrated by a recent randomized, double-blind study comparing the efficacy and tolerability of venlafaxine vs. medroxyprogesterone acetate vs. cyproterone acetate [10].

Other agents are being evaluated such as clonidine and gabapentin, however, more research on these agents is needed [5]. Complementary therapies, such as acupuncture, and food supplements, such as isoflavones, salvia, soy (e.g. tofu, tempeh, soy milk) or black cohosh extracts have also been used by patients and, despite lack of robust scientific evidence, they deserve attention as an additional treatment in well-informed patients [3, 5].

Sexual Dysfunction

The negative impact of ADT on libido and sexual function is well known. Decrease or loss of sexual desire and impotence are among the side effects most frequently reported by patients [11]. Patients and their partners should be informed about this side effect as it can cause anxiety for both. Although sexual problems are a very personal matter that each couple will have to work through in their own way, an open and honest communication is very important. It should be explained that when testosterone levels decrease, sexuality is not over, it is just different. Holding hands, physical closeness, caring and personal intimacy are also considered as very rewarding. It can also be advocated that physicians administering ADT should adopt a more positive attitude towards sexual side effects. From a historic review of the social and intellectual performances of eunuchs, Aucoin and Wassersug [12] suggest that given the right cultural setting and individual motivation, ADT may actually enhance, rather than hinder, both social and sexual performance. The capabilities and accomplishments of eunuchs in the past give ADT-treated men grounds for viewing themselves in a positive light where they are neither socially impotent nor sexually chaste [12].

Table 2. Practical recommendations for patients to deal with fatigue*Actions that can be taken*

- Balance rest and activities.
- Conserve your energy. Save your energy for the most important activities and most preferred activities. Keep a record of the times when you feel best. This will allow you to plan ahead to do the most important activities during those times.
- Schedule important activities throughout the day rather than all at once.
- Rest before you become fatigued. Frequent, short rests are more beneficial than one long nap.
- Pace yourself: a moderate pace is better than rushing through activities.
- Ask others to help you, delegate tasks when needed.
- Eat healthy. Contact a dietician for advice.
- Exercise regularly, take a short walk each day.
- Do things that you enjoy, watch a movie or listen to music. It will relax you and take your mind off cancer and therapy.

Actions that need to be avoided

- Avoid unnecessary activities.
- Avoid rests of more than 1 h during the day.
- Avoid heavy activities.
- Avoid stress.
- Try to stop smoking.

There are good treatment options for men suffering from impotence as a side effect of ADT, such as intracavernous penile injections of prostaglandins and/or phosphodiesterase-5 inhibitors, although it is known that phosphodiesterase-5 inhibition requires androgen to be effective [4]. The advantages and disadvantages of these treatment options should be discussed with the patient and his partner.

Fatigue and Its Impact on Quality of Life

Fatigue is one of the most common side effects of ADT. Although fatigue is very difficult to fight, lifestyle changes and especially physical exercises may help to alleviate fatigue and improve QoL. A systematic review on 34 trials examining the effectiveness of physical exercise in improving the physical functioning and psychological wellbeing of cancer patients during and after treatment suggested that, although most trials reviewed were of moderate methodological quality, cancer patients may indeed benefit from physical exercise [13]. The FRESH START trial randomized 543 subjects with newly diagnosed loco-regional breast cancer or PCa to receive a

10-month specific program promoting diet changes and physical exercise or nonspecific information. Although subjects in both arms significantly improved their lifestyle behavior to a more healthy one, significantly greater improvements were observed in subjects receiving the diet- and exercise-specific information [14]. Physicians should therefore try to convince patients to adopt a healthy lifestyle including a healthy diet and physical exercise. Some practical recommendations for patients on how to deal with fatigue are given in table 2.

Fatigue may be further aggravated by sarcopenia (loss of skeletal muscle mass) resulting from ADT [15]. Sarcopenia may directly impact on muscle strength and reduce physical activity. Maintaining or increasing physical activity is therefore critical in patients treated with ADT.

Anemia is another side effect of ADT that may worsen fatigue [5]. Physicians should therefore closely monitor hemoglobin levels in patients treated with ADT. Although there are effective medical therapies available to treat anemia (e.g. the subcutaneous administration of recombinant human erythropoietin), patients should also be advised to adopt a healthy diet. Patients may be referred to a dietician for further advice.

Psychological Side Effects

ADT may have psychological side effects such as reduced cognitive function (e.g. reduced concentration and memory problems) and emotional instability or even depression [4, 5]. It is important that physicians inform patients and relatives about these side effects and identify early signs of depression or decreased cognitive function in order to ensure rapid referral to a specialist (e.g. a neuropsychologist). It is as well important to explain these side effects to the patient's family so that they understand their nature and origin and can help the patient adapt to them [7].

Cancer Treatment-Induced Bone Loss

Several studies have shown a decrease in bone mineral density (BMD) in men treated with ADT [5]. These men also have an increased risk of fractures and are more likely to require hospitalization for those fractures [16]. A longer duration of ADT seems to increase the risk of fractures [17]. The prevention of osteoporosis in men treated with ADT is therefore critical and physicians should take

appropriate measures to monitor and minimize bone loss. The first steps in its prevention include encouraging patients to make certain lifestyle changes: cessation of smoking, moderate alcohol and caffeine consumption and regular weight-bearing exercises, also called resistance training exercise [5]. Patients should also be encouraged to consume a healthy diet with foods and beverages containing calcium (dairy) and vitamin D (fatty fish). Physical exercise is a very important part of osteoporosis prevention. Resistance exercise is particularly favorable in maintaining and/or improving bone mass and architecture, while being safe for older people [18, 19]. Physical activity outside, with the benefit of being exposed to sunlight, can also be recommended. Second, correct calcium and vitamin D supplementation is necessary. A systematic review including about 64,000 men and women showed that the intake of calcium (1,200 mg or more daily) or calcium with vitamin D (800 IU or more daily) reduced the frequency of osteoporotic fractures by 12% in both men and women of 50 years of age or older [20]. It is recommended that the daily intake of calcium for men with osteoporosis should be 1,200–1,500 mg [21], and that supplementation with cholecalciferol at doses of 800–2,000 IU should be given to maintain serum levels of hydroxyvitamin D at 30 ng/ml [22].

Physicians should closely monitor the patient's BMD by means of dual-energy X-ray absorptiometry (DEXA). Expert panels from the World Health Organization and National Osteoporosis Foundation recommend BMD assessment before initiation of ADT and at regular follow-ups during treatment [23]. Medical treatment with bisphosphonates, such as alendronate, pamidronate and zoledronate, should be considered in patients with fractures or T scores of < -2.5 [23]. Important in the use of any bisphosphonate is the concomitant administration of vitamin D and calcium as without adequate levels of these, bisphosphonates are ineffective [5]. The most promising agent in the treatment of cancer treatment-induced bone loss (CTIBL) is the RANK-L inhibitor, denosumab. Smith et al. [24] have recently reported the results of a randomized, placebo-controlled study evaluating the efficacy of 6-monthly injections of 60 mg of denosumab in 1,468 men receiving ADT for nonmetastatic PCa. Denosumab significantly increased BMD at the total hip (4.8% vs. placebo) and femoral neck (3.9% vs. placebo; $p < 0.0001$). Denosumab was associated with a 62% reduction in vertebral fracture (adjusted $p = 0.01$) at 36 months, with a marked reduction evident within the first year [24].

Metabolic and Cardiovascular Side Effects of ADT

ADT causes changes in the patient's body mass and composition [5, 15]. Suppression of testosterone levels causes a situation known as sarcopenic obesity, combining muscular atrophy and an increase in fatty tissue [25]. By creating an imbalance between lean and fatty mass, sarcopenic obesity induces many of the features of the metabolic syndrome such as increased subcutaneous mass, increased high-density lipoprotein cholesterol and increased adiponectin levels [26, 27]. One of the causes of these metabolic changes in men treated with ADT is the rapid induction of peripheral resistance to insulin, leading to type 2 diabetes [5, 28]. In addition, a decrease in physical activity due to fatigue associated with ADT may be involved [5]. The metabolic changes associated with ADT may have significant consequences for the cardiovascular health of ADT-treated men. Population-based studies have shown that ADT increases the risk of diabetes, coronary heart disease, myocardial infarction and sudden cardiac death [29–31]. Physicians should therefore carefully monitor the metabolic and cardiovascular parameters of patients treated with ADT, including blood pressure, serum lipid level, hemoglobin level and fasting serum glucose levels [4, 7]. Physicians should also encourage patients to adopt a healthy lifestyle including an appropriate low-fat diet and regular physical exercise.

Role of Exercise in the Prevention and Management of Side Effects Related to ADT

Resistance training is a form of strength training in which each effort is performed against a specific opposing force generated by resistance. Resistance exercise is used to develop the strength and size of skeletal muscles. Properly performed, resistance training can provide significant functional benefits and improvement in overall health and wellbeing. Studies conducted by Galvão et al. [32] demonstrated that 20 weeks of progressive resistance exercise performed in a rehabilitation clinic increased muscle strength and endurance and preserved whole-body lean mass with no change in fat mass. Segal et al. [33] demonstrated that men assigned to resistance exercise had less interference from fatigue on activities of daily living and a higher QoL than untrained men. Finally, the same group demonstrated that a combination of both resistance and aerobic exercise mitigated fatigue in men with PCa receiving radiotherapy with or without ADT

[34]. Resistance exercise generated longer-term improvements and additional benefits for QoL, strength, triglyceride levels, and body fat.

Conclusions

It is being increasingly recognized that, although the beneficial effects of ADT are clear, its side effects cannot only be bothersome and have a serious impact on QoL but also potentially cause serious medical problems. ADT should therefore never be initiated before conducting an in-depth discussion with the patient about its benefits, disadvantages and side effects, also taking into consideration the stage of the disease, as the balance between the benefits and disadvantages of ADT will be different for patients in different disease stages. For example, for a patient with metastatic PCa the trade-off of hot flushes for relief of pain and obstructive urinary symptoms may be very acceptable, while hot flushes may be difficult to tolerate for completely asymptomatic PCa patients. Urologists should also learn to see PCa in a more 'holistic' view and not only focus on oncological results since nowadays patients no longer see themselves as passive recipients of care. Therefore, we have to listen to patients' expectations and include patients' preferences. For instance, when selecting the most appropriate treatment modality, PCa patients treated with luteinizing hormone-releasing hormone agonists indicated that they would prefer fewer injections [35]. In this case the use of a 6-month formulation of a luteinizing hormone-releasing hormone agonist would clearly have an added value. Besides the well-recognized bothersome side effects of ADT such as reduced sexual function and hot flushes, there are also more serious side effects such as osteoporosis and metabolic changes leading to an increased cardiovascular risk. These side effects should be carefully monitored and appropriate actions need to be taken to prevent and manage them. In this regard, physicians should adopt a proactive attitude, especially when dealing with young patients with an expected long-term survival. Table 3 gives a checklist for monitoring and managing ADT-related side effects. Proper counseling of patients treated with ADT is necessary to help them recognize, prevent and/or manage side effects. Dietary advice may help patients adopt a healthy diet to minimize metabolic changes, anemia and osteoporosis. Physical exercise has been shown to play a major role and may prevent or minimize some of the more serious side effects of ADT, e.g. the decrease in BMD and increase in body mass. Furthermore, physical exercise

Table 3. Checklist for monitoring patients receiving ADT

Before initiating treatment

- 1 Inform the patient about the occurrence of hot flushes and provide lifestyle recommendations to avoid excessive triggering.
- 2 Inform the patient *and his partner* about libido, mood and cognitive changes. Encourage maintaining and even increasing social activities and networking, possibly referring to patient support groups.
- 3 Inform in due time the patient's general practitioner, cardiologist and endocrinologist about initiation of ADT. Advise the patient to schedule a follow-up visit with these specialists within 6 months.
- 4 Provide dietetic counseling and recommend resistance exercise. This will be done optimally by referring the patient to a dietician, physical therapist or by administering a specifically designed coaching program.
- 5 Search for risk factors of bone loss, and perform an immediate DEXA if present.

During treatment

- 6 In addition to PSA and testosterone measurements and imaging studies that are required for oncological follow-up, it is recommended to assess weight and abdominal perimeter (or preferably body fatty tissue content by impedance technique), blood pressure, and fasting cholesterol (total and HDL), triglyceride and glucose levels. In case of abnormalities, refer the patient to a specialist.
- 7 Advise a DEXA scan after 1–2 years of ADT.

may help fight fatigue, alleviate anxiety and depression, and improve QoL. Patients should therefore be encouraged to increase their physical activity. Exercise training should be tailored to the preexisting physical activity level of the patient and include regular resistance exercise [7]. Physicians should additionally carefully monitor BMD and metabolic and cardiovascular parameters such as blood pressure, abdominal perimeter, serum lipid levels, hemoglobin level and fasting serum glucose level. Specific recommendations should be directed towards the patient's general practitioner so that he can adapt his management of ADT-treated patients and monitor them on a regular basis. All ADT-treated men over the age of 65 should receive supplementary calcium and vitamin D to prevent osteoporosis.

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