

Androgen deprivation therapy: evidence-based management of side effects

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What's known on the subject? and What does the study add?

- The benefits of androgen deprivation therapy (ADT) are well recognized and a multitude of studies have documented the benefits of ADT in conjunction with other therapies. Given the widespread use of ADT due to its important clinical implications, it is imperative that clinicians understand the side effects to limit treatment-related morbidity. There are numerous well recognized adverse effects of ADT, including vasomotor flushing, loss of libido and impotence, fatigue, gynaecomastia, anaemia, osteoporosis and metabolic complications, as well as effects on cardiovascular health and bone density.
- Present study focuses on the most recent evidence-based treatment options for various side effects of ADT.

Objective

- To familiarize clinicians with the various side effects of androgen deprivation therapy (ADT). The present study focuses on the most recent evidence-based treatment strategies for the common side effects of ADT.

Methods

- A PubMed database search was conducted from 2000 to 2012.
- All prospective clinical studies were selected, including randomized and non-randomized clinical trials, as well as meta-analysis studies concerning preventive and therapeutic interventions for various side effects of ADT.
- 'The Oxford 2011 Levels of Evidence' classification system for treatment benefits was used to categorize selected studies.

Results

- Gabapentin shows moderate efficacy for the long-term treatment of hot flashes in a dose-dependent manner.
- A combined resistance/aerobic exercise programme leads to significant improvement in fatigue, sexual function

and cognitive function. A home-based/group exercise programme also improves fatigue and unfavourable metabolic changes.

- Denosumab increases lumbar spine, hip and radius bone mass density, and also reduces the risk of vertebral fractures in men receiving ADT for non-metastatic prostate cancer.
- Metformin coupled with lifestyle intervention is a safe, well-tolerated intervention for adverse metabolic changes. Toremifene improves the lipid profile.
- Intermittent ADT improves early side effects, such as hot flashes, sexual activity, fatigue, and quality of life, although its effect on long-term side effects remains inconclusive.

Conclusion

- Despite significant improvement in management strategies for the side effects of ADT, the best way of preventing side effects is to use ADT only when it is absolutely indicated.

Keywords

adverse effects, androgen deprivation therapy, evidence based practice, prostate cancer, therapy

Introduction

Androgen deprivation therapy (ADT) in the form of chemical castration with gonadotropin-releasing hormone

has established therapeutic benefits, either as primary treatment or in conjunction with other therapies, in men with locally advanced prostate cancer after radiotherapy or prostatectomy. There are well recognized adverse effects of

ADT, such as vasomotor flushing and fatigue, as well as some recently described metabolic complications, including insulin resistance and lipid alterations. Given the widespread use of ADT and the need to limit treatment-related morbidity, it is imperative that clinicians understand the side effects.

Methods

We conducted a PubMed database search from 2000 to 2012 and selected the most recent prospective clinical studies including randomized and non-randomized clinical trials and meta-analysis studies concerning preventive and therapeutic intervention for various side effects of ADT. 'The Oxford 2011 Levels of Evidence' was used to categorize the reviewed studies regarding treatment benefits (Level 1: systematic review of randomized trials or *n*-of-1 trials; Level 2: randomized trial or observational study with dramatic effect; Level 3, non-randomized controlled cohort/follow-up study; Level 4, case series, case-control studies or historically controlled studies; Level 5, mechanism-based reasoning). The present study focuses on the most recent evidence-based treatments for the side effects of ADT.

Results

Vasomotor Flushing

Affecting up to 80% of men on ADT, one of the most bothersome side effects is hot flashes. A loss of negative feedback in hypothalamic noradrenaline production as a result of sex hormones resets the hypothalamic thermoregulatory centre, leading to vasomotor flushing. Currently available therapeutic options for hot flashes can be divided into hormonal and non-hormonal treatments: cyproterone acetate, a steroidal antiandrogen, causes a remarkable reduction in hot flashes at the dose of 100 mg daily, which is comparable to the effect of progestational agents in a randomized clinical trial setting (Level of Evidence [LoE] 2) [1]. However, cyproterone acetate interferes with hormonal therapy and therefore progestational agents such as megestrol acetate and medroxyprogesterone acetate (20 mg once or twice daily) are considered as standard hormonal therapy for hot flashes (LoE 2) [2]. Hormonal treatment results in some undesirable side effects, such as an occasional increase in PSA levels by progestational hormones or breast enlargement and tenderness with oestrogen agents [2].

Various non-hormonal treatments have also been tested in this setting. Both selective serotonin and serotonin norepinephrine re-uptake inhibitors, such as sertraline (LoE 4), venlafaxine (LoE 2), paroxetine (LoE 3) and fluvoxamine (LoE 3), suppress hot flashes by modulating

central dopaminergic activity and appear to have a moderate effect on hot flashes. In a randomized trial, venlafaxine (75 mg daily) was shown to be significantly inferior to hormonal therapies in this regard (LoE 2) [1]. Common side effects, such as dry mouth, nausea, weight gain, night sweats and headache, as well as the need for dose adjustment with respect to age and liver function and to adjust other medications, also limit their daily usage [1].

Recent evidence from randomized clinical trials also shows the moderate efficacy of gabapentin, an antiseizure agent, for the long-term treatment of hot flashes in a dose-dependent manner, where a dose of 900 mg daily correlates with the highest response rate. Common side effects are leukocytopenia with influenza-like symptoms, depressed mood, somnolence, muscle and joint pain, and gastrointestinal symptoms, although the drug is usually well-tolerated (LoE 2) [3].

Traditional acupuncture for 10–12 weeks (twice weekly for 2 weeks and then once a week for 8–10 weeks) also appears to be an option with a moderate (43–78%), long-lasting (9 months) reduction in the frequency of hot flashes (LoE 2). It is considered to act through its effect on β -endorphin, serotonin and calcitonin gene-related peptide activity. Early side effects such as distress, fatigue and haematoma at the insertion site are negligible and there is no specific late adverse event [4]. However, these data should be interpreted with caution because they originate from non-placebo controlled trials. Although hot flashes can be minimized by the aforementioned therapies, there is no ideal solution for hot flashes and the significant risk of hot flashes should be discussed before initiating ADT.

Fatigue

Fatigue is a common consequence (\approx 43%) in men receiving long-term ADT. The loss of lean muscle mass and a concomitant increase in fat mass coupled with pain and depression is the most probable underlying mechanism.

Several well-designed clinical trials have shown the efficacy of exercise and muscle-strengthening programmes with respect to reducing the frequency and severity of fatigue in these patients as a result of improving muscle mass and strength, cardiorespiratory fitness, body function and psychosocial function. Based on a recent meta-analysis of randomized clinical trials, adherence to exercise regimens is currently recommended, including: (i) supervised clinical exercise consisting of progressive resistance training (chest and shoulder press, latissimus pull down, triceps extension, biceps curls, leg extension and curl, and abdominal crunches) with or without aerobic training (15–20 min of cardiovascular exercises, including cycling and walking/jogging at 65–80% of maximum heart rate) two or three times a week for 12 weeks [5] and (ii) an

unsupervised home-based exercise programme of moderate intensity (walking, stretching, light resistance training) three to five times a week plus group training once a week for 16 weeks [6].

The results of two ongoing trials evaluating the efficacy of home-based walking and high-load strength training programme on psychosocial function including fatigue are pending [7,8].

Sexual Side Effects

A decrease in libido and erectile dysfunction is a troubling side effect that occurs secondary to lack of testosterone, which results in decreased nitric oxide levels and loss of intracavernosal pressure. Management strategies for sexual side effects are mostly based on a consensus report from the multidisciplinary ADT Survivorship Working Group, which provides either evidence-based or consensus-based recommendations (LoE 4). These recommendations include the accurate preparation of the couple before administering ADT; medical optimization of ADT to minimize sexual side effects, such as parenteral oestrogen therapy in the form of transdermal oestradiol patches or gel, aiming to preserve libido; and individualized medical and psychological intervention for sexual sequelae, including sexual therapy techniques to invoke an awareness of sexual fantasies, a cognitive reframing of the sexual experience and mindfulness techniques [9]. Orally administered phosphodiesterase inhibitors may be less successful for treating erectile dysfunction in these patients compared to other aetiologies (LoE 3) and it is crucial to inform patients of the importance of physical and mental sexual arousal to trigger the mechanism of action and to maximize the effect of these drugs [9].

Other treatment options include vacuum erection devices, intracorporal injection therapy or the placement of a penile prosthesis. Treatment options for a patient with difficulty attaining orgasm include the use of sexual aids such as intracavernosal injections, vibrators and masturbatory or penetrative aids to induce orgasm. Other sources of stimulation, such as new breast sensitivity or perineal/perianal stimulation and mental adaptation to an altered masculine role, may also be beneficial [9]. Most of these suggestions, however, are based on small non-randomized studies. Data from randomized trials suggest the use of muscle-strengthening exercises as a beneficial auxiliary intervention in some patients (LoE 2) [10].

Skeletal Complications

Loss of bone mineral density (BMD) is another common consequence of ADT that is asymptomatic in most cases, although it may lead to fractures in up to 20% of men on

long-term ADT. Because the length of ADT correlates negatively with BMD, monitoring bone health and bone loss preventive measures are highly advised. It is recommended to perform a baseline evaluation of BMD by dual X-ray absorptiometry before initiating ADT, which is followed by regular BMD measurements based on the initial T-score. Suggested lifestyle changes include increased exercise, calcium (1500 mg) and vitamin D (800 IU) supplementation, cessation of smoking, decreased alcohol consumption, and normalization of body mass index (LoE 1) [11]. With respect to pharmacological intervention, bisphosphonates prevent bone loss and increase the BMD in patients with prostate cancer on long-term ADT. Selective oestrogen receptor modulators such as raloxifene and toremifene citrate have shown promising results with respect to increasing total hip, lumbar spine and femoral neck BMD in men on ADT (LoE 1) [12]. Denosumab, a human monoclonal antibody against RANKL (receptor activator of nuclear factor κ -B ligand), has been shown to increase lumbar spine, hip and radius BMD and to reduce the 3-year risk of new vertebral fractures by 62% at a dose of 60 mg injected subcutaneously every 6 months in men receiving ADT for non-metastatic prostate cancer (LoE 1) [13].

Anaemia

ADT leads to anaemia in as many as 90% of patients and, in most cases, is normochromic and normocytic. Most patients with mild anaemia require no treatment. However, treatment may be warranted in symptomatic patients with severe anaemia. Treatment needs to be individualized considering the risk/benefit ratio of treatment options such as erythropoiesis-stimulating agents (ESAs). Malnutrition and nutrients deficiencies such as iron and vitamin B₁₂/folate should be appropriately addressed by oral or parenteral supplementation. In patients with severe anaemia, metastatic cancer and a limited bone marrow reserve, regular blood transfusions may be the only effective measure (LoE 4). For other anaemic patients, there is strong evidence that ESA has a favourable haematological effect (LoE 2). However, the probability of an increased risk of thrombovascular events after this treatment remains a concern and the impact of ESAs on mortality and overall survival in patients with prostate cancer is controversial. The clinical benefits of other medical treatment options (e.g. low-dose dexamethasone) still need to be investigated [14].

Metabolic and Cardiovascular Effects

A recently recognized complication of ADT is the development of insulin resistance, diabetes mellitus and unfavourable changes in lipid profiles. ADT is certainly associated with metabolic changes; its association with

increased cardiac death, however, is much more controversial, and has not been seen in randomized controlled trials [15]. Because most men with prostate cancer treated with androgen deprivation are older, with either known cardiovascular disease or diabetes mellitus or risk factors for their development, a science advisory from the American Heart Association, American Cancer Society and American Urological Association has considered general preventive strategies such as screening protocols and lifestyle modifications for all men initiating ADT, including yearly lipid profiles, dietary modification or pharmacological treatment if these parameters become abnormal, smoking cessation and weight loss if they are overweight at baseline or become overweight, and regular exercise. For men with previous cardiovascular disease or men who develop cardiovascular disease from ADT, secondary preventative measures, such as statin therapy, antihypertensive therapy, glucose-lowering therapy and aspirin (unless contraindicated), are advised (LoE 4) [16]. A number of therapeutic interventions have also proven beneficial in this regard. Metformin (850 mg daily for two weeks and 850 mg twice a day) plus lifestyle intervention, including dietary advice and regular aerobic exercise for 6 months, is reportedly a safe, well-tolerated regimen leading to a significant reduction in abdominal girth, weight, body mass index and systolic blood pressure (LoE 2) [17]. Aggressive treatment for hyperlipidaemia is not currently recommended because the relationship between adverse cardiovascular events and ADT is not sufficiently understood. The effect of exercise intervention is conflicting where supervised clinical exercise shows no effect on body composition, whereas a home-based/group exercise programme improves systolic and diastolic blood pressure and waist and neck girth (LoE 2) [10].

Cognitive Effects

There is still a lack of convincing evidence concerning the deleterious effect of ADT on cognition, especially verbal, spatial and executive functioning. Advanced age, disease stage and co-morbidities may account for a significant proportion of cognitive disturbances in patients on long-term ADT. Currently, there is no definite recommendation for preventing or treating cognitive impairment in this population. Despite the promising results of short-term transdermal oestradiol therapy (LoE 3), orally administered oestradiol fails to improve cognitive parameters in patients receiving ADT (LoE 2) [2]. Given the serious side effects of exogenous oestradiol therapy, such as thromboembolism and a lack of consensus on the ideal timing for treatment (i.e. before or concomitant with ADT), exogenous oestradiol therapy is not currently recommended. Adherence to an exercise programme also appears to be an efficient countermeasure for cognitive

impairments in patients on ADT. A 12-week combined resistance/aerobic exercise programme reportedly leads to a significant improvement in cognitive function (LoE 2) [5].

Intermittent ADT

Intermittent ADT (IAD) as a cyclic therapy consisting of an on-treatment period lasting 6–9 months followed by an off-treatment period of variable length, based on PSA response, is an appealing alternative for continuous ADT (CAD), with comparable efficacy in terms of biochemical progression, progression-free survival and overall survival, as well as fewer side effects. To be more specific, there may be an improvement in early side effects such as hot flashes, sexual activity and fatigue, as well as quality of life, in patients with prostate cancer receiving IAD. Nevertheless, the effect of IAD on long-term side effects is inconclusive. There is no evidence of a reduced risk of anaemia and cardiovascular adverse events compared to CAD and its effect on BMD improvement is only minimal. In addition, no published data are available to show that metabolic changes in patients with prostate cancer treated with CAD can be diverted by the introduction of IAD. Therefore, it appears that more evidence is required to draw a conclusion on the potential advantage of IAD over CAD in terms of tolerability and safety profile (LoE 1) [18]. A recently reported 17-year randomized SWOG study concluded that IAD was non-inferior to CAD in extensive disease; however, IAD was statistically inferior in minimal disease, suggesting that CAD is the preferred treatment in this group [19].

Another important factor that should be considered is the variance in the pattern of ADT use. ADT has been commonly prescribed even when there is weak or no evidence of benefit. Interestingly, more of this variance was reportedly attributable to the physician than to patient and tumour characteristics. Therefore, primary care physicians should carefully consider the choice of urologist for their patients who may need ADT [20].

Discussion

The benefits of ADT are well documented, particularly when used as an adjunct to radiotherapy or surgery. However, it is imperative to individualize the risk–benefit ratio and the optimal length of ADT to minimize related side effects. Specialists treating patients with prostate cancer, as well as primary care providers, need to be aware of the potential for serious side effects, which may occur over years of therapy and have unrecognized lethal consequences. Active interventions, including exercise, diet modification and treatment of metabolic syndromes, are simple measures that can have profound effects. Prevention or mitigation of osteoporosis can also be achieved by

lifestyle modifications and several pharmacological interventions. Hyperlipidaemia should be aggressively managed to decrease cardiovascular disease. IAD can significantly reduce the early side effect profile at the same time as producing similar therapeutic benefits, although we await the results of several more phase III trials. Clinicians should consider and assess co-morbidities and functional status of patients before initiating ADT, keeping in mind that the best way of preventing side effects is to use ADT only when it is absolutely indicated. Given the side effect profile and lack of known benefit, it is prudent to consider active surveillance in elderly patients with PSA-only recurrences, particularly those with pre-existing cardiovascular disease, along with a close monitoring of the PSA level doubling time to help guide treatment decisions.

Conflict of Interest

None declared.

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Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density; CAD, continuous androgen deprivation therapy; ESA, erythropoiesis-stimulating agent; IAD, intermittent androgen deprivation therapy; LoE, Level of Evidence.