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Androgen deprivation therapy

Managing side effects

Background
Prostate cancer is the most common nondermatologic cancer in Australian men. Androgen deprivation therapy (ADT) as a modality of treatment is being increasingly used much earlier and for a longer period of time. Its various regimens all have side effects which influence the patient's health and quality of life.

Objective
This article discusses practical evidence based management options for treating the short and long term side effects of ADT.

Discussion
The side effects of ADT can be categorised as sexual, physical, metabolic, emotional and systemic. A combination of prediction and early recognition is useful in diagnosing side effects. Tailored strategies are available to combat the problems.

Table 1. Androgen deprivation therapies

Modality	Method
Surgical	• Bilateral orchidectomy
Medical	• LHRH agonist: – goserelin acetate – leuprorelin acetate
	• LHRH antagonist (not available in Australia): – abarelix
	• Antiandrogens: – steroidal – cyproterone acetate – nonsteroidal – flutamide, bicalutamide, nilutamide

Androgen deprivation therapy (ADT) has been the mainstay of management for advanced prostate cancer. It is increasingly used in younger men with nonmetastatic disease as neo-adjuvant therapy to pretreat (shrink) tumours before definitive radiotherapy, and also as adjuvant therapy after radiotherapy or radical prostatectomy.[1] In general, ADT achieved a remission in 80–90% of men with advanced prostate cancer, and results in a median progression free survival of 12–33 months.[2]

Mechanism of action

Androgen deprivation therapy acts to inhibit the action of androgens (primarily testosterone). The various ADT protocols act in the hypothalamic-pituitary-testicular axis to inhibit the production of testosterone and/or block testosterone receptors (*Figure 1*).[3]

Commonly available ADTs can be broadly organised into surgical and medical therapies (*Table 1*). While there is a wide selection of agents, luteinising hormone releasing hormone (LHRH) agonists are currently administered as monotherapy to approximately 90% of men receiving ADT.[4]

Side effects

Table 2 lists the side effects of ADT. *Table 3* gives practical, evidence based management options for combating these side effects.

Hot flushes

Hot flushes (or flashes) are the most common side effect, experienced by up to 80% of men undergoing ADT,[5] and are described as 'sudden, transitory sensations of warmth and flushing over the face and upper part of the body'. They are thought to occur as a result of a rapid decline in circulating steroid hormones. Flushes can begin fairly soon after starting ADT and long term prevalence is variable. At their worst, flushes can be debilitating.

Various treatment modalities have been trialled with varying success, although there is a lack of large, prospective randomised controlled trials. Traditionally the progestin, megestrol acetate (20 mg orally twice daily) has been used and is generally well tolerated (*Table 4*).

Figure 1. Mechanism of action of ADT

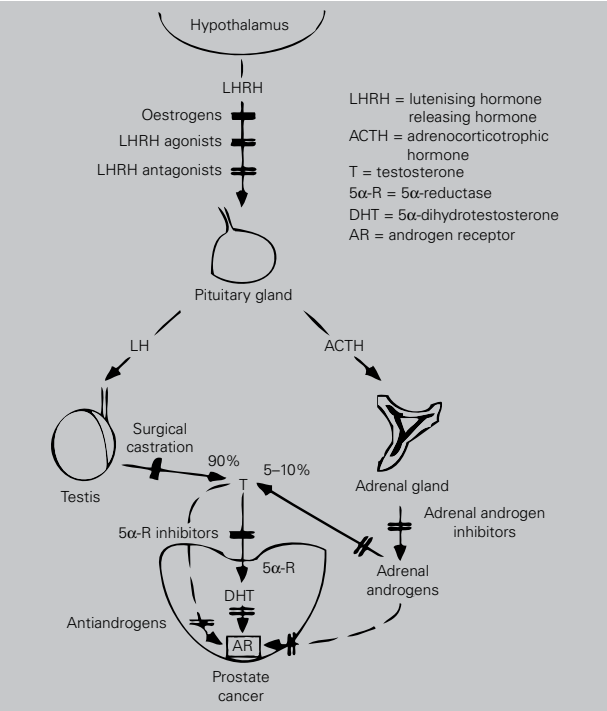

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Table 2. Side effects of androgen deprivation therapy

Sexual	• Erectile dysfunction • Loss of libido • Genital shrinkage
Physical	• Weight gain • Gynaecomastia • Muscle weakness and atrophy
Metabolic	• Osteoporosis • Anaemia • Hot flushes • Hypertension, diabetes, heart disease, lipid abnormalities
Emotional/cognitive	• Depression • Emotional lability
Systemic	• Fatigue • Lack of energy

Cyproterone acetate (50 mg orally twice daily) has also demonstrated efficacy, with 80% of patients showing improved symptoms.[6]

Antidepressants in the form of serotonin noradrenalin reuptake inhibitors (SNRIs) and selective serotonin receptor uptake inhibitors (SSRIs) have also been successful with venlafaxine and sertraline having shown improvement in symptom control.[7] Alternative therapies such as acupuncture, herbal preparations and vitamin E have shown some success in pilot studies.[5,8]

Although the best treatment option is unclear, a suggested plan is to begin with an SSRI or SNRI and reserve hormone therapy for refractory cases.[9]

Sexual side effects

Quality of life studies have found a significant decline in sexual interest in patients undergoing ADT, with erectile dysfunction being a major associated problem.[10–13] These changes are common and usually occur within the first few months of commencement of ADT.[5]

A less commonly reported but known side effect is genital shrinkage, which involves the loss of penile length and girth, as well as testicular shrinkage.[13]

Sexual dysfunction is best discussed before commencement of therapy. A clear understanding of the impact on the patient's quality of life must be determined. Involving sexual counsellors is of proven benefit and is wort hwhile to discuss issues regarding sexual performance, intimacy and relationship matters.

Loss of libido is an extremely difficult side effect to treat effectively. Strategies are emerging to minimise these effects, in particular the use of intermittent ADT.[14] Patients who maintain sexual interest have many treatment options available for erectile dysfunction. The oral phosphodiesterase type 5 inhibitors – eg. sildenafil citrate, tadalafil, vardenafil – are commonly utilised, although their efficacy varies due to phosphodiesterase-5 inhibition requiring the presence of androgen to be effective.[15] Another common treatment option is intracavernosal injection of alprostadil.

Penile prosthetic surgery with a range of inflatable and malleable implants has become popular over recent years with advanced prosthetic and surgical techniques (*Figure 2*). Another option is the use of vacuum constriction devices. Many patients are unaware or reluctant to ask for these options, and direct questioning by a trusted physician may allow for a frank and productive discussion about these side effects and further management options.

Osteoporosis

The association between ADT and accelerated loss of bone mineral density (BMD) and consequent fracture risk is now well established,[16,17] with ADT recognised as causing a 3–5% annual decrease in BMD and an up to six-fold increase per year in fracture risk.[18]

A number of recommendations have been made to prevent or reduce the risk of fractures including: smoking cessation, alcohol and caffeine reduction, and a balanced program of resistance and aerobic exercises.[19,20] In addition, supplementation with vitamin D (400 IU/day) and calcium (1000 mg/day) is recommended for all men commencing long term ADT, as often there is a pre-existing deficiency.[5] Vitamin D levels can be checked by measuring 25 hydroxy vitamin D.

Treatment with bisphosphonates has been shown to be highly successful in preventing high bone turnover and loss of BMD.[21] Alendronate, pamidronate and zoledronate are the three major bisphosphonates. Current guidelines recommend the use of bisphosphonates for all patients with proven metastatic disease, whereas for patients with nonmetastatic disease, treatment is generally considered for any patient with an insufficiency fracture or proven osteoporosis.[17,22]

Table 3. Management options for selected side effects

Side effects	Management
Sexual	
Erectile dysfunction	• Phosphodiesterase type 5 inhibitors • Intracarvernosal injection • Penile implant surgery
Genital shrinkage	• Cosmetic surgery
Metabolic	
Hot flushes	• SNRI or SSRI antidepressants (eg. venlafaxine, sertaline) • Hormone therapy (eg. megestrol acetate)
Cardiovascular disease	• Appropriate medical management and risk reduction
Anaemia	• Recombinant erythropoietin
Osteoporosis	• Lifestyle – smoking cessation, alcohol and caffeine reduction, exercise • Vitamin D and calcium supplements • Bisphosphonates
Physical	
Gynaecomastia	• Breast irradiation • Subcutaneous mastectomy, liposuction
Muscle atrophy, weakness and weight gain	• Resistance and aerobic exercises
Cognitive	
Depression and reduced attention and memory	• Support groups, psychotherapy, pharmacologic therapy

Table 4. Side effects of treatments for ADT related hot flushes

Treatment	Side effects
Megestrol acetate	• Chills • Weight gain • Carpal tunnel type pain • Fluid retention
Cyproterone acetate	• Nausea • Fatigue • Dyspnoea • Breast tenderness • Thromboembolism
Selective serotonin receptor uptake inhibitors	• Tremor • Dry mouth • Dizziness • Insomnia • Agitation • Anorexia
Vitamin E	• Increased bleeding risk

The bisphosphonate zoledronic acid, has not only been shown to reduce skeletal related events (including fractures) and reduce pain related to metastatic disease, but has also been proven to increase BMD.[22] In Australia, zoledronic acid is currently subsidised only for the treatment of patients with bone metastases from hormone resistant prostate cancer.[23]

Noted complications of bisphosphonates include nausea, constipation, gastro-oesphageal ulceration, renal impairment and osteonecrosis of the maxilla and mandible. These complications need to be discussed and monitored when managing patients on this therapy.

Body composition and metabolism

Multiple studies have shown significant alterations in metabolic indices in patients on long term ADT. These include significant increases in weight, fat body mass, fasting blood sugar level, serum cholesterol and leptin. In line with these effects, ADT has been shown to increase the risk of diabetes, coronary artery disease, acute myocardial infarction, and sudden cardiac death.[25–27] Furthermore, the most common cause of death in men with prostate cancer who are well controlled is an adverse cardiac event.[28]

There are no current protocols for the prevention and management of these metabolic and cardiovascular effects. It is reasonable, however, for patients to be assessed for risk before treatment commencement and to be closely monitored for these changes during therapy. Appropriate medical management to minimise risk will need to be initiated and tailored to the individual patient. Part of this management will involve an exercise regimen, which has been shown to be helpful in managing weight gain and insulin resistance.[20]

Mental health and cognitive function

Testosterone has neuropsychological effects in men which impact on cognitive function, mood and self esteem. As such, diminished levels of testosterone associated with ADT often produce a degree of depression. Sexual dysfunction, fatigue and lack of energy are also likely contributors to depressive mood in ADT patients. Along with diminishing quality of

life, these changes can place a strain on relationships and worsen self image, leading to social isolation and exacerbating further depression.

Management of depression may involve a combination of psychotherapy, support groups and pharmacologic therapy. A regular resistance exercise program has shown to be of benefit if fatigue is a contributing factor.[20]

Anaemia

Within 1 month of initiating ADT, most men experience a greater than 10% decline in haemoglobin levels, resulting in a normochromic normocytic anaemia. In 13% of patients this produces symptomatic anaemia, with a resulting decrease in quality of life. The anaemia typically resolves after discontinuation of ADT and can also be easily corrected with subcutaneous recombinant human erythropoietin (150 U/kg 3 times per week) if deemed appropriate by a haematologist.[4]

Gynaecomastia and breast tenderness

Gynaecomastia is attributed to an increase in the ratio of oestrogen to androgen activity. It is often associated with breast pain and can lead to irreversible fibrosis when present for at least 1 year.[29] The incidence has been shown to vary with the type of ADT, ranging from 1–16% with LHRH agonists to 79% with nonsteroidal anti-androgen therapy.[30] Treatment options include breast irradiation (which may relieve breast pain but is seen to be less effective in reducing breast size) or surgery (subcutaneous mastectomy and liposuction).

Although there is evidence showing an increased risk of breast cancer in patients receiving oestrogen therapy and a theoretical risk due to the relative increase in oestrogen activity on breast tissue, there is paucity of evidence suggesting a link with current ADT regimens.[31]

Alternative regimens of ADT

Intermittent androgen deprivation therapy

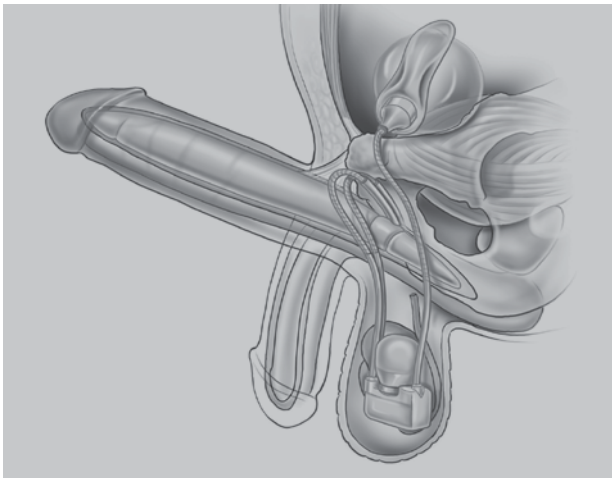
Intermittent androgen deprivation therapy (IADT) has been proposed as an alternative approach to not only minimise long term side effects but also to delay development of the androgen independent state.[13]

The proposed method involves utilising hormone suppression in a cyclic fashion, with induction treatment for a fixed interval or until maximal response is achieved (usually defined by prostatic specific antigen [PSA] criteria, generally <4). The therapy is discontinued and re-initiation based upon predefined threshold levels of PSA, generally 10–20 as agreed upon by the urologist or oncologist and patient. By restoring the body's hormonal axis, IADT aims to reduce treatment related effects during periods of ADT withdrawal.

Significant improvements in quality of life have been demonstrated with the use of IADT. One study demonstrated that libido increased in 75% of patients and erections improved in 62% of patients while being deprived of treatment, while hot flushes disappeared in 60% and energy levels improved in 42% of patients.[32]

The bone sparing effect of IADT has also been clearly established, with one study showing a loss of 2–4% at 2 years compared with a loss of 10% with continuous ADT.[33]

Figure 2. Three piece inflatable penile implant



The use of IADT remains controversial however, as its impact on disease control and survival compared to continuous ADT remains uncertain.[34] Although several published phase II trials have shown that IADT does not compromise the time to progression or survival in men with prostate cancer, and interim results from ongoing phase III trials have shown comparable efficacy to continuous ADT, its use remains contentious but promising.[35,36]

Sequential androgen blockade

Sequential androgen blockade is a regimen utilising a 5a-reductase inhibitor (eg. finasteride) in conjunction with an anti-androgen (eg. cyproterone acetate) in order to block the conversion of testosterone to its active metabolite dihydrotestosterone, and also to prevent testosterone and dihydrotestosterone from binding to the androgen receptor (*Figure 1*). The potential benefits over an LHRH analogue are derived by leaving circulating testosterone levels intact while achieving androgen deprivation at the cellular level. Although having demonstrated efficacy, this modality is still in trial phase and is considered experimental.

Delayed treatment

There are no clearly established benefits to commencing ADT upon diagnosis of prostate cancer (early treatment) as opposed to waiting until a patient becomes symptomatic from the primary lesion or metastases (delayed treatment). Evidence supporting early commencement of ADT in reducing disease progression and complications due to progression must be balanced against the potential improvements in quality of life afforded by delaying therapy.

Conclusion

The increasing trend of younger men with prostate cancer potentially leads to the earlier use of ADT if attempts at cure are unsuccessful. This means that increasing numbers of men will be using ADT for

longer periods. As a result, potential long term side effects need to be addressed early.

While the well established sexual side effects of ADT are distressing, concerns over metabolic changes including cardiovascular risk and physical and mental wellbeing, are increasingly being acknowledged. Together with current strategies, the advent of newer ADT protocols will help combat these side effects, therefore improving quality of life for these men.

Conflict of interest: none declared.

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