Osteoporosis from androgen deprivation therapy in prostate cancer treatment

BACKGROUND

Bone complications from metastatic disease in prostate cancer have been well documented. Osteoporosis from androgen deprivation therapy (ADT) can further impair quality of life in this already susceptible age group.

OBJECTIVE

We aimed to assess the intermediate and long term effects of ADT on bone density and the development of osteoporosis in men with prostatic cancer, and outline some practical assessment, management and treatment options.

DISCUSSION

Osteoporosis, exacerbated by the use of ADT, reduces both the survival and quality of life of men who may otherwise live for many years with their well controlled prostate cancer. Hence, both preventive and treatment options should be explored and tailored to the individual, including lifestyle modifications (exercise, smoking cessation), vitamin D and calcium supplementation, and the use of bisphosphonates.

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Androgen deprivation therapy (ADT) is used increasingly in the treatment of prostate cancer. Its efficacy in all stages of prostate cancer has been well documented in recent years.[1–3] Androgen deprivation therapy has a significant side effect profile (*Table 1*). One of the most significant of these is osteoporosis, particularly with long term therapy.[4] Accelerated bone leaching and declining bone mineral density in this older, osteoporotic susceptible group, further compounds the skeletal complications of those with prostate cancer. This is of significant concern as one-third of Australian men aged over 60 years suffer from osteoporotic fractures,[5] with this figure expected to double by 2026 and quadruple by 2051.[6]

Osteoporosis and fractures carry a significant morbidity and mortality. Up to 20% of men with hip fractures die during initial hospital admission or within 6 months.[7] Men also have higher morbidity and associated complications from hip fractures than women.[8] Therefore, preventive strategies and treatments for osteoporosis, particularly in the context of ADT and prostate cancer are needed.[9]

Method

We reviewed the published literature on the prevention and management of osteoporosis secondary to ADT in men with prostate cancer by researching the MEDLINE database (from January 1966 to April 2005) and the abstracts and texts from recent meetings.

Discussion

ADT for prostate cancer

The combined use of luteinising hormone releasing hormone (LHRH) agonists (*Table 2*) and anti-androgens results in total androgen blockade. More men will be subject to the effects of osteoporosis as ADT is used increasingly in the management of early and localised prostate cancer in combination with external beam radiotherapy.[3]

Osteoporosis from ADT

Although the association between hypogonadism and low bone mineral density (BMD) has been established,[10–12] the mechanism of bone loss in osteoporosis due to ADT is not well understood. Theories include the absence of circulating testosterone which bind to androgen receptors on osteoblasts mediating its proliferation,[13] or indirectly through reduced substrate for the peripheral conversion of testosterone to oestrogen which positively maintains bone mass.[14] The effect of androgen activity on muscle strength which in turn effects bone mass is also important.[12]

The reduction of bone mass in hypogonadal men

and postmenopausal women is characterised by osteoclastic activation and increased bone turnover. The initial ADT associated bone loss is not only significantly higher, but persists when compared to the slowing in later menopause.[15] While the magnitude and prevalence of low BMD among men commencing ADT is unknown,[16] BMD loss is estimated at 3–5% annually in the first few years[17] with measurable changes occurring as little as 9 months after the commencement of LHRH agonist therapy.[18] Shahinian[19] recently showed that ADT is associated with an increased fracture risk in older men with prostate cancer. In this important study, 19.4% of those who received ADT had a fracture, compared with a 12.6% rate of fracture in those not receiving ADT.[19] In addition, a significant dose response relationship was established between the number of doses of ADT administered and increasing fracture risk.

Table 1. Side effects of ADT

Hot flushes
Tiredness
Reduced libido
Erectile dysfunction
Genital shrinkage
Weight gain
Hair loss
Reduced higher mental function
Gynaecomastia
Deep venous thrombosis
Pulmonary embolus
Gastrointestinal upset
Liver dysfunction
Shortness of breath
Anaemia
Osteoporosis
Muscle weakness
Sleep disturbance
Unpleasant dreams
Flare reaction

Table 2. Common androgen deprivation therapies

LHRH agonists
Goserelin acetate (Zoladex)
Leuprorelin acetate (Lucrin Depot, Eligard)
Antiandrogens
Cyproterone acetate (Androcur, Cyprone, Cyprostat, Procur)
Flutamide (Eulexin, Fugerel, Flutamin)
Bicalutamide (Cosudex)
Nilutamide (Anandron)
Other
Surgical orchidectomy

Diagnosis

Due to its multifactorial aetiology, screening recommendations in men have not yet been established. Rather, consideration of factors such as age, physical activity, tobacco and alcohol use, and the presence of hypogonadism need to be considered when deciding the timing of screening.[9,13] Any fractures induced by minimal trauma require confirmation on plain X-ray, or computerised tomography/nuclear medicine scanning. Determining BMD is by dual energy X-ray absorptiometry (DEXA) testing. DEXA scans of the femoral neck or total hip is still considered the gold standard and is suggested before ADT commencement.[17,20] A follow up DEXA scan after 12 months is recommended, and annual scans continued if there are significant losses in BMD. In those with borderline BMD scores on the initial DEXA scan, a follow up scan at 6 months might be considered, however the Medicare Benefits Schedule only allows a rebate for scans at annual intervals. The additional use of biochemical markers of bone turnover as independent risk factors for fracture may influence the decision to treat. These may be particularly useful in patients near the radiological osteoporotic cut-off, or for monitoring response to osteoporosis treatment.[21]

Management

Management of patients on ADT and its effect on BMD involves detailed informed consent and risk/benefit analysis of various treatments.[13] Effective conservative measures of lifestyle modification include smoking cessation,[22] alcohol and caffeine reduction, and a balanced program of resistance[23,24] and aerobic exercises.[25]

Vitamin D and calcium

Although the efficacy of vitamin D and calcium supplementation in osteoporosis prevention has not been studied specifically in patients on ADT, it has been documented to be effective in other at risk groups including men aged over 65 years (by increasing their BMD)[26] and in patients starting on corticosteroids (by preventing lumbar and forearm bone loss).[27] It is likely that similar benefits would be obtained in patients on ADT.

Table 3. Available bisphosphonates

Alendronate sodium (Fosamax)
Disodium etidronate (Didronel)
Residronate sodium (Actonel)
Sodium clodronate tetrahydrate (Bonefos)
Tiludronate disodium (Skelid)
Disodium pamidronate (Aredia)
Zoledronic acid (Zometa)

Calcium supplementation should aim to maintain total daily calcium intake at 1200–1500 mg per day, while vitamin D status should be determined and supplementation tailored to treat deficiency.[20,28–30] In Australia, calcium is available in its carbonate, chloride, citrate and phosphate forms with most preparations containing 250–600 mg calcium per tablet. Calcium citrate is less cost effective,[31] but may be preferred in renal calculi patients as citrate in urine inhibits calcium oxalate precipitation.[32] Calcium supplements taken in the evening may have the advantage of suppressing nocturnal bone resorption,[32] and importantly will not reduce morning bisphosphonate absorption.

Bisphosphonates

Bisphosphonates are potent, specific osteoclast inhibitors preventing bone resorption with a documented efficacy in both men with primary osteoporosis[33] and in men with prostate cancer without bone metastases on ADT (intravenous pamidronate prevented BMD loss and intravenous zoledronic acid increased BMD[29,34]). The bisphosphonate, zoledronic acid, has also been shown to reduce skeletal related events including fractures and reduce pain in men with hormone refractory prostate cancer with bony metastases.[35] Bisphosphonates available under the Pharmaceutical Benefits Scheme (PBS) are shown in *Table 3*, but only oral preparations of alendronate (Fosamax™) and residronate sodium (Actonel™) may be prescribed on authority prescription in cases of established osteoporosis. Intravenous zoledronic acid (Zometa™) is currently authorised only for the treatment of bone metastases from hormone resistant prostate cancer. A prospective bisphosphonate trial for men on ADT for treatment of localised carcinoma of the prostate is being conducted at present by the

Trans-Tasman Radiation Oncology Group (TROG). One of the objectives of this randomised multicentre trial – Randomised Androgen Deprivation and Radiotherapy (RADAR) – is to test the hypothesis that use of zoledronic acid will reduce osteopenic fractures, improve BMD, delay onset of bony metastases, and improve quality of life.

Intermittent ADT

Intermittent ADT has been proposed as a possible alternative to minimise its long term side effects, particularly osteoporosis. Suggestions include LHRH agonist therapy until the prostate specific antigen (PSA) falls to its lowest point (eg. PSA <4) and to recommence only if PSA levels rise again (eg. PSA 10–20). Grossfeld[36] has shown clinical improvements in health related quality of life measured using SF-36[37] and University of California Los Angeles Prostate Cancer Index[38] during the off phase cycle of intermittent ADT. This strategy may be helpful in minimising side effects other than ostoeporosis.[17,18] Further evaluation of this regimen is required as its efficacy and safety is uncertain.

Conclusion

Excess bone loss and osteoporosis is a common problem in men on ADT for prostate cancer. These patients are at increased risk of fracture related morbidity and mortality and therefore minimisation of the impact of ADT on bone loss should be a priority at the initiation of therapy. Standard osteoporosis screening and management recommendations for prostate cancer patients on ADT are still evolving, particularly for those with early stages of disease. Evidence suggests that screening with DEXA scans should take place at the initiation of ADT, and then approximately every year after its commencement. Lifestyle modification measures aimed at limiting bone loss such as smoking cessation, alcohol reduction, regular weight bearing exercise, together with calcium and vitamin D supplementation are essential in all patients commencing ADT therapy. Treatment with oral bisphosphonates should be considered for any patient with an insufficiency fracture or DEXA proven osteoporosis. Intravenous bisphosphonates should be considered in patients with bony prostatic metastases, especially those with hormone resistant disease. Their prohibitive cost essentially limits their use to this group at present. Many questions remain on the benefits and efficacy of intermittent ADT on the various stages of prostate cancer but can be contemplated in men at high risk for osteoporosis.

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