Management of bone toxicity in men treated with androgen deprivation therapy

JOANNA DAVIES, AJAY AGGARWAL AND HEATHER PAYNE

THE CASE

A 72-year-old man presented to the urology clinic with lower urinary tract symptoms and an elevated prostate-specific antigen of 51.3ng/ml. He was subsequently diagnosed with T2B N0 M0 prostate cancer Gleason 5+4 in five of 12 cores, maximum core length 75 per cent. He was treated with neoadjuvant luteinising hormone-releasing hormone (LHRH) agonist, radical radiotherapy and three years’ adjuvant LHRH agonist. Prior to starting treatment he underwent assessment of his bone mineral density (which was normal) and was commenced on prophylactic vitamin D and calcium supplementation, as well as being given lifestyle advice. During treatment, he developed polymyalgia rheumatica and was treated with prednisolone and alendronate.

In this new series, the authors present cases of men being treated with androgen deprivation therapy, and highlight their management to prevent and treat associated toxicities. The first article in this series will consider the potential bone toxicity of luteinising hormone-releasing hormone agonists.

The symptomatic benefits of androgen deprivation therapy (ADT) as primary management of advanced prostate cancer and the survival advantages when used in the adjuvant setting for locally advanced disease are well established. The side-effects of ADT are well recognised, but should not prevent the use of hormone treatment for those men who will benefit. However, the potential risks should be considered and discussed with all men embarking on hormone therapy so that preventative strategies can be implemented where possible and early detection of toxicities and intervention can be achieved.

Given the high prevalence and survival rates of prostate cancer, assessment and management of the long-term sequelae...
of both the disease and its treatment are essential. Bone health is rapidly being recognised as one of the most important considerations when managing patients treated with ADT. This is used in both metastatic and locally advanced disease and treatment is frequently continued over long time periods. The effects on bone occur as a result of drug-induced hypogonadism, which causes lower levels of circulating testosterone and oestrogen. This in turn leads to increased levels of bone resorption and reduced levels of bone formation, with subsequent reduction in bone mineral density (BMD) and increased risk of fractures (Figure 1).1,2

It has been shown that the relative risk of hip fracture in men is 3.0 (range 1.7–5.4) for each standard deviation decrease of BMD at the hip.3 Data suggest a negative association between skeletal fractures and both quality of life and overall survival in patients treated with ADT.4,5 In spite of these facts, there is little comprehensive guidance regarding screening and management of this important treatment complication,6 and practices are known to vary between clinicians.7

THE EXTENT OF THE PROBLEM

Traditionally, osteoporosis has been considered to affect predominantly postmenopausal women. However, it is increasingly being recognised that a large proportion of men are also affected and it is often underdiagnosed and undertreated.8 It is estimated that one-third of all hip fractures worldwide affect men and it is known that following hip fractures men have a higher mortality than women.8

The World Health Organization (WHO) defines osteoporosis as a BMD of 2.5 standard deviations below the mean BMD of a young healthy adult (the t-score).9 Osteopaenia is defined as a BMD of between 1 and 2.5 standard deviations below the mean BMD of a young healthy adult.

Osteoporosis rates in patients with prostate cancer are high. Morote et al. demonstrated osteoporosis rates of 35.4 per cent in hormone-naïve men with non-metastatic prostate cancer (age range 54–89 years) compared to 80 per cent in patients treated for 10 years with ADT.10 There is evidence that the length of ADT is associated with the amount of loss of BMD11 and also with increased fracture rates.12 It is unclear if intermittent androgen blockade has a different effect on BMD.13 Evidence suggests that reduction in BMD can be detected within a few months of starting ADT and is maximal in the first year of treatment, with an average reduction of 3–7 per cent in BMD per year.1,10,14 This is significantly greater than the normal reduction in BMD seen in aging men, which is estimated as 0.75 per cent per year.15 It is also interesting to note that there is evidence that, even without treatment with ADT, prostate cancer is associated with lower BMD.16

Retrospective information from the records of more than 50000 men diagnosed with prostate cancer in the SEER database has been evaluated in order to determine the fracture risk for men treated with ADT.17 The results demonstrated the occurrence of any fracture in 19.4 per cent of men treated with ADT compared with 12.6 per cent of men with prostate cancer who were not androgen deprived. The relative risk of fractures increased with the duration of therapy.

As in the general population, a number of patient characteristics are known to be protective, including Afro-Caribbean ethnicity and high body mass index (BMI). Factors increasing the risk of osteoporosis include a sedentary lifestyle, alcohol, smoking, age, thyroid dysfunction, glucocorticoid use and vitamin D deficiency.18 As prostate cancer most commonly occurs in older men, some of these pre-existing risk factors are more likely to be present, as demonstrated in our case.

SCREENING AND DIAGNOSIS

The European Association of Urology recommends assessing the BMD of all men starting on long-term ADT.18 The screening investigation most commonly used is dual-energy X-ray absorptiometry (DEXA), which assesses BMD at two sites: the lumbar spine and hip.

Patients with confirmed osteoporosis or osteopaenia with associated risk factors (outlined below) should commence treatment as discussed in the next section. If treatment is not required, it is usually recommended that the DEXA scan should be repeated at two-yearly intervals.

As well as using the DEXA results to guide management, it is also important to conduct a thorough assessment of a patient’s osteoporosis risk prior to starting ADT. This includes checking for risk factors, including past history of fragility fracture, family history, concurrent corticosteroid therapy, low BMI of less than 19kg/m2, heavy smoking and high alcohol intake. In these patients it may be appropriate to start treatment even in the absence of DEXA evidence of low BMD or in patients with a t-score of greater than −2.5.19 Fracture risk can be estimated using the WHO fracture risk assessment tool and treatment can be planned accordingly.20
TREATMENT TO IMPROVE BONE HEALTH

Men should receive guidance on non-pharmacological measures to preserve bone health prior to commencing ADT. This includes regular exercise, smoking cessation, reduction of alcohol intake and maintenance of a healthy BMI.13

In men receiving ADT, progressive training improves muscle strength, functional performance and balance, while gentle regular exercise reduces cancer-related fatigue, especially when delivered in supervised programmes. Regular exercises are also important to maintain and build healthy bones. These should include weight-bearing exercise (regular walking), flexibility exercises (gentle yoga), resistance exercises that build muscle and weight training or water exercise. A randomised controlled trial of resistance and aerobic exercise in 121 men receiving radical radiotherapy plus ADT for prostate cancer demonstrated a significant improvement in muscle strength, abdominal fat, triglyceride levels and quality of life.21

The overall risk of osteoporosis can be reduced by ensuring sufficient vitamin D and calcium in the diet, with advice to eat more foods such as soya products, spring greens, beans and fish with soft bones (sardines and pilchards). It is also recommended that calcium and vitamin D supplementation should be given to men commencing ADT if dietary intake may be inadequate.7 This has been shown to be most effective in doses of 800IU of vitamin D and 1200mg of calcium per day for reducing osteoporotic fractures in men and women.22

Bisphosphonates are used in primary and secondary prevention of osteoporotic fractures and act by inhibiting osteoclast-mediated bone resorption. Their role is well established in managing osteoporosis in postmenopausal women, but there is less evidence in men. However, the data that do exist support the use of oral bisphosphonates as in women.19

In prostate cancer, bisphosphonates are commonly used to manage skeletal-related events in metastatic disease. While there is less extensive evidence for their use in managing ADT-related bone loss, there is evidence to support the use of oral alendronate and intravenous pamidronate or zoledronic acid in this setting.23–25 However, there is not a consensus as to which individual drug and dosing regimen should be used.19 This is likely to be guided by clinical factors and local policy, including cost considerations.

Selective oestrogen receptor modulators (such as raloxifene and toremifene) have been shown to increase BMD and reduce fracture risk in patients with prostate cancer.26,27 However, there is an increased incidence of venous thromboembolism in patients treated with these drugs.28

Denosumab is a fully humanised monoclonal antibody that specifically targets and inhibits RANK-L-mediated activation of osteoclasts. It has been approved by NICE for the management of osteoporosis in postmenopausal women and also for managing bone metastases in patients with certain tumours. The Hormone Ablation Bone Loss Trial showed that in men with prostate cancer at increased risk of fracture treated with ADT, denosumab resulted in significantly increased BMD and reduced vertebral fracture rates without causing increased toxicity or adverse events.19 Denosumab is currently licensed in the USA and EU for this indication, but in the UK is not currently approved for this by NICE.

CONCLUSION

The patient from our case who was commencing on long-term ADT was managed appropriately with initial BMD assessment, lifestyle advice and calcium and vitamin D supplementation. When he developed polymyalgia rheumatica and was commenced on glucocorticoid therapy, he had acquired an additional osteoporosis risk factor and therefore oral bisphosphonate therapy was also prescribed. He will continue to have repeat DEXA scans at yearly intervals with a view to a change to systemic bisphosphonate therapy should the BMD decrease further.

Declaration of interests

Heather Payne has attended and received honorarium for advisory boards and served as a consultant for Astra Zeneca, Janssen, Johnson and Johnson, Sanofi, Aventis, Takeda, Amgen, Ferring and Novartis.

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