

Editorial

Osteoporosis and prostate cancer

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Prostate cancer has just become the most commonly registered cancer of males in the United Kingdom, overtaking lung cancer in the registration sweepstakes, and is the second most common cause of male cancer deaths. Deaths have trebled over the last 30 years, plateauing in the mid-1990s but recently increasing again (Office for National Statistics, 2001).

Locally advanced and metastatic prostate cancer is treated with antiandrogens and the importance of the side effects of treatment have become more significant as the incidence of this malignancy has increased. These side effects from treatment range from hot flushes, impotence, breast tenderness and enlargement, and diarrhoea to the physically more significant side effects, which include anaemia, loss of muscle bulk, neurological dysfunction, and osteoporosis. All of these side effects occur as a consequence of androgen deficiency. We would argue that the development of osteoporosis is the most important of these side effects and that we need to be more proactive in our management of this condition.

The risk of osteoporotic fracture as a consequence of antiandrogen therapy has been described in five studies. In a group of 235 patients with prostate cancer, the cumulative risk of fracture at 7 years was 28% in 59 castrated men and 1% in 176 men treated with a GnRH agonist (Daniell, 1997). In a second study, 9% of 224 men treated with an LHRH agonist had a fracture over a median follow-up of 22 months; seven of these men had fractures resulting from osteoporosis, eight men from trauma, and five of mixed aetiology (Townsend *et al*, 1997). In a third study of 218 men, 6% had an osteoporotic fracture during 6 or more months treatment with anti-androgen therapy (Hatano *et al*, 2000); in a fourth study, 20% of 181 men treated for 10 years had osteoporotic fractures (Oefelein *et al*, 2001). Fracture rates were described in 429 men with prostate cancer treated by bilateral orchiectomy. There were 267 fractures in 161 men. The increased risk due to osteoporosis was reported as a standard incidence ratio of 3.50 (95% CI 2.71–4.43) (Melton *et al*, 2003).

The increased risk of fracture in these men is due to accelerated loss of bone mineral density and is of early onset. Decreases of 6.6% at the lumbar spine have been seen only after 6 months of treatment and decreases of 6% at the femoral neck after 18 months treatment (Diamond *et al*, 1998). In a French study, changes in bone mineral density were evaluated in 12 men with prostate cancer treated with triptorelin. Men with metastases, radiographic

evidence of osteoporosis, or pre-existing conditions associated with accelerated bone loss were excluded from the study. Bone mineral density was measured at baseline, 6, 12, and 18 months. Bone mineral density of the lumbar spine and femoral neck tended to decrease from month 6, but only reached statistical significance at 18 months (Maillefert *et al*, 1999). In an American study, changes in bone mineral density were evaluated in 26 men with prostate cancer treated by orchiectomy or with GnRH agonists. Bone mineral density was measured at 6–42 months. The average bone mineral density of the hip decreased by 7.6% during the first orchiectomy, and similar rates of bone loss were observed among men treated with the GnRH agonists. Rates of bone loss were highest among inactive and obese men (Daniell *et al*, 2000).

These significant changes in bone mineralisation can be prevented. This has been shown by a recent study, where patients with locally advanced or recurrent nonmetastatic prostate cancer receiving leuprolide were randomised to receive pamidronate given every 3 months for 1 year. In the bisphosphonate group bone mineral density did not decrease, while in the control group mineralisation decreased by 3.3% in the lumbar spine and 2.1% at the hip (Smith *et al*, 2001). This benefit has been confirmed in an Australian study (Diamond *et al*, 2001) and in an American study where 106 patients were randomised to receive 3 monthly Zoledronic acid for 1 year (Smith *et al*, 2003a). An alternative approach might be to use an antiandrogen without adverse effects on bone. Bicalutamide monotherapy increases serum levels of testosterone and oestradiol, indicating that osteoporosis might be less likely than with other antiandrogens. Urinary markers of bone turnover in bicalutamide-treated patients were higher than in gonadotrophin-releasing hormones against treated patients (Smith *et al*, 2003b). However, there have been no studies that have assessed bone mineralisation densities in patients treated with bicalutamide as compared with other antiandrogens. In clinical practice, bicalutamide is frequently given with a gonadotrophin-releasing hormone agonist and the effects of this combination on bone turnover are not known.

So, it would appear that there is a clear way to limit the effects of antiandrogen treatment on bone and that is by giving bisphosphonate treatment prophylactically. What is unclear is the bisphosphonate dosage regimen to be used. There are new, highly effective third-generation bisphosphonates currently available and it may be that a limited trial is required to investigate this issue of dosage and frequency of bisphosphonate administration.

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