Reducing Bone Loss from Androgen Deprivation in Prostate Cancer Using Raloxifene

Smith MR, Fallon MA, Lee H, Finkelstein JS. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:3841–6.

Study Overview

Objective. To evaluate the effects of raloxifene on bone mineral density (BMD) in men receiving a gonadotropin-releasing hormone (GnRH) agonist for nonmetastatic prostate cancer.

Design. Randomized, prospective, open-label study.

Setting and participants. Participants were recruited at Massachusetts General Hospital in Boston between February 2000 and February 2002 ($n = 44$). All participants were receiving treatment with a GnRH agonist for nonmetastatic prostate cancer for ≥ 6 months at study entry. Men with bone metastases or evidence of progressive disease (serum prostate-specific antigen > 150% nadir value) were excluded. Men with metabolic bone disease, osteoporosis, history of deep venous thrombosis or pulmonary embolus, serum calcium < 8.4 or > 10.6 mg/dL, or serum creatinine concentration > 2.0 mg/dL were also excluded. Participants were randomly assigned to receive raloxifene (60 mg orally per day) or no raloxifene for 12 months. Participants were not blinded to treatment assignment and continued treatment with a GnRH agonist. Compliance was assessed with patient diaries. All participants received calcium carbonate (500 mg daily) and a daily multivitamin containing 400 IU vitamin D. Study personnel were blinded to the treatment assignments. Participants were evaluated at baseline and 6 and 12 months with measurement of serum and urine samples, BMD, and body composition (as measured by dual energy x-ray absorptiometry).

Main outcome measures. Percent change in BMD of the posteroanterior lumbar spine from baseline to 12 months. Percent changes in BMD, body composition, gonadal steroids, and biochemical markers of bone turnover from baseline to 12 months were compared between groups using *t* tests.

Main results. Baseline characteristics were similar in both groups. Mean serum testosterone levels at baseline were in the castrate range in both groups. Mean BMD of the posteroanterior lumbar spine increased by 1.0 ± 0.9% in men treated with raloxifene and decreased by 1.0 ± 0.6% in men who did not receive raloxifene ($P = 0.07$). The difference in percent change from baseline to 12 months between both groups was 2.0% (95% confidence interval [CI], –0.2%–4.0%). BMD of the total hip increased by 1.1 ± 0.4% in men treated with raloxifene and decreased by 2.6 ± 0.7% in men who did not receive raloxifene ($P < 0.001$). Similar between-group differences were observed in the femoral neck ($P = 0.06$) and trochanter ($P < 0.001$). The between-group differences in percent change from baseline to 12 months were 3.7% (95% CI, 2.0%–5.4%) for the total hip, 3.9% (95% CI, 1.9%–5.9%) for the trochanter, and 2.0% (95% CI, –0.1%–4.0%) for the femoral neck. Changes in serum total testosterone and estradiol levels did not differ significantly between the groups. In raloxifene-treated men, changes in BMD of posteroanterior lumbar spine and total hip did not correlate with either baseline estradiol levels or baseline free-estrogen index. In men treated with raloxifene, changes in serum concentration of amino-terminal propeptide of type I collagen and urinary excretion of deoxypyridinoline did not correlate with either baseline estradiol levels or baseline free-estrogen index. Mean changes in body mass index, lean mass, fat mass, and serum lipoproteins did not differ significantly between groups.

Conclusion. In men receiving a GnRH agonist, raloxifene significantly increases BMD of the hip and tends to increase BMD of the spine.

Commentary

GnRH agonists are commonly used in the treatment of prostate and breast cancers. In general, these agents are minimally toxic relative to chemotherapy and have proven effective in the management of both early and advanced stages of disease. Androgen deprivation therapy is associated with decreased BMD and an increased risk of fracture [1,2]. Recently, Smith et al demonstrated that bisphosphonate therapy (pamidronate) significantly lessened bone loss when combined with androgen deprivation therapy in patients with advanced prostate cancer [3]. The optimal dosing and schedule of bisphosphonate therapy remain undefined.

In this study, Smith et al examine the role of an oral anti-

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estrogen therapy (raloxifene) in improving BMD in patients with nonmetastatic prostate cancer receiving GnRH-agonist treatment for at least 6 months. Raloxifene, like tamoxifen, is a selective estrogen receptor modulator (SERM) that has "pro-estrogenic" properties on bone. In a large randomized prospective trial in postmenopausal women without cancer, raloxifene was associated with an improvement in BMD and lowered low-density lipoprotein cholesterol [4]. Similar benefits have been seen with tamoxifen. In the current study, raloxifene was associated with improvements in BMD in the hips of men receiving concurrent GnRH-agonist therapy.

This study's greatest strength is its randomized prospective design. Although small, the groups were well-balanced and had castrate-range testosterone levels at enrollment. This is an important study because it is one of the few trials examining the role of SERMs in men with cancer, and it is the first randomized study in men with raloxifene. Raloxifene was well-tolerated and associated with few serious toxicities. Interestingly, unlike the Delmas et al trial in women [4], raloxifene was not associated with improvements in lipid profiles. Whether raloxifene contributes to fewer fractures in men with prostate cancer receiving androgen deprivation therapy remains to be seen. As well, raloxifene is not risk-free, as it appears to contribute to an increased risk of thromboembolic events (1 pulmonary embolus in this study), which is similar to the well-described increased thromboembolic risk associated with tamoxifen in women. This risk aside, SERMs may be an acceptable alternative to intravenous bisphosphonate therapy in men at risk for bone density loss due to androgen deprivation.

Applications for Clinical Practice

SERMs appear to confer similar bone protection in men as in women receiving androgen deprivation therapy for cancer. Thromboembolic risk should be discussed with all patients receiving SERM treatment. Intravenous bisphosphonate therapy is currently approved for the adjunctive treatment of patients with advanced cancer involving the bones at risk for pain and fracture.

–Review by David R. Spigel, MD

References

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