Contribution of Androgen Deprivation Therapy to Elevated Osteoclast Activity in Men with Metastatic Prostate Cancer

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ABSTRACT

Purpose: Biochemical markers of both osteoblast and osteoclast activity are elevated in men with osteoblastic metastases from prostate cancer. Androgen deprivation therapy (ADT), the mainstay of therapy for advanced prostate cancer, increases markers of osteoblast and osteoclast activity, even in the absence of bone metastases. Little is known about the relative contributions of ADT and skeletal metastases to elevated bone turnover in men with prostate cancer.

Experimental Design: To evaluate the relative contributions of ADT and skeletal metastases to osteoblast and osteoclast activity, we performed a cross-sectional study in three groups of men with advanced prostate cancer: (a) hormone-naïve men without bone metastases; (b) castrate men without bone metastases; and (c) castrate men with bone metastases. The primary study end points were serum levels of bone-specific alkaline phosphatase (BSAP), a marker of osteoblast activity, and N-telopeptide (NTX), a marker of osteoclast activity.

Results: Serum levels of both BSAP and NTX were significantly higher in groups of castrate men (groups 2 and 3) than in hormone-naïve men (group 1; P < 0.01 for all comparisons). Among castrate men, serum BSAP was significantly higher in men with bone metastases than in men without bone metastases (P = 0.01). In contrast, serum levels of NTX were similar in groups 2 and 3 (P = 0.33).

Conclusions: The unintended effects of ADT on the skeleton are sufficient to explain increased osteoclast activity in castrate men with bone metastases. These results may have important implications for the optimal timing and schedule of osteoclast-targeted therapy in men with advanced prostate cancer.

INTRODUCTION

Prostate cancer metastasizes primarily to the skeleton. On radiographic evaluation, these bone metastases are described as “osteoblastic” based on excessive new bone formation. The biology of osteoblastic bone metastases may be more complex, however, than suggested by their radiographic appearance. Osteoclast number and activity are increased in bone metastases, in bone adjacent to metastases, and in distant uninvolved bone (1, 2). Additionally, biochemical markers of both osteoblast and osteoclast activity are elevated in men with metastatic prostate cancer (3–7). In a small prospective study of men with metastatic prostate cancer, markers of osteoclast activity predicted independently the risk of subsequent skeletal complications (8). These observations form the basis for evaluation of osteoclast-targeted therapies in men with osteoblastic metastases.

Androgen deprivation therapy (ADT) by either bilateral orchiectomy or treatment with gonadotropin-releasing hormone agonist is the mainstay of therapy for advanced prostate cancer. Medical or surgical castration adversely affects bone metabolism. ADT increases markers of osteoblast and osteoclast activity, decreases bone mineral density, and increases fracture risk (9–12). Thus, treatment-related osteoporosis may account for some of the skeletal complications experienced in men with advanced prostate cancer. This distinction may have important implications in our understanding of bone complications in prostate cancer, and in the timing and schedule of bone-targeted therapy.

Little is known about the relative contributions of ADT and skeletal metastases to increased bone turnover in men with bone metastases from prostate cancer. To address this question, we conducted a cross-sectional study in three groups of men with prostate cancer: (a) hormone-naïve men without bone metastases; (b) castrate men without bone metastases; and (c) castrate men with bone metastases.

PATIENTS AND METHODS

Subjects were recruited from the Massachusetts General Hospital Cancer Center. Three groups of men were analyzed. The first group included men with rising prostate-specific antigen (PSA) after radical prostatectomy or radiation therapy, no clinical or radiographic evidence of skeletal metastases, and no current ADT (group 1, hormone-naïve nonmetastatic). The second group included men on ADT, no clinical or radiographic evidence of skeletal metastases, and stable disease by PSA Working Group criteria (Ref. 13; group 2, castrate nonmetastatic). The third group included men with radiographically proven skeletal metastases who were receiving ADT (group 3, castrate metastatic). Group 3 included men with stable disease and men with progressive, androgen-independent disease, by PSA Working Group criteria (13). Markers of osteoblast activity appear to plateau after 6
months of ADT (10). Accordingly, men who had received less than 6 months of ADT were excluded from groups 2 and 3.

Men with Paget’s disease, hyperthyroidism, Cushing’s disease, hyperprolactinemia, chronic liver disease, or chronic renal insufficiency (serum creatinine >2.0 mg/dl) were excluded. Men were also excluded if they had received glucocorticoids, calcitonin, or suppressive doses of thyroxine within 1 year, or had ever received any bisphosphonate therapy. Subjects in groups 1 and 2 had never been treated for prostate cancer with chemotherapy, palliative radiation therapy, radionuclides, estrogens, or PC-SPES. Men in group 3 had not received chemotherapy, palliative radiation therapy, estrogens, or PC-SPES for a minimum of 6 weeks, and had not received radionuclides for a minimum of 12 weeks, before entry into the study.

The study was reviewed and approved by the institutional review board, and all of the subjects gave written informed consent.

Serum concentrations of bone-specific alkaline phosphatase (BSAP) and N-telopeptide (NTX) were measured in the core laboratory for the Massachusetts General Hospital General Clinical Research Center. Samples for all of the subjects were analyzed at the same time. Serum BSAP concentrations were measured by enzyme immunoassay with a sensitivity of 0.5 units/liter and intra- and interassay coefficients of variation of 3.5 and 6.5%, respectively (Metra Biosystems, Mountain View, CA). Serum NTX concentrations were measured by enzyme immunoassay with a sensitivity of 0.5 nm bone collagen equivalents and intra- and interassay coefficients of variation of 5.5 and 3.6%, respectively (Osteomark, Ostex International, Seattle, WA). The normal ranges (mean ±2 SDs) for BSAP and NTX were 15.0–41.3 units/liter and 5.4–24.2 nm BCE, respectively. Serum concentrations of testosterone, PSA, and alkaline phosphatase were measured in the Massachusetts General Hospital clinical laboratory.

Values are reported as the mean ± the SE, unless otherwise indicated. Comparison between groups was calculated using two-sided t tests, and Ps less than 0.05 were considered statistically significant.

### RESULTS

**Subject Characteristics.** Sixty-seven subjects were included in the analyses. Men in the castrate metastatic group were older than men in the other two groups (Table 1). Mean testosterone concentrations were significantly lower in groups 2 and 3 than in group 1. Serum PSA was higher in group 3 than in group 2. Consistent with the burden of metastatic disease to bone, mean serum alkaline phosphatase was higher in group 3 than in the other groups.

**Bone Turnover Markers.** Serum concentrations of BSAP, a marker of osteoblast activity, differed significantly between the groups (Fig. 1). Mean serum BSAP was higher in both groups of castrate men than in hormone-naïve men (P < 0.01 for each comparison). Additionally, mean serum BSAP was significantly higher in the castrate metastatic group than in the castrate nonmetastatic group (P = 0.01).

Serum concentrations of NTX, a marker of osteoclast activity, were significantly higher in castrate men, with or without bone metastases, than in hormone-naïve men (P < 0.001 for each comparison). In contrast to the results with BSAP, however, mean serum NTX levels were similar between the castrate metastatic and castrate nonmetastatic groups (P = 0.33).

We also compared men in the castrate nonmetastatic group with the subset of men in group 3 with progressive, androgen-independent disease. In this subset of 17 men (median PSA, 44.7; mean alkaline phosphatase, 147 ± 22), mean serum BSAP was significantly higher than in the castrate, nonmetastatic group (58.4 ± 15.3 versus 33.3 ± 2.2; P = 0.02). Even in this subset of men with progressive disease, NTX did not differ significantly from men in the castrate, nonmetastatic group (25 ± 3.8 versus 20.5 ± 1.2; P = 0.27).

### DISCUSSION

This study demonstrates that levels of serum NTX, a marker of osteoclast activity, are significantly higher in castrate men than in hormone-naïve men but similar between castrate men with bone metastases and castrate men without bone metastases. In contrast, serum BSAP levels, a marker of osteoblast activity, are significantly higher in castrate men than in hormone-naïve men and significantly higher in castrate men with
bone metastases than in castrate men without bone metastases. These results suggest that the adverse effects of ADT on the skeleton are sufficient to explain elevated osteoclast activity in men with bone metastases.

Our observation that markers of osteoclast activity are elevated in castrate men with metastatic disease is consistent with earlier reports (3–6, 14). These studies attributed elevated osteoclast activity to tumor-mediated bone destruction. Although not specified in most studies, the majority of subjects probably had castrate testosterone levels given that ADT is the cornerstone of treatment for advanced prostate cancer. In the one study that specified current treatment, 30 of 32 men with skeletal metastases received ADT (4).

This study may have important implications for the optimal timing and schedule of bisphosphonates and other osteoclast-targeted therapy in men with prostate cancer. In a randomized controlled trial of men with bone metastases and progressive prostate cancer despite ADT, zoledronic acid (4 mg i.v. every 3 weeks) decreased significantly the risk of skeletal related events, a composite endpoint consisting of radiation to bone, fractures, spinal cord compression, change in antineoplastic therapy to treat bone pain, and surgery to bone (14). Zoledronic acid decreased urinary NTX by ~70%. In a 1-year randomized controlled trial in postmenopausal women with osteoporosis, zoledronic acid (4 mg i.v. once) decreased markers of osteoclast activity by about 60% and increased bone mineral density (15).

In another 1-year randomized controlled trial, zoledronic acid (4 mg i.v. every 12 weeks) increased bone mineral density in castrate men with nonmetastatic prostate cancer (16). Our results raise the possibility that a bisphosphonate dose/schedule sufficient to increase bone mineral density in castrate men may also be adequate to prevent skeletal-related events in castrate men with bone metastases.

The study design was cross-sectional and prospective studies are needed to confirm our observations. Of interest, markers of osteoclast and osteoblast activity were prospectively evaluated in the randomized control trial of zoledronic acid in men with bone metastases and disease progression despite ADT (14). Mean bone alkaline phosphatase levels increased progressively in the placebo group over 15 months. In contrast, urinary NTX levels remained stable throughout the study. The marked disparity between changes in markers of osteoblast and osteoclast activity in a large group of men with progressive metastatic disease supports the observations of our cross-sectional study.

We excluded men receiving chemotherapy or palliative radiation therapy from our castrate metastatic group to avoid the confounding effects of these treatments on bone metabolism. Despite these exclusions, PSA and alkaline phosphatase were markedly elevated in this group, consistent with substantial bone metastases. Nevertheless, different results may be observed in men receiving chemotherapy or palliative radiation therapy because of either more extensive disease or the unintended effects of these other treatments on bone metabolism.

In summary, serum levels of both BSAP and NTX are significantly increased by ADT in men with nonmetastatic prostate cancer. In contrast, BSAP but not NTX increases further in the presence of bone metastases. These findings have important implications in our understanding of bone metabolism, and may affect the manner in which bone-targeted therapy is studied and used in men with prostate cancer.

**REFERENCES**

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