Failure to Suppress Markers of Bone Turnover on First-Line Hormone Therapy for Metastatic Prostate Cancer Is Associated With Shorter Time to Skeletal-Related Event

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Abstract

Biomarkers to identify patients with metastatic prostate cancer who are destined to have a shorter response to testosterone suppression are limited. In a cohort of 63 patients, failure to suppress markers of bone turnover while receiving therapy was associated with a shorter time to progression. This suggests that more durable anti–prostate cancer activity is associated with less cancer-associated bone turnover.

Background: Elevated markers of bone turnover are prognostic for shorter survival in castration-resistant prostate cancer. We aimed to determine the prognostic value of bone turnover markers in metastatic hormone-sensitive prostate cancer. **Patients and Methods:** Markers of bone turnover (urine deoxypyridinoline [DPD] and N-telopeptide, serum bone alkaline phosphatase (AP), and osteocalcin [OC]) from baseline and after 6 months of study were assessed in men enrolled in a prospective metastatic prostate cancer trial with androgen deprivation therapy (ADT) with or without risedronate (ClinicalTrials.gov, NCT00216060). **Results:** Serum samples were collected from 63 patients with bone involvement and a median follow-up of 39.7 months. A multivariate model using Cox regression—which included prostate-specific antigen (PSA) nadir, bisphosphonate treatment, and extent of metastases—showed that suppression of bone turnover markers after 6 months of therapy compared with baseline was significantly associated with longer skeletal-related event (SRE)-free survival. ADT without bisphosphonate therapy was also associated with a decline in markers of bone turnover, presumably resulting from direct anticancer activity. Elevated baseline bone turnover markers were not prognostic. **Conclusion:** Failure to suppress bone turnover while receiving ADT, even when otherwise responding to therapy, may identify patients with hormone-sensitive metastatic prostate cancer who are destined for a shorter time to SREs and progression.

Clinical Genitourinary Cancer, Vol. 12, No. 1, 33-40
Keywords: Androgen deprivation therapy, Bone turnover, Prostate cancer, Skeletal-related events

Introduction

Prostate cancer afflicts approximately 240,000 men per year in the United States and causes about 33,000 deaths.[1] Bone metastases occur in about 90% of patients with metastatic prostate cancer and cause significant morbidity from pain, pathologic fractures, and spinal cord compression.[2] Although effective for palliation of symptoms and control of prostate cancer growth, androgen deprivation therapy (ADT) as medical or surgical castration with or without androgen receptor inhibition increases bone turnover and reduces bone mineral density.[3] In patients with metastatic castration-resistant prostate cancer (CRPC), intravenous administration of the bisphosphonate zoledronic acid and the receptor activator of nuclear factor-κB ligand inhibitor denosumab decrease the rate of cancer-related SREs compared with placebo,[4,5] whereas pamidronate did not confer a benefit in CRPC.[6]

Regarding patients with metastatic prostate cancer who are beginning ADT, long-term follow-up of a study by Dearnaley et al

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Submitted: Mar 23, 2013; Revised: Jul 27, 2013; Accepted: Jul 31, 2013; Epub: Oct 12, 2013

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2013.07.002

demonstrated that oral clodronate, when compared with placebo, prolonged time to progression and overall survival (5-year overall survival, 30% vs. 21%; $P = .03$).[7] Data on SREs were not presented in this study; however, an improvement in serum total alkaline phosphatase (AP) levels was noted after treatment in the clodronate arm.[8] Follow-up phase III studies in the same patient population are ongoing to assess the ability of zoledronic to delay SREs (Cancer and Leukemia Group B [NCT00079001] and MRC [NCT002684760]. In addition to prostate cancer increasing bone turnover, such turnover is also increased by ADT itself. Numerous studies have shown that bisphosphonates prevent ADT-induced bone loss (measured by dual-energy x-ray absorptiometry) and decrease ADT-induced increase of markers of bone turnover (alkaline phosphatase [AP], osteocalcin [OC], deoxypyridinoline [DPD], N-telopeptide [NTX]).[9-11]

The benefit that is seen with zoledronic acid and denosumab in CRPC, but is not seen with pamidronate, is presumed to result from the lower potency of the latter; zoledronic acid is 150 to 850 times more potent than pamidronate.[12] The notion that greater suppression of bone turnover would be beneficial is supported by observations that robust bone turnover (elevated markers of bone turnover) is associated with more SREs and a shorter time to progression in patients with bone metastases emanating from CRPC, non–small-cell lung cancer, breast cancer, and myeloma.[13,14] Conversely, normalization of bone markers within 3 months of bisphosphonate therapy for patients with breast cancer or multiple myeloma correlated with decreased risks of a first SRE, disease progression in bone, and death.[15]

The impact of bone turnover in patients beginning ADT for metastatic disease is not well characterized. The net effect of ADT on bone turnover is speculated to be complicated by competing effects. Namely, although ADT itself increases bone turnover, the anticancer effect of ADT will also decrease tumor burden, which may in turn decrease bone turnover and delay progression and SREs when compared with no therapy. Effective direct anticancer hormone therapy with abiraterone in CRPC has been shown to decrease SREs.[16] In this article, we detail the association between time to SREs and changes of markers of bone turnover after commencing ADT for metastatic prostate cancer.

Patients and Methods

Patients

Samples were collected from patients enrolled in a prospective clinical trial (ClinicalTrials.gov, NCT00216060) after approval by the institutional review boards of participating centers. All patients were $\geq$ 18 years of age, had provided written informed consent before study registration, and were required to have histologically or cytologically documented prostate adenocarcinoma with radiographic (computed tomographic [CT] scan or bone scan) evidence of bone metastases, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, and adequate organ function. Patients were excluded if they had diseases of abnormal bone metabolism (including Paget disease, untreated hyperthyroidism, untreated hyperprolactinemia, untreated Cushing disease), or had undergone > 4 months of adjuvant hormone therapy, previous hormone therapy for biochemical-only disease, or hormone therapy within 12 months of study except when used within 1 month for the management of metastatic disease. Patients in this study were allowed to receive only the bisphosphonate risedronate 30 mg daily or matching placebo. Randomization stratification variables included age $\geq$ 70 years vs. < 70 years, ECOG PS 0 to 1 vs. 2, and minimal vs. extensive metastatic disease. Minimal disease was defined as metastases limited to the pelvic and axial skeleton, and extensive disease was defined as metastases involving the appendicular skeleton or visceral metastases. The trial was slow to accrue and closed after 63 of a planned 360 patients were enrolled.

All patients were treated with ADT in the form of luteinizing hormone–releasing hormone agonist therapy or surgical castration. Combined androgen blockade with the use of antiandrogens in addition to ADT was at the discretion of the treating physician. Antiandrogen therapy as monotherapy was not allowed, nor was intermittent ADT. Treatment with risedronate/placebo on both arms was continued until the occurrence of SREs, serologic progression without symptoms, symptomatic progression of bone disease, unacceptable toxicity, or death. In addition to risedronate/placebo, all patients were treated with oral calcium carbonate 500 mg per day with at least 400 IU of vitamin D per day.

Patient and Disease Evaluations

Baseline CT scan of the abdomen and pelvis, chest radiograph or CT scan, bone scan, lumbosacral spine radiograph, and tumor measurements were recorded within 28 days of registration. History and physical examination, ECOG PS, laboratory measurements (including serum prostate-specific antigen [PSA] and baseline toxicity grading per National Cancer Institute NCI Common Terminology Criteria for Adverse Events, version 3.0) were collected within 14 days before registration and every 12 weeks thereafter while in the study. Imaging studies were repeated every 12 weeks. A 10-mL urine sample (second specimen in the morning between 5 AM and 8 AM after an overnight fast, collected at home, and stored at 4°C until clinic visit) and 2 separate 10-mL whole blood samples processed for serum were collected before therapy initiation, after 24 weeks of treatment, and at the occurrence of an SRE. Markers of bone turnover included DPD, urine NTX, urine creatinine, serum bone alkaline phosphatase (BAP), and serum OC. Details of the assay methods are provided in the Supplementary Data.

All tumor responses were assessed per Response Evaluation Criteria in Solid Tumors. An SRE was defined as the occurrence of any of the following: a pathologic fracture, spinal cord compression, palliative radiation or surgery to bone, an increase in pain medication dose by 20 mg intramuscular morphine equivalence or a doubling of morphine equivalence from baseline, or an asymptomatic vertebral compression fracture. Treatment failure with hormone therapy was defined as the occurrence of either disease progression per Response Evaluation Criteria in Solid Tumors or the occurrence of an SRE. Serologic response and progression was assessed per the Prostate Cancer Working Group.[17]

CRPC was defined as (1) progressive serologic disease, progressive measurable disease, or progressive nonmeasurable disease (eg, symptomatic progression of bone disease or new pleural effusion resulting from progressive cancer) and (2) development of a cancer-related SRE, which must have been documented by an appropriate